Rationale, study design, and implementation of the ACS1 study: effect of azilsartan on circadian and sleep blood pressure as compared with amlodipine

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Objective The ACS1 (Azilsartan Circadian and Sleep Pressure – the first study) is a multicenter, randomized, open-label, two parallel-group study carried out to investigate the efficacy of an 8-week oral treatment with azilsartan 20 mg in comparison with amlodipine 5 mg.

Materials and methods The patients with stage I or II primary hypertension will be randomly assigned to either an azilsartan group (n = 350) or an amlodipine group (n = 350). The primary endpoint is a change in nocturnal systolic blood pressure (BP) as measured by ambulatory BP monitoring at the end of follow-up relative to the baseline level during the run-in period. In addition, we will carry out the same analysis after dividing four different nocturnal BP dipping statuses (extreme-dippers, dippers, nondipper, and risers).

Conclusion The findings of this study will help in establishing an appropriate antihypertensive treatment for hypertensive patients with a disrupted circadian BP rhythm. *Blood Press Monit* 19:123–128 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCBs), which are used as first-line antihypertensive drugs, have been shown to exert potent and stable antihypertensive effects on hypertension. Azilsartan, a novel ARB, has been reported to be more effective in lowering BP than other ARBs, and to have a potent antihypertensive effect over 24 h, on the basis of previous clinical studies [1–3]. Amlodipine, however, is deemed to have the most potent and sustained antihypertensive effect among the existing CCBs [4–7]. Our previous studies showed that amlodipine lowered nocturnal blood pressure (BP) and daytime BP comparably in patients with a non-dipper-type (reduced dipping of nocturnal BP) circadian BP rhythm [4], whereas azilsartan lowered nocturnal BP more extensively than daytime BP in patients with a non-dipper-type rhythm [3]. The results indicate that the effects of these two drugs on the nocturnal BP and on nocturnal BP fall may be different and may lead the management of hypertension by studying nocturnal BP patterns. However, to the best of our knowledge, there have been no comparable studies of whether there is a class effect of nocturnal BP reductions accompanied by an improvement in nocturnal BP patterns between two different antihypertensive drugs. Thus, we hypothesized that azilsartan induces a more extensive reduction in nocturnal BP than amlodipine and also a more effective restoration of nocturnal dipping from disrupted patterns to a normal dipper-type circadian BP rhythm.

To validate this hypothesis, we designed an investigator-initiated multicenter, randomized (dynamic allocation), open-label, two parallel-group study, the ACS1 (Azilsartan Circadian and Sleep Pressure – the first study), which will be carried out to investigate the efficacy of azilsartan on nocturnal BP and a circadian BP rhythm in comparison with amlodipine, as evaluated using ambulatory blood pressure monitoring (ABPM) in hypertensive patients.

Materials and methods
Primary objective

To evaluate the efficacy of an 8-week oral treatment with azilsartan 20 mg in lowering nocturnal systolic BP in comparison with amlodipine 5 mg in patients with stage I or II primary hypertension. Daily doses of azilsartan 20 mg and amlodipine 5 mg are normally used in clinical practice in Japan and are considered eligible for the management of adult patients aged 20 years or older with mild-to-moderate hypertension.

Organization and management

The ACS1 Society, based at the medical offices of the Division of Cardiovascular Medicine, Jichi Medical

University School of Medicine, plays a central role in carrying out the study. The study protocol, which has been approved by the ACS1 Society, was reviewed by the Jichi Medical University Institutional Review Board (IRB) for its scientific and ethical properties, conflicts of interest, etc., and granted approval. At study sites without an IRB, the study has been initiated after it has been reviewed and approved by the Hattori Clinic IRB.

To ensure transparency of the study, activities related to the study secretariat, data management, and statistical analyses will be contracted out to the contract research organization (CRO), Sogo Rinsho Médéfi Co., Ltd (Tokyo, Japan), and the study will be initiated after the written operation procedures and protocols for individual study-related activities have been predefined. With respect to data management activities, the CRO is responsible for developing an electronic data capture system in accordance with the Electronic Records and Electronic Signature Guidelines and for ensuring the quality of the data by managing the history of data entries by investigators and performing data verification using a data check program.

To ensure the quality of data at each study site, monitoring activities will be contracted out to a second independent CRO, ASKLEP Inc. (Tokyo, Japan), which will be tasked with monitoring the study in accordance with the predefined monitoring plan. The monitoring activities that will be performed during the study include confirming the signed informed consent form for all participants and visiting 10% of these participants.

Finally, to ensure the quality of the entire study, auditing activities will also be contracted out to a third independent CRO, Linical Co., Ltd (Tokyo, Japan), which is required to on-site audit the study on a regular basis throughout the duration of the study in accordance with the predefined audit plan.

This system of complete study management using three independent CROs will safeguard the quality of this investigator-initiated study while preventing potential bias from the individual doctors or the sponsor company.

Eligibility criteria of patients

The inclusion and exclusion criteria of this study are shown in Tables 1 and 2, respectively. Participants who fulfill all the inclusion criteria (Table 1) and do not fulfill any exclusion criteria (Table 2) will be enrolled in the study.

Informed consent

A total of 99 sites will participate in the study. The investigators shall explain to participants who fulfill all the inclusion criteria and no exclusion criteria the aim of the study, the procedures to be followed, and so forth, using an informed consent form and information sheet.

Table 1 Inclusion criteria of the ACS1 study

1. Stage I or II primary hypertension
2. Sitting SBP of 140–179 mmHg or sitting DBP of 90–109 mmHg at two time points, namely, the start of the run-in period and the start of treatment (week 0)
3. Aged ≥ 20 years
4. Written informed consent obtained before participation in the study
5. Able to visit the study site during the run-in period on an outpatient basis

ACS1, Azilsartan Circadian and Sleep Pressure – the first study; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2 Exclusion criteria of the ACS1 study

1. Secondary hypertension, stage III hypertension (sitting SBP ≥ 180 mmHg or sitting DBP ≥ 110 mmHg), or malignant hypertension
2. Multiple antihypertensives (≥ 2) before the 2-week washout period
3. Treated within 2 weeks before the start of the run-in period with the following drugs: antihypertensives, antianginals, ant-arrhythmics, or digitalis
4. Mean 24-h SBP of <130 mmHg and average 24-h DBP of <80 mmHg as measured by ABPM at the start of the run-in period
5. Any of the following cardiovascular diseases and chronic kidney disease within 24 weeks before the start of the run-in period:
   Cardiac diseases: myocardial infarction or coronary revascularization
   Cerebrovascular diseases: cerebral infarction/hemorrhage or transient ischemic attack
   Advanced hypertensive retinopathy: hemorrhage or exudative papilledema
6. History or clinical manifestations of any of the following cardiovascular diseases: valvular disease, atrial fibrillation, angina pectoris/congestive heart failure/arrhythmia requiring drug therapy, or symptomatic peripheral artery disease
7. Shift worker
8. History of hypersensitivity or allergies to azilsartan, amlodipine, or their related drugs
9. Participation in another clinical study
10. Pregnant or possibly pregnant woman or nursing mother
11. Poorly controlled BP (≥ 180/110 mmHg) from the time of informed consent to the start of antihypertensive treatment
12. Any symptom or abnormal laboratory finding that requires early termination of the study between informed consent and the start of antihypertensive treatment
13. Ineligible for participation in this study in the investigator's or the subinvestigator's opinion

ABPM, ambulatory blood pressure monitoring; ACS1, Azilsartan Circadian and Sleep Pressure – the first study; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Participants will be registered in the electronic case report form (eCRF) system to begin the run-in observation in the order of their signing of the informed consent form. In cases in which participants must discontinue previous intake of antihypertensives to be enrolled in the study, the discontinuation will begin only after written informed consent for study participation has been obtained. Overall enrollment will be completed when the planned sample size for the entire study is reached.

The investigator will create a participant code list to protect participants' personal information, and the information will remain anonymous.

Randomization

This is an open-label, two parallel-group study. Participants are randomized in a 1:1 ratio to receive oral azilsartan 20 mg or amlodipine 5 mg once daily using a dynamic allocation algorithm. Stratified randomization will be performed by the Registration Center at the start of treatment (week 0) by the dynamic allocation

algorithm with consideration of the four nocturnal dipping groups (extreme dippers, dippers, nondippers, and riser) determined on the basis of the data from ABPM at the start of the run-in period, age, sex, and prevalence of chronic kidney disease or type 2 diabetes mellitus.

For randomization of participants, the principal investigator or the investigator's designee will provide the necessary information, including the participant's ID code, to the Registration Center. The ID code of the antihypertensive to be administered to each participant will then be provided by the Registration Center. The principal investigator or another investigator will prescribe the antihypertensive to each participant according to the ID code assigned to the participant and enter the information on the prescribed antihypertensive on the CRF of the participant.

Antihypertensive drugs and concomitant drugs

Any antihypertensive drug should be stopped by day −1 of a 2-week washout period before the 1-week run-in period (no treatment is given). The use of any antihypertensive drugs, including azilsartan and amlodipine, will be prohibited during the run-in period.

During the treatment period, participants will orally take azilsartan 20 mg or amlodipine 5 mg, according to their group allocation, once daily before or after breakfast in the morning.

Concomitant use of any antihypertensive drugs other than the allocated investigational drugs, antianginal drugs, antiarrhythmics, digitalis preparations, and potassium supplements will be prohibited throughout the study.

No particular restrictions will be placed on treatments other than antihypertensive drugs.

Treatment protocol

A schematic of the study design is shown in Fig. 1. Participants will start treatment with either antihypertensive after examination at the start of treatment (week 0) and visit the study site every 2 weeks until the end of treatment (week 8).

Twenty-four-hour ABPM

ABPM will be performed at the start of the run-in period and at the end of treatment (week 8). A well-validated automatic ABPM device (TM-2431; A & D Inc., Saitama, Japan) will be attached to the participant at an outpatient visit to measure BP continuously for at least 26 h until the following day. ABPM will be performed twice during the study period, at the start of the run-in period and at the end of treatment (week 8), beginning at 10 : 00 (±2 h) in both cases. BP will be measured every 30 min. At the end of the treatment period (week 8), the allocated antihyperten-

Fig. 1
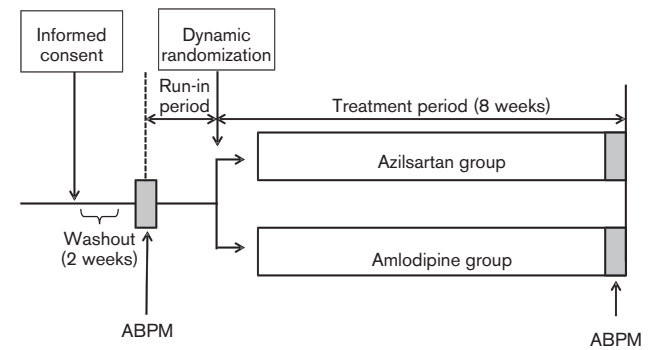
Study design of the ACS1 study. This study consists of a 1-week run-in period and an 8-week treatment period. ABPM was performed twice, that is, once during the run-in period and once at the end of the treatment period (week 8). ABPM, ambulatory blood pressure monitoring; ACS1, Azilsartan Circadian and Sleep Pressure – the first study.

sive will be administered in the morning after the start of ABPM. On the following day, the study medication will be administered after the end of ABPM. At the completion of ABPM, the BP data collected by the ABPM device (TM-2431) that were returned by the participant will be transferred to the ABPM Analysis Terminal (Dr Pro Tough; A&D Inc.), and then retrieved by the electronic data capture system for registration.

Nocturnal BP will be defined as the average of the BP values from the time when the patient goes to bed until the time he or she gets out of bed and daytime BP will be defined as the average of the BP values recorded during the rest of the day. Focusing on the effect of two different drugs for nocturnal BP reduction in different nocturnal BP patterns and the improvement in abnormal nocturnal BP patterns, we will also subclassify the study patients into the following 4 different dipping-status groups according to the percentage of nocturnal systolic blood pressure (SBP) dipping at baseline and followed up [100 − (1 − nocturnal SBP/daytime SBP)]: (a) extreme-dippers, a fall in nocturnal SBP of at least 20%; (b) dippers, a fall of at least 10% but less than 20%; (c) nondippers, a fall of at least 0% and less than 10%; and (d) risers, a fall of less than 0%.

Home BP monitoring

To perform a preliminary examination on the mutual relation between home BP and ABPM, the patients will be asked to self-measure their BP according to the Japanese guidelines for the management of hypertension (JSH2009) [8], and the results of as many daily measurements as possible of sitting systolic BP, diastolic BP, and pulse rate will be collected. Participants will measure their own BP at home before taking antihypertensive drugs in the morning and before bedtime at the

start of the run-in period and at the end of the treatment period (week 8). To provide representative results of the 3-day period around the days of ABPM, the results of as many measurements (before taking antihypertensive drugs and before bedtime) as possible on the 3 days closest to the day of ABPM will be collected.

Endpoint evaluation
The primary and secondary endpoints are shown in Table 3.

Sample size determination
The primary endpoint of this study is a change in the mean nocturnal systolic BP. On the basis of the previously reported changes in nocturnal BP with azilsartan and amlodipine, the sample size was calculated for statistical analysis by Student's *t*-test at a two-sided significance level of 0.05, as described below.

The change in the mean nocturnal BP with azilsartan 40 mg was reported to be − 15.3 ± 16.3 mmHg (mean ± SD) [1]. On the basis of this result and the following findings, the decrease in nocturnal BP with azilsartan 20 mg is estimated to be equivalent to that with azilsartan 40 mg: (a) azilsartan medoxomil is a prodrug of azilsartan and exists as azilsartan in the plasma. (b) The plasma concentration–time profile of azilsartan 20 mg administered as a single dose was reported to be comparable with that of azilsartan medoxomil 40 mg, (application document: *http://www.info.pmda.go.jp/info/syou-nin_index.html*), indicating that the two drugs have similar antihypertensive potency. (c) Azilsartan medoxomil 40 and 80 mg were reported to have an almost equivalent 24-h antihypertensive effect [2]. Amlodipine 5 mg was re-ported to decrease nocturnal BP by − 11.1 ± 13.5 mmHg (mean ± SD) [5].

On the basis of the above findings, the between-group difference (azilsartan 20 mg – amlodipine 5 mg) in the

mean change in the mean nocturnal systolic BP was estimated to be − 4.2 mmHg, with the standard deviation in each group estimated to be 15.8 mmHg. To show the superiority of azilsartan to amlodipine with a 90% power of test, 299 participants are required in each group. Because we assume that ∼ 15% of the study population will be excluded during the treatment period on the basis of the results of a previous phase 3 study of azilsartan [1], 350 participants will be enrolled in each group (700 in total).

Statistical analysis
The statistician should carry out each statistical analysis in a blinded manner using appropriate alternative identifiers of the groups (e.g. groups A and B) to mask the allocation of the antihypertensives. When estimating the between-group differences, two types of analysis will be carried out (e.g. group A – group B and group B – group A). For interpretation, the results of the azilsartan group – the amlodipine group, which will become available to the study statisticians after code breaking, will be used.

The following analysis sets are, respectively, used to assess (a) efficacy, (b) the robustness of the results for the primary endpoint, and (c) safety: (i) the full analysis set (FAS) defined as all enrolled participants who have received the investigational drug at least once after randomization, (ii) the per protocol set defined as all enrolled participants who have received the investiga-tional drug at least once after randomization, who fulfill the eligibility criteria, and who have no significant protocol deviations, and (iii) the safety analysis set defined as all enrolled participants who have received the investigational drug at least once.

In primary and secondary analyses, the two-sided 95% confidence interval (CI) of the between-group difference in the mean change in the mean nocturnal systolic BP, the primary endpoint, will be determined using the FAS. Azilsartan can be considered as (a) superior to amlodipine in the primary analysis if the upper limit of the two-sided 95% CI is below 0 and (b) noninferior to amlodipine in the secondary analysis if it is less than the noninferiority margin Δ [1.11 mmHg, which is 10% of the absolute decrease in the mean nocturnal systolic BP with amlodipine 5 mg (11.1 mmHg) [5]]. From the viewpoint of sensitivity analysis, the analysis carried out in the FAS will be repeated using the per protocol set to assess the robustness of the results. In addition to these analyses, the data from the FAS will be analyzed for the entire group as well as for each of the subgroups with different circadian BP rhythms.

For the secondary and other endpoints, the two-sided 95% CI of the between-group difference in the mean change in each endpoint and the associations among the mean change in each endpoint will be determined using

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Table 3 Primary and secondary endpoints of the ACS1 study

Primary endpoint
    Change in the mean nocturnal SBP as measured by ABPM at the end of the
       treatment period (week 8) from the beginning of the observation period
Secondary endpoints
    Change in the absolute value of the difference from the targeted value of
       nocturnal SBP dipping[a]
    Change in the percentage from the shift of abnormal dipping patterns (riser,
       non-dipper, and extreme-dipper patters) to the normal dipper pattern
    Change in the mean nocturnal DBP level
    Change in the mean 24-h SBP level
    Change in the mean 24-h DBP level
    Change in the urinary albumin/creatinine excretion ratio (UACR)
    Change in N-terminal pro-B-type natriuretic peptide (NTproBNP)
    Change in high-sensitive cardiac troponin T (hs-cTnT)
    Change in fasting glucose
    Change in homeostasis model of assessment – insulin resistance (HOMA-IR)[b]
    Adverse events

ABPM, ambulatory blood pressure monitoring; ACS1, Azilsartan Circadian and Sleep Pressure – the first study; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]The targeted value has been set as 15% of the nocturnal SBP dipping.
[b]HOMA-IR = fasting glucose (mg/dl) × fasting insulin (μU/ml)/405.

the FAS. The data from the FAS will also be analyzed in the entire group, in each treatment group, and in the subgroups with different circadian BP rhythms.

To assess the safety of treatment, the incidence of adverse events from the start to the end of treatment (weeks 0–8) will be analyzed for each group using safety analysis set.

Discussion

The recent guidelines recommend strict 24-h BP control, including morning BP and nocturnal BP control, to prevent cardiovascular diseases effectively [8–10]. In the PIUMA study, the incidence rate of cardiovascular events was reported to be 1.79 (per 100 person-years) for dipper hypertensive participants and 4.99 for nondipper hypertensive participants versus 0.47 for participants with normal BP [11]. A previous study carried out by our group showed a 2.7-fold increased cardiovascular risk in riser-type compared with dipper-type hypertensive patients [12]. This indicates that high nocturnal BP levels, as well as high daytime BP levels, are associated with an increased risk of cardiovascular events. In addition to these findings, it has been reported that a disrupted circadian BP rhythm of either the nondipper type or the riser type may have worse effects on the brain, heart, kidneys, and other organs [13–15] and may be associated more closely with the occurrence of cardiovascular events than the normal circadian BP rhythm of the dipper type [16].

Some reports show that, even among normotensive participants, those with a non-dipper-type pattern are more likely to have increased risks of the progression of organ damage [17] and cardiovascular events [18] than those with a dipper-type pattern. Moreover, in another study of ABPM carried out in healthy adult participants with normal BP (average age: 30 years) to assess the risk of coronary calcification by coronary CT over 10–15 years, a four-fold or greater increase in the risk was found for the nondipper/riser type versus the dipper type, even after adjustment for other related factors, including age and BP levels [19]. In this study, not only nondipper/risers but also extreme-dippers (with marked nocturnal BP fall > 20%) showed a four-fold increase in the risk of coronary calcification compared with dippers [19]. We have previously shown that an extreme-dipper pattern is also a risk for silent cerebral disease (silent cerebral infarcts and white matter lesion detected by brain MRI) and clinical stroke events [13,16]. These findings suggest that both extremes of a disrupted circadian rhythm, that is, extreme-dipper and riser patterns, are associated with cardiovascular risk independent of 24-h BP level.

In the Japan morning surge-target organ protection study using candesartan, even in the medicated hypertensives [20], urinary albumin/creatinine excretion ratio (UACR) and B-type natriuretic peptide (BNP) are associated more closely with nocturnal BP than daytime BP [21]. In addition, the medicated patients with isolated nocturnal hypertension (well-controlled morning and evening BPs self-measured by home BP monitoring, but increased nocturnal BP measured by ABPM) showed higher UACR and BNP levels compared with those with well-controlled nocturnal BP [22]. However, it is not clear which type of antihypertensive medication is more suitable to lower the nocturnal BP and to restore the normal circadian BP pattern, and finally to reduce the measures of organ damage.

The Japanese Guidelines for the Management of Hypertension 2009 [8] and the ESH-ESC2013 Guidelines for the Management of Arterial Hypertension [9] recommend ARBs and CCBs as the first-line antihypertensive medications. Among ARBs, azilsartan, a novel ARB, has been shown to be more effective at lowering BP than other ARBs and to have a potent antihypertensive effect over 24 h in previous clinical studies [1,3]. Azilsartan has also been suggested to be effective in restoring the normal circadian BP rhythm to a normal 'dipper' type from those abnormal variations in the riser, nondipper, and extreme-dipper types [1]. Amlodipine, however, has also been shown to have a potent and sustained antihypertensive effect over 24 h among the existing CCBs in previous clinical studies [4–7], whereas it has not been elucidated whether CCBs can restore a normal dipper-type pattern from an abnormal circadian BP rhythm [4]. It is a characteristic of amlodipine that the higher the baseline BP level, the more extensive will be the BP reduction [7]. Thus, in the nondippers and risers, a higher nocturnal BP level would be reduced comparably to the daytime BP level, and dipping status may not be altered by amlodipine [4]. At present, there are no available data directly comparing the effects of azilsartan and amlodipine on restoring the nocturnal BP, although both are expected to be effective for reducing the 24-h BP level through their potent antihypertensive effects, whereas they may have differential effects on nocturnal BP and the dipping status of nocturnal BP.

From this point of view, the ACS1 aims to clarify the efficacy of azilsartan and amlodipine not only with respect to 24-h BP but also in terms of nocturnal BP to help establish an antihypertensive treatment regimen. In addition, the study will clarify any potential ability of these drugs to restore the disrupted patterns of circadian BP rhythm (riser, nondipper, and extreme-dipper patterns) to a normal dipper-type pattern, which could contribute toward the development of an antihypertensive treatment regimen for hypertensive patients with these disrupted circadian BP patterns. Through the implementation of ACS1, we will be able to propose an updated antihypertensive treatment strategy, especially targeting nocturnal BP, which could lead to a reduction in cardiovascular events in those patients with an abnormal circadian BP rhythm. As secondary endpoints, we will assess cardiorenal biomarkers such as UACR and BNP in

relation to the reduction of nocturnal BP in the entire group, each treatment subgroup, and the subgroups with different nocturnal dipping statuses.

In the substudy of ACS1, patients will self-measure their home BP data in the morning before taking the assigned antihypertensive and in the evening before going to bed. The correlation between ABPM and home BP measurements will be explored to find any significance and this will allow us to presume the time-course profile of 24-h BP, even when ABPM data are not available, from the results of home BP monitoring.

The ACS1 will be carried out completely in accordance with ethical guidelines and in partial compliance with the ICH-GCP, such as through the introduction of monitoring and auditing activities to ensure the quality of the study. In addition, to ensure the objectivity and quality of the study data, data management and statistical analysis activities will be contracted out to third-party organizations, which will perform these activities according to predefined operation procedures. Thus, ACS1 will be a Japan model of the leading investigator-initiated study carried out under strict management to avoid interventions by the funding company or investigators.

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