Original Article

The Japan Morning Surge-1 (JMS-1) Study: Protocol Description

Joji ISHIKAWA[1)], Satoshi HOSHIDE[1)], Seiichi SHIBASAKI[2)], Yoshio MATSUI[2)], Tomoyuki KABUTOYA[4)], Kazuo EGUCHI[1), 4)], Shizukiyo ISHIKAWA[3)], Thomas G. PICKERING[5)], Kazuyuki SHIMADA[1)], and Kazuomi KARIO[1)], on behalf of the JMS-1 Study Group

Morning blood pressure is reported to be more closely related to hypertensive organ damages such as left ventricular mass index, microalbuminuria and silent cerebral infarcts, than blood pressure at other times of the day. Morning blood pressure may play an important role in the pathogenesis of hypertensive target organ damage. Increased sympathetic nerve activity is reported to be one of the mechanisms of morning hypertension; however, there are no available data that show whether strict home blood pressure control, especially in the morning period, can reduce target organ damage. The Japan Morning Surge-1 (JMS-1) study includes hypertensive outpatients with elevated morning systolic blood pressure (≥135 mmHg) as assessed by self-measured blood pressure monitoring at home. All enrolled patients are under stable antihypertensive medication status. Exclusion criteria are arrhythmia, chronic inflammatory disease, and taking α-blockers or β-blockers. The target number of patients to be enrolled in the JMS-1 study is 600, and the aim is to evaluate differences in the markers of hypertensive target organ damage, such as brain natriuretic peptide and the urinary albumin excretion/creatinine ratio. All of the patients are randomized to an experimental group or a control group, with randomization to be carried out by telephone interviews with the patients' physicians. In the experimental group, patients begin taking additional antihypertensive medication just before going to bed. This consists of doxazosin 1 mg/day, which then is increased to 2 mg/day and 4 mg/day, with a β-blocker added after a 1-month interval until the morning systolic blood pressure is controlled to less than 135 mmHg. Patients in the control group continue the treatment they are receiving at the enrollment for 6 months. Blood pressure levels, adverse effects, and hypertensive target organ damage before and after the study are evaluated. In the JMS-1 study, we will evaluate whether strict morning blood pressure control by sympathetic nervous system blockade using an α-blocker, doxazosin, and with the addition of a β-blocker if needed, can reduce hypertensive target organ damage. (*Hypertens Res* 2006; 29: 153–159)

***Key Words*: morning hypertension, multicenter randomized clinical trial, doxazosin, hypertensive target organ damage**

From the [1)]Division of Cardiovascular Medicine and [3)]Division of Community and Family Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan; [2)]Miwa Municipal Hospital, Yamaguchi, Japan; [4)]Chichibu Municipal Hospital, Chichibu, Japan; and [5)]Behavioral Cardiovascular Health and Hypertension Program, Columbia Presbyterian Medical Center, Columbia, USA.

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Address for Reprints: Kazuomi Kario, M.D., COE (Center of Excellence) Program, Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, 3311–1, Yakushiji, Shimotsuke 329–0498, Japan. E-mail: kkario@jichi.ac.jp

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Introduction

Morning blood pressure (BP) is reported to be related to hypertensive target organ damages such as left ventricular hypertrophy (*1*, *2*), microalbuminuria (*3*), silent cerebral infarcts (*4*) and carotid intima-media thickness (*5*). Sympathetic nerve hyperactivity is one of the mechanisms that leads to morning hypertension (*6*, *7*), and an α1-blocker, doxazosin, taken just before going to bed, is reported to decrease the BP level, especially in the morning period (*8*). However, there are no available data that show whether strict control of morning BP can reduce hypertensive target organ damage.

Morning BP is usually measured using ambulatory BP monitoring. Recently, self-measured BP at home has been widely evaluated in clinical settings. Morning BP in home BP is measured at rest and in a sitting position, whereas that in ambulatory BP is measured during varying physical activities and positional changes. There is little reported data about BP control based on home BP monitoring. Staessen *et al*. (*9*) reported that antihypertensive management based on home BP monitoring resulted in a higher 24-h BP level than that based on clinic BP. However, in Staessen's study, no allowance was made for the fact that home BP tends to be lower than clinic BP, and the same target level was used for both home and clinic BP.

A high morning BP can occur for two reasons: sustained nocturnal hypertension and exaggerated morning BP surge (*10*). We previously showed that a morning BP surge in ambulatory BP monitoring was associated with an increased risk for stroke events independently of the 24-h BP level (*4*). We consider that the ME difference—*i.e.*, the morning systolic BP (SBP) minus the evening SBP—measured by home BP monitoring may be a possible substitute for morning BP surge measured by ambulatory BP monitoring (*11*); however, there are no available data that show whether the ME difference in home BP monitoring is associated with hypertensive target organ damage and whether doxazosin, taken just before going to bed, reduces the ME difference of SBP in home BP monitoring and thus the hypertensive target organ damage.

As markers of hypertensive target organ damage, we chose brain natriuretic peptide (BNP) and the urinary albumin excretion/creatinine ratio (UAR). BNP is reported to be elevated in hypertensive patients with left ventricular hypertrophy (*12*) and diastolic dysfunction (*13*, *14*). Even in a general population, subjects with increased plasma BNP levels are reported to have higher risk for development of systolic and diastolic heart failure (*15*) and cardiovascular events (*16*).

An increase in the UAR is a predictor of development of hypertension (*17*), and insufficient control or hypertension is associated with a risk of deterioration of the UAR (*18*). The UAR is an early marker of atherosclerosis (*19*) and hypertensive target organ damage in the kidney (*20*, *21*), and patients with an even slightly elevated UAR are reported to be at

Table 1. Patients Selection of the JMS-1 Study

Positive selection criteria
1. Morning systolic blood pressure ≥135 mmHg
2. Stable antihypertensive medication status (>3 months)
Exclusion criteria
1. Arrhythmia
2. History of heart failure
3. Presence of orthostatic hypotension
4. Dementia
5. Presence of malignant disease
6. Chronic inflammatory disease
7. Taking α-blocker and/or β-blocker

JMS-1, Japan Morning Surge-1.

The purpose of the Japan Morning Surge-1 (JMS-1) study is to examine whether strict BP control by doxazosin using home BP monitoring, especially targeting the morning BP level, can reduce hypertensive target organ damage, as indicated by such factors as BNP and the UAR.

Methods

Selection of Patients (Table 1)

Positive Selection Criteria

In this study protocol, we select hypertensive outpatients who have uncontrolled morning SBP (≥135 mmHg). The patients must have been under stable antihypertensive medication status for 3 months. Morning BP is measured using self-measured BP monitoring at home according to the Japanese Society of Hypertension Guidelines for Management of Hypertension (*23*). BP values are written by the patients on a sheet of paper and reported to their own physicians. Morning SBP is the average of the first measurements of SBP for 3 days (3 points) in the 1-week period before visiting the physician's office.

Exclusion Criteria

We exclude patients who have arrhythmia, a history of heart failure, presence of orthostatic hypotension, dementia, presence of malignancy or chronic inflammatory disease, and those who are taking an α-blocker or β-blocker. In patients who have arrhythmias such as atrial fibrillation, there is a greater possibility of measuring BP incorrectly. Users of α-blockers and β-blockers are excluded from this study because an α-blocker and a β-blocker are included in the protocol. The absence of any history of heart failure with/without admission is confirmed by an interview of the patients by their physicians. Coronary arterial disease and/or peripheral vascular disease, diabetes mellitus, hyperlipidemia, and renal dysfunction are not in the exclusion criteria and the decision to enroll patients with these conditions is made by their physicians.

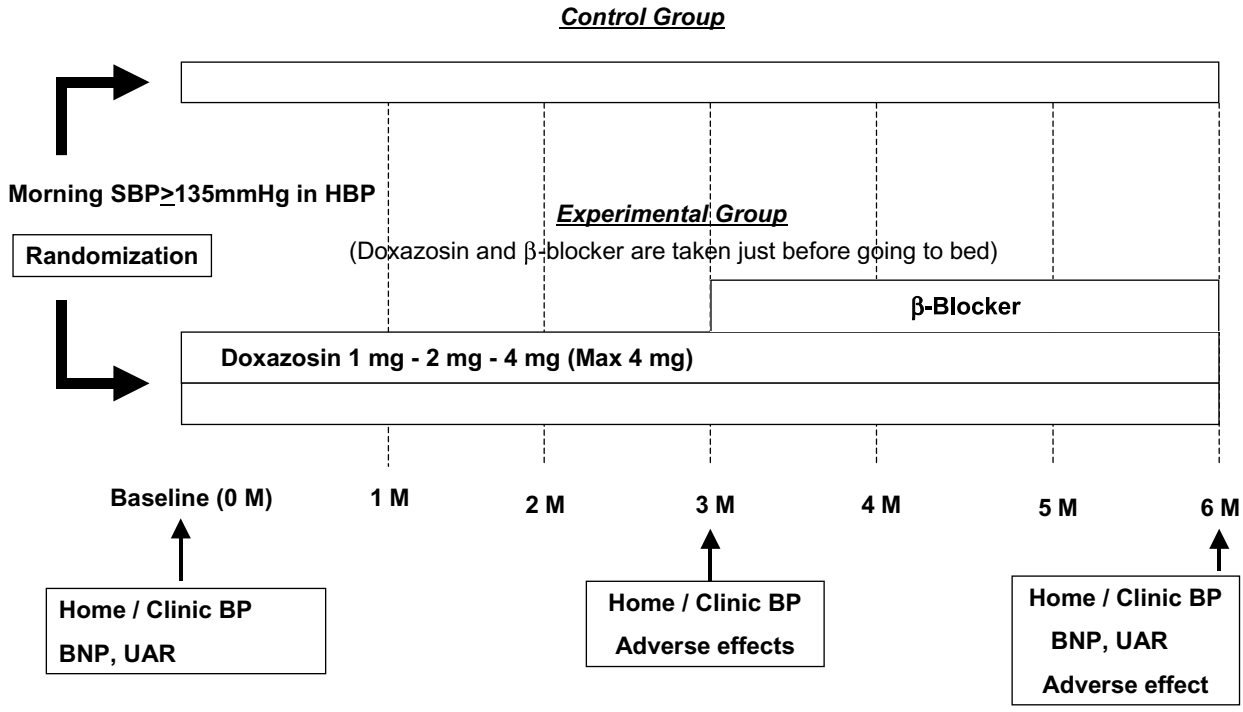

Fig. 1. *Outline of the design of the JMS-1 study. JMS-1, Japan Morning Surge-1; HBP, home blood pressure; BNP, brain natriuretic peptide; UAR, urinary albumin excretion/creatinine ratio; M, month.*

Randomization

Randomization is carried out by telephone interviews with the physicians at the time of the enrollment of patients. Physicians report only the study ID and morning BP level to the center, and patients are then assigned to the experimental group or control group. No stratifications of age or BP levels are considered in the randomization.

Treatment of Patients

Study Medication

Doxazosin 1 mg/day, taken just before bedtime, is added to the treatment regimen of patients in the experimental group (Fig. 1). All of these patients are then followed up at 1-month intervals, and the dose of doxazosin is increased to 2 mg/day and then 4 mg/day until the morning SBP becomes less than 135 mmHg. If the morning SBP is still more than 135 mmHg even after patients are taking doxazosin 4 mg/day, a β-blocker (atenolol 25 mg/day) is added just before bedtime. In institutes where atenolol is not available, other β-blockers that are taken once daily can be used. Patients in the control group continue the antihypertensive medication they were taking at enrollment for 6 months.

Measurements

Guidelines for Self-Measured BP at Home

All of the measurements of home BP must be conducted using a validated cuff oscillometric device, HEM-705IT (*24*) (Omron, Healthcare, Kyoto, Japan). BP measurements at home are performed according to the 2004 Japanese Society of Hypertension Guidelines for Management of Hypertension (*23*). Patients are instructed to place the cuff on the same arm throughout the measurements and to measure BP in a sitting position after more than 2 min of rest. BP measurements are repeated twice in the sitting position after a 30-s interval, and then performed twice in a standing position in the same way as in the sitting position. Patients write all of the results of BP and pulse rate measurements on a sheet of paper and report them to their own physicians. Morning BP is measured within 1 h after waking, after urination, and before breakfast and taking antihypertensive medication. Evening BP is measured before going to bed, and patients are instructed to avoid measuring evening BP just after taking a bath, drinking alcohol, or smoking.

Clinic BP

Clinic BP is measured at the office by a method similar to that used for self-measured BP at home.

Questionnaire

At enrollment, 3 months after the study begins, and at the end of the study, physicians ask their patients about the presence of dizziness, falls, syncope, and headache in the morning, and the frequency of awaking and going to the toilet during the night.

Biochemical Examination

Blood samples are drawn from the vein in the morning in a fasting state. Blood examination is performed at the enrollment and at the end of the study. We measure the levels of fasting glucose, serum insulin, hemoglobin A1c, and serum creatinine. BNP levels are measured using radioimmunoassays (Shionogi Inc., Ohsaka, Japan).

Urine Examination

Spot samples of urine are collected in the morning. We subject the samples to proteinuria and UAR measurement at the enrollment and at the end of the study. The urinary microalbumin level is measured using the immunoturbidimetric method (Mitsubishi Kagaku Iatron Inc., Tokyo, Japan). Urine creatinine is measured by Jaffe reaction without deproteinization and then quantified by a photometric method. The ratio of the urinary albumin level to the urinary creatinine level is calculated afterward as the UAR.

Electrocardiography

Electrocardiography is performed using validated machines at the individual institutes. Physicians report the presence of left ventricular hypertrophy as assessed by Sokolow-Lyon criteria (SV1+RV5≥35 mm and strain pattern).

Options

As substudies, we evaluate the brachial-ankle pulse wave velocity and carotid augmentation index (Form; Colin Medical Technology, Komaki, Japan).

Discontinuation of Randomized Treatment

Patients leaving the randomized part of the study are classified as withdrawals or defectors. The physicians report the reasons for stopping randomized treatment.

Withdrawals

Patients are classified as withdrawals when the primary physician concludes that they will be at risk if the study medication is continued. Possible reasons for withdrawal are adverse events, unexpected worsening of a patient's clinical condition, the necessity of administering drugs not allowed by the study protocol, uncontrolled hypertension, or orthostatic hypotension.

Uncontrolled hypertension is defined as a BP consisting of at least 200 mmHg SBP and 130 mmHg diastolic BP (DBP) according to office measurements. Orthostatic hypotension is defined as a drop in the SBP of at least 20 mmHg with dizziness or a fall from a standing position. The orthostatic change the difference between the BP measurements in the sitting and standing position.

Defectors

Patients who take the initiative to stop randomized treatment are classified as defectors. Patients can withdraw informed consent or request to stop the study for any reason. Patients who discontinue the randomized treatments because of symptoms or adverse events between visits are evaluated to fully document the nature of the event.

Definition and Documentation of Adverse Events

An adverse event is defined as any undesired or unexpected medical event that occurs in a patient during the study, even if there is no apparent relationship to the study medication, including intercurrent illness. Physicians document all adverse events on case report forms to the Coordinating Committee of the JMS-1 study. An independent Safety Committee reviews the reports and all adverse events are classified as serious or non-serious events. The definition of a serious adverse event is one that leads to death, is life-threatening, requires or prolongs hospitalization, causes persistent disability or discomfort, or necessitates an intervention to prevent any of the aforementioned outcomes. Non-serious adverse events are those that do not meet the criteria of serious adverse events.

Safety Considerations

The Coordinating Committee receives the reports on all adverse events. The investigators responsible for the study review the adverse events and monitor the safety of this study.

Statistical Methods

Analysis of data is performed with SPSS computer software (SPSS Inc., Chicago, USA).

Sample Size

In the sample size calculations, we assume an SD of BNP of 20 pg/ml and a dropout rate of 10%. A total of 500 patients, 250 in each arm, are required to detect in a two-sided test within each arm of the study a mean difference in BNP of 5 pg/ml between the experimental group and the control group with 80% power and 5% significance.

This sample size can also detect a mean difference in UAR of 10 mg/g Cr with an SD of 40 mg/g Cr between the 2 groups with 80% power and 5% significance.

Patient Population to Be Analyzed

The statistical analysis considers two groups of patients. The intention-to-treat analysis includes all patients who have at least one set of BP measurements available for each period of randomized treatment. In the case of missing data, the last observation is carried forward. For patients dropping out of

the study, the last measured BP is included in the analysis. The treatment-received analysis involves all patients who fulfill all eligibility criteria, do not take any drugs prohibited by the protocol, and undergo a complete evaluation at the end of each treatment period.

Analysis of Primary End Points

The primary end points consist of the changes in BNP levels and the UAR, and are tested by non-paired Student's *t*-test.

Analysis of BP

BP analysis is conducted using the average of 2 measurements for 3 days (6 points) in the sitting position. Differences of blood pressure between the experimental group and the control group are tested by the non-paired Student's *t*-test.

Ethics

The JMS-1 study complies with the ethical principals of and guidelines for good clinical practice outlined in the Helsinki Declaration. Each participating institute receives approval for the study from the institutional review board of the Jichi Medical University School of Medicine. Written informed consent is obtained from all enrolled patients.

Discussion

We have presented the protocol of the JMS-1 study, which is expected to clarify whether strict morning BP control by sympathetic nerve blockade using an α-blocker, doxazosin, and an additional β-blocker can reduce the morning BP level at home, and thereby reduce hypertensive target organ damage.

Morning BP *vs.* the Average of Morning and Evening BP

Morning BP tends to be higher than that at other times of the day (*11*). Morning BP may play an important role in the pathogenesis of hypertensive organ damage or cardiovascular events (*1*, *3*); however, most of the Western guidelines (*25*–*27*) recommend evaluating the home BP by taking the average of the morning and evening BP levels. On the other hand, the Japanese Society of Hypertension Guidelines for Management of Hypertension (*23*) recommends measuring home BP at least in the morning.

Morning BP includes the trough effect of once-daily antihypertensive medication (*28*) and can be a pitfall of current hypertension therapy (*10*). Therefore, morning BP has the possibility of remaining high (≥135 mmHg) even among hypertensive patients with well-controlled clinic BP (*29*) (masked morning hypertension). Masked hypertension (*30*) is reported to be associated with an increase in hypertensive target organ damage (*31*) and cardiovascular events (*32*). Control of BP at the time of maximal cardiovascular risk, especially in the morning, seems to be beneficial (*33*).

Ambulatory BP *vs.* Home BP to Evaluate Morning Hypertension

Studies comparing clinic and outpatient BP values have traditionally measured BP using ambulatory BP monitoring. Ambulatory BP is reported to be a stronger prognostic parameter for cardiovascular events than home BP (*34*), because it includes BP during sleep and physical activity. However, it is difficult to perform ambulatory BP monitoring for all patients (*35*). Self-measured BP at home has been widely evaluated in recent clinical studies. And although home BP–guided management of hypertension seems to be beneficial, there is little data to confirm this. Staessen (*9*) showed that there was an economic advantage in reducing the number of antihypertensive medications in a home BP–guided treatment group, although the clinic BP level was higher in the home BP–guided treatment group due to the white coat effect. In Staessen's report, the target home BP was the average of the morning and evening DBP. Thus the JMS-1 study may be the first to address whether specific BP control, especially in the morning using home BP monitoring, is beneficial for reducing hypertensive target organ damage.

Doxazosin *vs.* Other Antihypertensive Drugs

It has been reported that morning BP is affected by sympathetic nerve overactivity (*6*) and endothelial dysfunction (*36*) in the morning period, and α1-blockers have been reported to suppress morning sympathetic nerve activity and BP levels (*7*). Doxazosin, a long-acting α1-blocker, is reported to reduce BP in the morning more than at other times of the day when it is taken just before bedtime (*8*). Other long-acting antihypertensive drugs, such as angiotensin-converting enzyme inhibitors or calcium channel blockers, are also reported to be effective for controlling morning BP (*37*); however, these drugs lower BP throughout the day. We consider that doxazosin, taken just before bedtime, has a time-specific effect on BP, especially in the morning period.

Morning BP Surge and Home BP Monitoring

A high morning BP can occur for two reasons: sustained nocturnal hypertension and exaggerated morning BP surge (*10*). Some epidemiologic data have shown that nocturnal hypertension and non–dipper-type BP variability are associated with increased risk of cardiovascular events (*38*) and hypertensive target organ damage (*39*). Recently, we reported that morning SBP surge is an independent risk factor for cerebral infarction (*4*) in older hypertensives. Morning SBP surge is usually detected by ambulatory BP monitoring, and the ME difference as measured by home BP monitoring is a possible substitute for morning SBP surge (*11*). We also aim to clarify whether the ME difference in home BP monitoring can be a marker of target organ damage and whether improvement of the ME difference can ameliorate hypertensive target damage.

Conclusion

In the JMS-1 study, we will evaluate whether strict morning BP control by an α-blocker, doxazosin, and an additional β-blocker can reduce hypertensive target organ damage.

Appendix

Participants and Participating Centers

Shizukiyo Ishikawa, Jichi Medical University School of Medicine; Kazuo Eguchi, Jichi Medical University School of Medicine, Shioya General Hospital and Sano Municipal Hospital; Toru Hashimoto, Jichi Medical University School of Medicine; Masato Morinari, Jichi Medical University School of Medicine; Satoshi Hoshide, Jichi Medical University School of Medicine and Oyama Municipal Hospital; Yoko Hoshide, Sato Clinic; Motoyuki Ishiguro, Ishiguro Clinic; Toshio Nakayama, Nakayama Clinic; Hideo Hirose, Kosaka-cho Clinic; Naoshi Yamada, Yamada Brain Surgery Clinic; Akio Yoshimura and Makoto Yamashita, Mishima Clinic; Masanori Harada and Hitoshi Nishimura, Nishiki Central Hospital; Ruri Kaneda, Josai Hospital; Yoshio Matsui and Seiichi Shibasaki, Miwa Municipal Hospital; Mitsunobu Murata, Koga Red Cross Hospital; Joji Ishikawa, Koga Red Cross Hospital and Sano Municipal Hospital; and Yasuyuki Mizumori, Ieshima Clinic and Uzuka Clinic (total 20 physicians and 16 institutes).

Coordinating Committee: Yumiko Yoshida, Tsutomu Sudo, and Kazuo Okuhara: Biomedis.

Safety Committee: Yoshiaki Murakami, Yukihiro Hojo, Keiji Yamamoto, Takeshi Mitsuhashi, Takaaki Katsuki: Division of Cardiovascular Medicine, Jichi Medical University School of Medicine.

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