Original Article

The MUSCAT Study: A Multicenter PROBE Study Comparing the Effects of Angiotensin II Type-1 Receptor Blockers on Self-Monitored Home Blood Pressure in Patients with Morning Hypertension: Study Design and Background Characteristics

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Elevated morning home blood pressure (MHBP) has been reported to have a close relationship to cerebro-cardiovascular events and hypertensive target organ damages, and hence is regarded as a predictor of cardiovascular events. However, there is no evidence that lowering of MHBP can improve morbidity, mortality or target organ damage. In recent guidelines, angiotensin II type-1 receptor blockers (ARBs) are recommended as the first-choice drugs for antihypertensive therapy. Pharmacological characteristics differ among ARBs, and some are suggested to have greater efficacy in lowering MHBP than others. In preparation for the MUSCAT study, we surveyed both self-monitored MHBP and office blood pressure (OBP) in 1,234 patients with essential hypertension. Among them, 367 patients had diabetes mellitus (DM) and 229 suffered from chronic kidney disease (CKD). More than 64% ($n=790$) of patients had morning hypertension. In MUSCAT, we will investigate the different effects of four ARBs (losartan, candesartan, valsartan, and telmisartan) in patients with morning hypertension, with a focus on the drugs' MHBP-lowering efficiency. Secondly, we will evaluate the different actions of the four ARBs on cardiovascular surrogate markers, such as the brachial-ankle pulse wave velocity, high-sensitive C-reactive protein level, and urinary albumin excretion/creatinine ratio. Patients will be randomized into four arms, and given one of the four "sartans" once daily for 12 months. MHBPs and surrogate markers will be examined at baseline and after 1 year of follow-up. In the stratified analysis, we will determine the significance of MHBP reduction on cardiovascular risk management. (*Hypertens Res* 2008; 31: 51–58)

Key Words: telmisartan, candesartan, valsartan, losartan, microalbuminuria

Introduction

Hypertension is one of the major risk factors of cardiovascular disease (*1, 2*). Treatment of hypertension reduces morbidity and mortality, preserves organ function and prevents cardiovascular complications. Based on many evidences, some guidelines recommend that blood pressure (BP) should be suppressed to below target levels, which depend on risk factors and complications (*3–6*). It has been shown that early-morning hypertension has a close relation to cerebrocardiovascular events (*7, 8*). Also, it has been reported that morning

Table 1. Outpatient Background

	NT (*n*=244)	WHT (*n*=200)	MHT (*n*=306)	CHT (*n*=484)	*p* value
Age (years)	63	65	68*	67*	<0.001
Sex (male/female)	110/134	75/125	132/174	233/251	n.s.
OBP (mmHg)	126/75	152/83	129/74	155/84	
MHBP (mmHg)	125/77	127/77	149/84	153/84	
BMI (kg/m^2)	24.1	24.3	24.1	24.5	n.s.
Smoking (%)	19	16	18	18	n.s.
Dyslipidemia (%)	49	50	47	43	n.s.
Diabetes (%)	29	22	35*	30	<0.05
IHD (%)	9	9	10	10	n.s.
Stroke (%)	6	9	10	10	n.s.
CKD (%)	18	12	21*	20*	<0.05
Hyper uricemia (%)	12	9	13	14	n.s.
Habitual drinking (%)	27	20	27	28	n.s.

NT, normotensive; WHT, white-coated hypertensive; MHT, masked hypertensive; CHT, continuous hypertensive; OBP, office blood pressure, MHBP, morning home blood pressure; BMI, body mass index; IHD, ischemic heart disease; CKD, chronic kidney disease. *p* value are analyzed using 1-way ANOVA.

home blood pressure (MHBP) is related to organ dysfunctions such as left ventricular hypertrophy (*9*), microalbuminuria (*10*), silent cerebral infarcts (*11*) and carotid intima-media thickness (*12*). In addition, masked hypertension has been shown to be associated with hypertensive target organ damages (*13*, *14*), and is regarded as a predictor of cardiovascular events (*15*, *16*). Thus, the importance of MHBP has increased in clinical practice, although there is no actual evidence that lowering MHBP to ideal levels can improve morbidity, mortality or target organ damage.

Morning BP can be measured either using an ambulatory BP monitoring (ABPM) device or by self-monitoring with a manometer. ABPM has been used to evaluate morning BP, but it has been reported that the reproducibility of ambulatory BP measurement is poor and that the evaluation of the efficacy and duration of antihypertensive drugs on the basis of ABPM is affected by several effects, including the placebo effect (*17*, *18*). Because of both the development of devices for home BP measurement and the establishment of practical guidelines, self-measured BP has recently been used in clinical settings (*19*).

Angiotensin II type-1 receptor blockers (ARBs) are recommended as the first-choice agents for antihypertensive therapy in the guidelines mentioned above. However, it has been suggested that the efficacy and duration of action differ among ARBs. For example, we previously reported that the antihypertensive effect of telmisartan is stronger and longer than that of losartan, and sufficient to decrease MHBP based on self-monitored MHBP measurements (*20*). Other authors observed different durations of action and different efficacies among four ARBs examined herein (*21*). Further, some studies have shown differences in antihypertensive effect among ARBs using ABPM (*22–24*). However, these studies have all
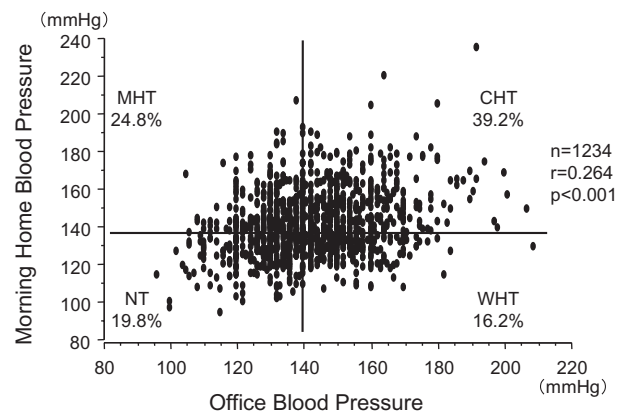

Fig. 1. *The distribution of systolic blood pressure (SBP) in the 1,234 patients with hypertension. There was a significant but weak relationship between office SBP and morning home SBP. NT, normotensive; WHT, white-coat hypertensive; MHT, masked hypertensive; CHT, continuous hypertensive. p values were analyzed by a single regression analysis.*

been relatively short, with durations of about 1 month or, in the case of our own previous study, no more than 3 months.

Therefore, in this Multicenter PROBE Study Comparing the Effects of Angiotensin II Type-1 Receptor Blockers on Self-Monitored Home Blood Pressure in Patients with Morning Hypertension (MUSCAT study), we aim to evaluate the long-term efficacy and duration of action on MHBP of four ARBs in patients with morning hypertension. In addition, we will examine whether lowering MHBP can ameliorate the independent risk factors for cardiovascular morbidity and mortality.

Table 2. Inclusion and Exclusion Criteria for MUSCAT Study

Inclusion criteria

   1. Outpatients who are/were diagnosed with hypertension

   2. Aged over 20 years old and less than 85 years old

   3. Morning home systolic blood pressure measured by themselves show ≥135 mmHg

Exclusion criteria

   1. Outpatients who have an allergy against ARBs

   2. Pregnancy

   3. Obstructive biliary disease or whose T.Bil ≥1.5 mg/dL

   4. Liver cirrhosis or whose either AST or ALT ≥100 IU

   5. Who are on hemodialysis or whose serum Cr ≥2.0 mg/dL or whose serum potassium level is ≥5.6 mEq/L

   6. Who are considered as unsuitable for this study by their physicians

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MUSCAT: Multicenter PROBE Study Comparing of the Effects of Angiotensin II Type-1 Receptor Blockers on Self-Monitored Home Blood Pressure in Patients with Morning Hypertension. ARB, angiotensin II type-1 receptor blocker; T.Bil, total bilirubin; AST, aspartate amino-transferase; ALT, alanine amino-transferase; Cr, creatinine.

Methods

Patient Background Investigation

To enroll patients in preparation for the MUSCAT study, we investigated the management of office blood pressure (OBP) and MHBP in 1,234 outpatients who were diagnosed with hypertension around Okayama in the western part of Japan between July 1, 2004 and June 30, 2005 (Table 1). All patients were between 20 and 85 years of age. MHBP was measured using an electronic manometer at home as described by the Japanese Society of Hypertension guidelines for self-monitoring of blood pressure at home (*19*). The average value taken on at least three consecutive days before visiting the physician's office was considered as the patient's MHBP. Informed consent was obtained from all participants.

In Table 1, we divided all patients into four categories: 1) continuous hypertensives, who had uncontrolled systolic OBP (OSBP; ≥140 mmHg) and uncontrolled systolic MHBP (MHSBP; ≥135 mmHg); 2) masked hypertensives, who had controlled OSBP (<140 mmHg) and uncontrolled MHSBP; 3) white-coat hypertensives, who had uncontrolled OSBP and controlled MHSBP (<135 mmHg); and 4) normotensives, who had both controlled OSBP and controlled MHSBP.

There were 790 subjects with morning hypertension. For each of these subjects, we examined the following cardiovascular risk factors by reference to their medical charts: body mass index (BMI), smoking, dyslipidemia, diabetes, ischemic heart disease (IHD), stroke, chronic kidney disease (CKD), hyperuricemia, habitual drinking, and number of antihypertensive drugs taken. CKD was defined in terms of NHANES III (*25*) as follows. 1) Structural or functional abnormalities, defined as abnormal findings on histological examination, urinalysis, biochemical examination, or imaging studies for a duration of 3 months or longer regardless of glomerular filtration rate (GFR). 2) GFR <60 mL/min/1.73 m^2 regardless of

the primary disease based on the Cockcroft-Gault equation. The results are shown in Table 1 and Fig. 1.

Patient Recruitment into MUSCAT

Among the 1,234 patients who participated in the above-described background investigation, we enrolled hypertensive outpatients who had uncontrolled MHSBP regardless of OSBP. The inclusion and exclusion criteria are shown in Table 2.

Study Design

The MUSCAT study is an investigator-initiated, multicenter study with a prospective, randomized, open-label, blinded endpoint evaluation (PROBE) design (*26*). The primary aim of the MUSCAT study is to compare the antihypertensive efficacy of four ARBs on MHBP in patients with morning hypertension. A secondary goal is to compare the beneficial effects of the four ARBs on several cardiovascular surrogate markers. Finally, we aim to determine the influence of morning-BP reduction on the surrogate markers listed in Table 3.

Study Medications

Figure 2 outlines the design of the MUSCAT study. Patients will be administered one of four ARBs once daily after breakfast for a year. Randomization will be accomplished by the envelop method—*i.e.*, each physician will randomly choose an envelop that assigns the patient to one of four drug–administration arms (losartan 50 mg, candesartan 8 mg, valsartan 80 mg, or telmisartan 40 mg). As a rule, the dosages of ARB will be fixed during the enrollment. However, physicians will be allowed to change the regimens of other antihypertensive drugs as needed to maintain OBP at the following levels: less than 140/90 mmHg in elderly patients (>65 years old), less than 130/85 mmHg in young and middle-aged patients, and

Table 3. Primary and Secondary Endpoints

1. Primary endpoints
   1) Decrease of morning home systolic blood pressure
   2) The number of patients who have < 135 mmHg in morning home systolic blood pressure after 1 year treatment
2. Secondary endpoints
   1) Decrease of morning home diastolic blood pressure
   2) Decrease of office systolic and diastolic blood pressure
   3) Improvement of practical parameters; baPWV, UAR, hsCRP

baPWV, brachial-ankle pulse wave velocity; UAR, urinary albumin excretion/creatinine ratio; hsCRP, high sensitive C-reactive protein.
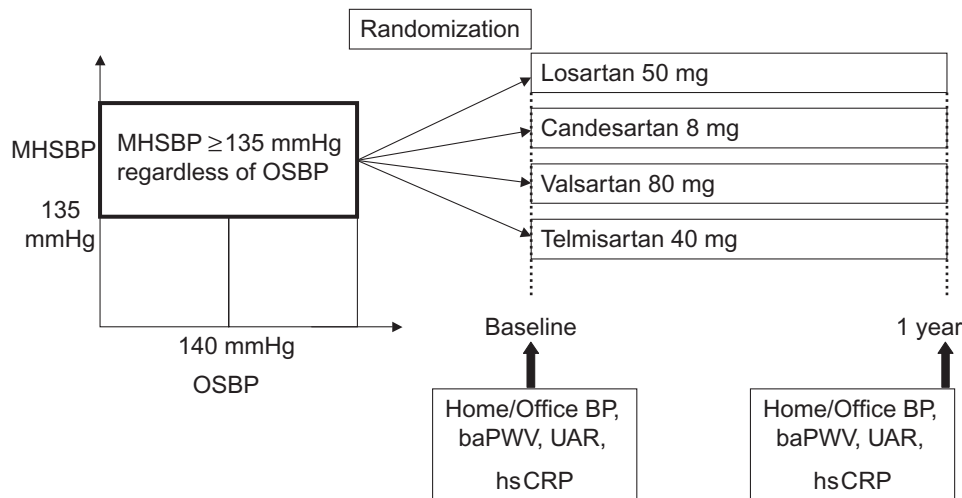

Fig. 2. *Outline of the design of the MUSCAT study, a Multicenter PROBE Study Comparing the Effects of Angiotensin II Type-1 Receptor Blockers on Self-Monitored Home Blood Pressure in Patients with Morning Hypertension. Details are described in the Methods section. Note that there is no wash-out period. MHSBP, morning home systolic blood pressure; OSBP, office systolic blood pressure; baPWV, brachial-ankle pulse wave velocity; UAR, urinary albumin excretion/creatinine ratio; hsCRP, high sensitive C-reactive protein.*

less than 130/80 mmHg in patients with diabetes or renal disease. The physician will be required to report any such changes. Patients already receiving ARBs will discontinue them, and start with the selected ARB without a wash-out period.

BP Measurement

All measurements of MHBP will be conducted using an HEM-747-IC electronic manometer (Omron Colin Co., Ltd., Tokyo, Japan) according to the Japanese Society of Hypertension guidelines for self-monitoring of blood pressure at home (*19*). All patients will measure their MHBP by themselves once daily within 1 h after waking up, after urination, before breakfast, before administration of antihypertensive drugs and after 1 to 2 min of rest in a sitting position. Patients will record their BP results and report them to their own physicians. Monthly MHBP will be determined as the average of all measurements before the next examination. Patients will

be asked to visit the doctor's office between 9:00 and 11:00 AM every month, where conventional OBP will be measured after a 5-min rest in a sitting position.

Parameters Evaluated

We examined the following parameters at enrollment and will examine them again at the end of 1 year of follow-up: brachial-ankle pulse wave velocity (baPWV), urinary albumin excretion/creatinine ratio (UAR), high sensitive C-reactive protein level (hsCRP), ECG, cardiopulmonary ratio (CTR), and the levels of serum creatinine (Cr), serum uric acid (UA), hemoglobin A1c (HbA1c), serum total cholesterol, serum low density lipoprotein cholesterol, high density lipoprotein cholesterol, and serum triglycerides.

baPWV will be measured after 5 min of rest in a supine position, using Form ABI/PWV (Omron Colin Co., Ltd.). UAR will be measured with latex agglutination using spot urine samples (SRL Inc., Tokyo, Japan). hsCRP will be
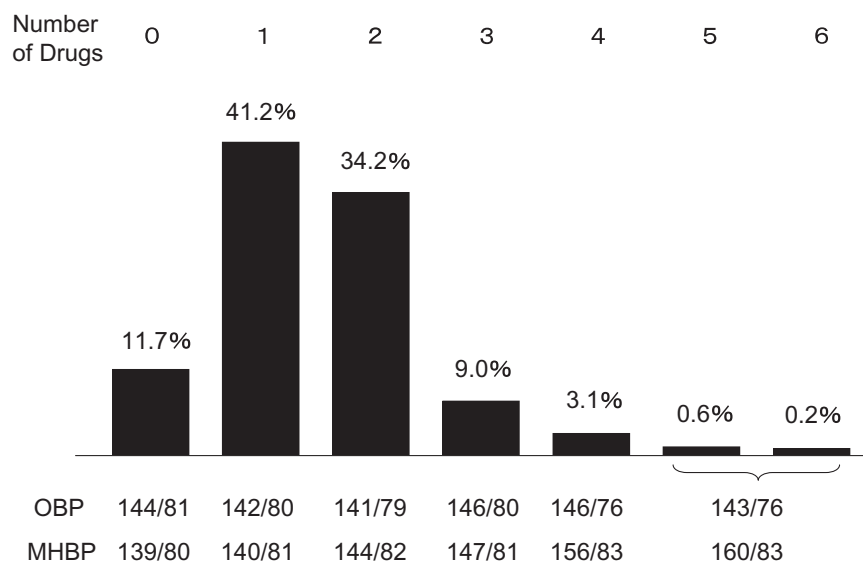
Number of Drugs	0	1	2	3	4	5	6
	11.7%	41.2%	34.2%	9.0%	3.1%	0.6%	0.2%
OBP	144/81	142/80	141/79	146/80	146/76	143/76	
MHBP	139/80	140/81	144/82	147/81	156/83	160/83	

Fig. 3. *The number of antihypertensive drugs used. OBP and MHBP values are the average of blood pressure (mmHg) in each category. OBP, office blood pressure; MHBP, morning home blood pressure.*

assessed with a validated high-sensitivity assay, particle-enhanced immunonephelometry using the BN Systems (SRL Inc.). ECG will be performed using validated machines at the individual institutes. We will calculate SV1+RV5 as an index of left ventricular hypertrophy. The CTR will be calculated from X-ray film.

Adverse Effects and Safety Considerations

All patients will be questioned about adverse events or symptoms at each visit. If serious adverse effects occur, even if there is no apparent relationship to the study medication, physicians will be required to discontinue the study drug. Both serious and non-serious adverse effects must be reported to the steering office, and the Safety Committee will review the data.

The Safety Committee, the members of which will not be involved in the administration of the trial, will monitor all endpoints and medically serious and non-serious adverse events, and will inform the steering office if there is a recommendation to discontinue the trial. All four ARBs employed in the MUSCAT study have been approved by the Japanese Ministry of Health, Labour and Welfare for more than 1 year, and thus the trial will be covered under Adverse Health Effect Relief Services Pharmaceuticals and Medical Devices Agency (PMDA; http://www.pmda.go.jp/english/index.html) in the event of serious events requiring hospital admission.

Ethics

The study protocol has been approved by the Okayama Uni-versity Institutional Review Board (accredited ISO9001/ 2000) and by local ethic committees at the respective institutes where available. It is undertaken in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies in Japan. All patients enrolled in the MUSCAT study will provide fully informed written consent.

Statistical Methods

Sample-Size Determination
In the sample-size calculations, according to our previous study (*20*), we assume an SD of the decrease of MHBP of 22.5 mmHg. Each group will need to consist of 67 patients in order to detect a mean difference in MHBP of 15.6 mmHg in a two-sided test between at least two ARB groups of the study with 80% power and 5% significance. Assuming that the dropout rate is 10%, a total of 74 patients will thus be required in each arm.

Statistical Analysis
The intention-to-treat analysis will include all patients for whom at least one set of BP measurements is available. In the case of missing data, the last observation after 8 months of treatment will be carried forward. For patients dropping out of the study, the last BP will be included in the analysis. BP analysis will be conducted using the 1-month average BP measurements. Differences among the four groups will be evaluated by one-way ANOVA. Changes between before enrollment and after treatment in a group will be analyzed using Student's paired *t*-test or Wilcoxon's rank test, where appropriate.

Discussion

We have described the protocol of the MUSCAT study. This study is expected to reveal the different abilities of four ARBs to lower MHBP (losartan 50 mg, candesartan 8 mg, valsartan 80 mg and telmisartan 40 mg). The dosages of each ARB are regarded as equivalent to amlodipine 5 mg in terms of OBP-suppression efficiency by the Japanese Ministry of Health, Labour and Welfare based on phase II studies performed in Japan. In general, the maximal BP-reducing effect of ARBs occurs a few months after starting treatment. In this sense, because we will examine OBP and MHBP throughout the course of 1 year, we hope to clarify the true BP-lowering effect of ARBs in a clinical setting. In addition, this study will monitor the time course of BP control, especially MHBP control, using ARBs.

It has been suggested that both morning and evening BP should be measured to evaluate the morning minus evening systolic BP difference (ME difference). The ME difference has been shown to be an independent predictor of stroke and silent cerebral infarcts (*11*). In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure Guidelines (*5*), the self-measured BP level was determined as the average of all BPs measured in the morning and evening. However, the Ohasama study showed that morning BP measured by self-measured BP monitoring was an independent predictor of future stroke and mortality (*27*, *28*). Thus, the best method for evaluating self-measured BP remains uncertain, although MHBP is clearly important in all methods. In terms of compliance, one measurement of BP seems to be easier for patients compared to more than two measurements. In addition, it is suggested that multiple home BP measurements have the strongest predictive power for stroke risk in the Japanese population (*29*). Therefore, in this study, we will examine MHBP once daily.

Two clinical studies have demonstrated that baPWV is an acceptable marker of vascular damages (*30*, *31*). baPWV is increased according to the severity of hypertension in all age groups (*32*). Left ventricular hypertrophy is associated with hypertension, increased baPWV, and the extent of vascular calcification in hemodialysis patients (*33*). ARBs can improve baPWV (*20*, *34*, *35*), and the effects of ARBs on baPWV are greater than the effects of calcium channel blockers (*36*). However, we previously suggested that losartan and telmisartan may have different abilities to lower baPWV (*20*). In the MUSCAT study, therefore, we will also compare the baPWV-lowering abilities of the four ARBs.

A number of large, prospective epidemiologic studies have indicated that hsCRP is a strong independent predictor of future cardiovascular events, including myocardial infarction, ischemic stroke, peripheral vascular disease, and sudden cardiac death among individuals without known CVD (*37*, *38*). Recent epidemiological evidence has indicated a link between hypertension and increased C-reactive protein levels, and there are some indications that C-reactive protein may predict the future development of hypertension (*39*). It has been reported that some kinds of ARBs markedly reduce serum levels of CRP (*40*). However, there has been no report on the relationship between MHBP reduction and hsCRP reduction. In the MUSCAT, therefore, we will also examine the different effects of the four ARBs on MHBP and hsCRP.

UAR has been established as a major target organ damage of hypertension (*3–6*). An increase in the UAR is a predictor of development of hypertension (*41*), atherosclerosis (*42*), coronary heart disease (CHD) or death (*43*, *44*), and an early marker of both diabetic and nondiabetic renal diseases (*45*). In this study, we aim to investigate the relationship between UAR and the reduction of MHBP.

Our preliminary work for the MUSCAT constitutes the first investigation of the distribution of hypertensives in western Japan. Our results show that more than 50% of patients with hypertension in western Japan are still uncontrolled with respect to OBP (Fig. 1). Furthermore, 64% of treated patients are categorized with morning hypertension. This finding is consistent with previous reports in eastern Japan (*46*), suggesting that our patients are representative of the distribution over Japan as a whole.

In terms of the patient characteristics, one-third of the patients with morning hypertension have diabetes (Table 1). It has been reported that patients with diabetes have higher MHBP (*10*). In the Japanese population, morning hypertensives with diabetes tend to have complications and organ damage (*10*, *47*). Our survey is consistent with these reports. By our definition of CKD, one-fifth of the morning hypertensives enrolled in this study have CKD. This finding suggests that there may be more hypertensives with CKD than previously reported (*46*).

We counted the number of antihypertensive drugs prescribed to each patient in addition to the engaged ARB (Fig. 3). Seventy-five percent of participants were using one or two additional antihypertensive drugs. The control of the average OSBP was the same irrespective of the number of drugs, but the average MHSBP increased with increasing number of drugs used. This suggests that it is very difficult to control BP all day long.

In conclusion, in the MUSCAT trial, we will evaluate the BP-lowering efficacy and duration action of four ARBs (losartan, candesartan, valsartan, and telmisartan) and their effects on cardiovascular risk factors. This study will also clarify the significance of ARB-induced MHBP reduction for the management of cardiovascular risk factors.

(Kawasaki Medical School, Division of Nephrology; Dr. Tomita is a Fellow of the Japan Society of Hypertension). We would also like to thank Professor Alan Daugherty (University of Kentucky, Cardiovascular Research Center) for his careful reading of this manuscript and helpful comments.

Appendix

Participants and Participating Centers

Katsue Sunahori, Ibara Central Hospital; Kiichi Komoto, Hiroo Hashimoto, Shinji Fukuda, Innoshima General Hospital; Yoshio Kikuchi, Fumio Kondo, Uwa Municipal Hospital; Hideyuki Okamoto, Okamoto Naika Clinic; Masashi Muguruma, Okayama Kinen Hospital; Yasushi Yamasaki, Jun Wada, Hitomi Kataoka-Usui, Kosuke Yozai, Sakiko Sasaki-Ohga, Okamaya University Hospital; Takashi Ogasa, Ogasa Naika Clinic; Yasuaki Mino, Yasushi Takahashi, Chikage Sato, Ochiai Hospital; Kazuyuki Fujino, Masami Hashimoto, Onomichi Shimin Hospital; Takanobu Nakashima, Kato & Namiki-dori Hospital; Akiko Ueno, Koji Takasugi, Kurashiki Kosai Hospital; Yoshio Nanba, Konko Hospital; Eriko Katayama, Hiromichi Fujiwara, Sato Hospital; Hisanao Norii, Sayo Central Hospital; Yuko Okazaki, Jonan Clinic; Taro Sugimoto, Sugimoto Clinic; Takashi Nakamura, Tomoko Michiue-Tsukinoki, Hiroyuki Kitayama, Yuuki Takazawa, Takahashi Central Hospital; Keita Ishii, Chugoku Central Hospital; Kazuharu Murakami, Tamashima Central Hospital; Yoshikazu Hayashi, Tsujii Hayashi Naika Clinic; Ryo Nagase, Tsuyama Central Hospital; Masaya Takeda, Nihonbara Hospital; Kazushi Harada, Harada Naika Clinic; Mitsuhiro Iwahashi, Jiro Yamana, Higashi-hiroshima Memorial Hospital; Tomoko Miyoshi, Himeji Daiichi Hospital; Tetsuya Fukuda, Hidetoshi Kagawa, Himeji Red Cross Hospital; Hajime Sato, Motofumi Sasaki, Himeji Central Hospital; Shuzo Hirakawa, Hirakawa Naika Clinic; Chiharu Okada, Atsuko Ashiba, Akira Okamoto, Minami-Okayama Medical Center; Sho Yunoki, Kenji Soda, Miwa Memorial Hospital.

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