Original Article

The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS): Protocol, Patient Characteristics, and Blood Pressure during the First 12 Months

JATOS Study Group*

The benefits of a systolic blood pressure (BP) below 150–160 mmHg are well established; whether a systolic BP of less than 140 mmHg provides additional benefits remains controversial. This study was designed to compare the 2-year effect of a strict treatment to maintain systolic BP below 140 mmHg (group A) and that of a mild treatment to maintain systolic BP at between 140 and below 160 mmHg (group B). The study design followed the Prospective Randomized Open Blinded End-point (PROBE) study. The subjects were elderly patients (65–85 years old) who consistently had a systolic BP of 160 mmHg or higher. The baseline drug was efonidipine hydrochloride (efonidipine), a long-acting dihydropiridine calcium antagonist. The primary endpoints were stroke, cardiac disease, vascular disease, and renal failure. After a run-in period of 2 to 4 weeks, 2,165 patients were assigned to group A and 2,155 patients to group B. There were no significant differences between the groups in sex, age, baseline BP, or other cardiovascular risk factors. The systolic BP was 7.2 mmHg lower ($p<0.0001$) and the diastolic BP 2.4 mmHg lower ($p<0.0001$) in group A than in group B after 12 months of treatment. As of this interim analysis, primary endpoints have occurred in 87 patients (stroke in 58 patients, cardiac disease in 27 patients, occlusive arterial disease in 1 patient, and renal failure in 1 patient). Five patients have died of stroke and 2 patients of myocardial infarction. The primary-endpoint-related morbidity rate was 20.9/1,000 patient-years, and the mortality rate was 1.7/1,000 patient-years. Currently available results indicate that this study, one of the largest randomized trials of antihypertensive therapy in elderly patients in Japan, was conducted safely. The final results are expected to provide important and practical information for the management of hypertension in elderly patients. (*Hypertens Res* 2005; 28: 513–520)

***Key Words*: essential hypertension, systolic blood pressure, calcium antagonists, efonidipine hydrochloride**

Introduction

The rapid growth of the elderly population in industrialized countries has led to an increased incidence of hypertension and hypertension-related cardiovascular diseases (*1*, *2*). The management of hypertension in the elderly has therefore assumed new importance. Systolic blood pressure (SBP) increases steadily with age, whereas diastolic blood pressure (DBP) increases until 55 years and then declines (*3*). In the National Health and Nutritional Examination Survey (NHANES) study, isolated systolic hypertension was present in 65% of all hypertensive patients older than 60 years (*1*). SBP is a more important predictor of target organ damage than DBP in the elderly (*4*).

Recent guidelines for the management of hypertension rec-

*The details of the JATOS study group are shown in the Appendix.

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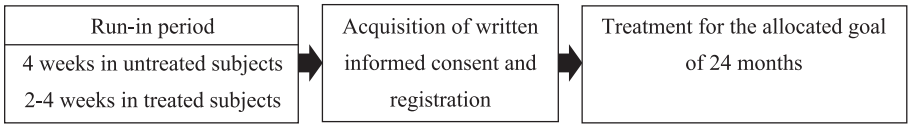

Fig. 1. *Flow-chart of the study.*

ommend a similar target blood pressure (BP) for young, middle-aged, and elderly patients, *i.e.*, BP should be maintained below 140/90 mmHg, or at much lower levels in patients at increased risk because of concurrent diseases such as diabetes mellitus or renal disease (*5*–*7*). Although the benefits of maintaining SBP below 150–160 mmHg have been confirmed by placebo-controlled trials (*8*, *9*), the additional benefits of lowering the SBP to below 140 mmHg remain controversial (*10*, *11*). Furthermore, the relation of the BP level to morbidity and mortality was unclear in the Hypertension Optimal Treatment (HOT) trial, which assessed the optimal target BP by randomly assigning a large number of elderly hypertensive patients to treatments targeting a DBP of ≤90 mmHg, ≤85 mmHg, or ≤80 mmHg and treating them with felodipine as a baseline drug for 3.8 years (*12*). An epidemiological study suggested that critical SBP levels associated with an abrupt increase in mortality in elderly persons were higher than the SBP levels defining hypertension in conventional guidelines (*13*). The hypertension management guidelines issued by the Japanese Society of Hypertension emphasize that BP should be reduced very slowly and carefully in elderly patients, because aggressive antihypertensive treatment may accelerate target organ damage (*14*). Thus, the optimal antihypertensive treatment for elderly hypertensive patients remains a matter of debate.

We organized the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) to investigate how far SBP should be lowered in hypertensive patients.

Methods

Purpose

The main objective of JATOS was to compare the 2-year effect of a strict treatment to maintain SBP below 140 mmHg (group A) with that of a mild treatment to maintain SBP at between 140 and below 160 mmHg (group B) in elderly patients with persistent elevation of SBP. The study design followed that described for the Prospective Randomized Open Blinded End-point (PROBE) study (*15*). The baseline drug was efonidipine hydrochloride (efonidipine), a long-acting dihydropiridine calcium antagonist (*16*, *17*).

Subjects

The subjects were male or female outpatients, 65 to 85 years of age, with essential hypertension who consistently had a SBP of 160 mmHg or higher during the run-in period. The patients were untreated or had received the same drug(s) for at least 4 weeks. Treated subjects were eligible if efonidipine could be added or substituted for one of the drugs given before study entry.

Patients were excluded if they had been receiving efonidipine or had any of the following conditions: a DBP of 120 mmHg or above, secondary hypertension, recent stroke (less than 6 months previously) or signs and symptoms of stroke, a recent myocardial infarction or coronary angioplasty (less than 6 months previously), angina pectoris requiring hospitalization, congestive heart failure of NYHA class II or higher, persistent arrhythmias such as atrial fibrillation, dissecting aneurysm of the aorta or occlusive arterial disease, hypertensive retinopathy, serum aspartate aminotransferase or serum alanine aminotransferase levels more than double the respective upper limits of normal, poorly controlled diabetes mellitus (fasting blood sugar of 200 mg/dl or higher or HbA1c of 8% or higher), renal dysfunction (serum creatinine of 1.5 mg/dl or higher), or malignant disease or collagen disease. Patients considered unsuitable as subjects were also excluded.

During a run-in period (4 weeks in untreated subjects and 2–4 weeks in treated subjects), the subjects were examined at least twice and BP was measured at least twice per visit, using a sphygmomanometer with the patient in a sitting position after 5–10 min of rest. The averaged BP was calculated for each visit. The pulse rate was also measured. All eligible patients consistently had a SBP of 160 mmHg or higher during the run-in period. Chest X-ray films and ECG were obtained, and routine laboratory examinations, including urinalysis, hematological examinations, and serum chemical analysis, were also performed during the run-in period.

Randomization

Written informed consent was obtained from eligible patients after they had been given a thorough explanation of the purpose, methods, and implications of the study. The doctors in charge then sent a registration form describing the subjects' characteristics and their risk factors, such as diabetes mellitus or history of cardiovascular disease, to the registration office by facsimile. Histories of previous diseases such as stroke, cardiac disease, and renal disease were carefully taken. Left ventricular hypertrophy was assessed on chest X-ray films, ECG, or echocardiography. Diabetes mellitus was diagnosed according to the guidelines of the Japan Diabetes Society

Table 1. Baseline Characteristics

	Group A (SBP<140 mmHg)	Group B (140≤SBP<160 mmHg)
n	2,165	2,155
Male/female	863/1,302	823/1,332
Age (years)	73.5±5.3	73.7±5.2
Body mass index (kg/m^2)	23.6±3.4	23.6±3.5
Prior treatment (%)	55.3	57.2
SBP/DBP (mmHg)	171.6±9.7/89.1±9.7	171.5±9.8/89.0±9.5
History of stroke or CVD (%)	9.5	8.7
LVH (%)	49.3	50.6
Diabetes mellitus (%)	11.9	11.6
Hyperlipidemia (%)	52.2	51.3

Figures are number of cases or mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; LVH, leftt ventricular hypretrophy.

(*18*), and hyperlipidemia was diagnosed according to the guidelines of the Japan Atherosclerosis Society (*19*). Subjects who were receiving treatment for diabetes mellitus or hyperlipidemia were considered to have these diseases.

Immediately after registration, the registration office randomly assigned the subjects to group A or B, and informed the investigators of the treatment assignments. The assigned treatment was given for 2 years. The registration period was from April 1, 2001 through December 31, 2002, and the treatment period ended on December 31, 2004.

Treatment

Treatment was started with efonidipine at a daily dose of 20 to 40 mg (once daily), which was given alone in untreated subjects and was added or substituted for one of the drugs given before study entry in treated subjects. The substitution of efonidipine for one of the prior drugs was performed without a washout period. The daily dose of efonidipine was increased to 60 mg (once or twice daily), if needed. The investigators were asked to adjust the dosage and concurrently use drugs other than calcium antagonists so that the allocated target BP would be reached in about 3 months after start of treatment.

The subjects were asked to visit their doctors every 2–4 weeks. Physical findings including BP and heart rate, adverse reactions or complications were examined at each visit. Routine laboratory examinations were performed every 6 months, and chest radiographs and ECG were obtained during the run-in period and at the end of treatment. Figure 1 shows a flowchart of the study.

Endpoint Evaluation

Endpoints were evaluated by the members of the Endpoint Evaluation Committee, who were blinded to the treatment assignments of the subjects. Primary endpoints were cerebrovascular disease (cerebral hemorrhage, cerebral infarction, transient ischemic attack, subarachnoid hemorrhage, and other types of cerebrovascular disease), cardiac disease (myocardial infarction, angina pectoris requiring hospitalization, and heart failure), vascular disease (dissecting aneurysms of the aorta and occlusive arterial disease), and renal dysfunction (acute or chronic renal failure; doubling of the serum concentration of creatinine to a value of 1.5 mg/dl or higher). Subjects who died within 28 days after the onset of cerebrovascular, cardiac, vascular, or renal disease were considered to have died from these diseases. The Endpoint Evaluation Committee considered cardiovascular disease to include stroke, cardiac disease, and vascular disease. Arrhythmias such as atrial fibrillation and paroxysmal atrial tachycardia were not included as primary endpoints, but were considered laboratory abnormalities. Secondary endpoints were deaths from any cause, morbidity other than cardiovascular disease, changes in BP and heart rate, and any problems in regard to safety.

Determination of Sample Size

The post-marketing survey of efonidipine showed that the incidence rate of cardiovascular events was about 4% per 2 years (*20*). Given that the difference in the incidence of primary endpoints between strict treatment (group A) and mild treatment (group B) is 2% (3% in one and 5% in the other), we estimated by the Poisson conditional score approach (*21*) that 1,605 subjects per group (3,210 subjects in total) would be required to show a difference with a two-sided α level of 0.05 and 80% power. Because the dropout rate was estimated to be 20%, we set the target number of subjects at 4,000.

Interim Analysis

An independent Data and Safety Monitoring Board reviewed the study results at the end of August, 2003, when the dura-

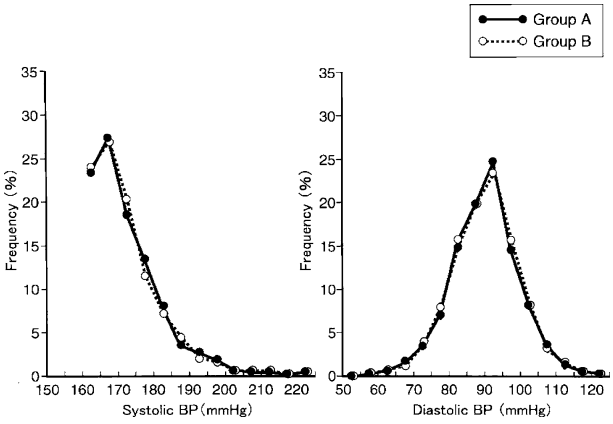

Fig. 2. *Frequency distribution of SBP and DBP at randomization in groups A and B. The BP distribution is similar in the two groups.*

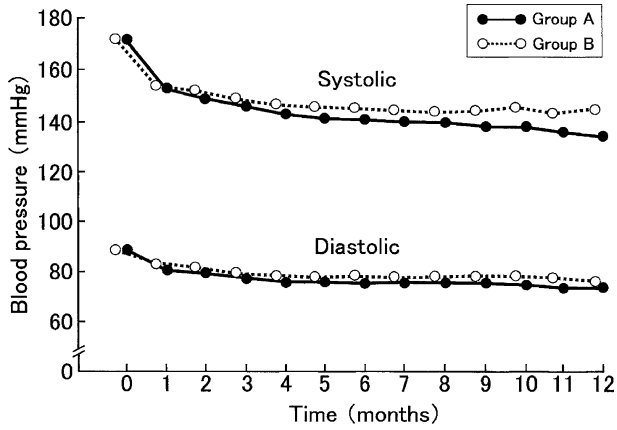

Fig. 3. *Time courses of SBP and DBP during the first 12 months of treatment. The difference in BP between the two groups increased with time. SBP was significantly lower in group A than group B after 1 month of treatment (*$p = 0.0063$*) and thereafter (*$p < 0.0001$*), and DBP was significantly lower in group A than group B after 3 months of treatment (*$p < 0.0001$*), after 4 months of treatment (*$p < 0.0005$*), and thereafter (*$p < 0.0001$*).*

tion of treatment multiplied by the number of subjects enrolled had reached half of the target value (8,000 patient-years). Since there were no problems with regard to safety, the Board recommended to the Steering Committee that the trial be continued, without modifying the protocol.

Statistical Analysis

The effectiveness of the two treatments was compared according to the "intention-to-treat." The analysis included comparison of the incidence of the primary endpoints between the two treatment groups by the χ^2 test, assessment of the relations between the incidence of primary endpoints and the changes in BP or the achievement of treatment goals, and comparison of the secondary endpoints between the two groups.

Organization

JATOS was a collaborative study of Japan Physicians Association and the Japanese Society of Hypertension, and was sponsored by Shionogi & Co., Ltd. The protocol was approved by the ethics committee of Japan Physicians Association and by the executive committee of the Japanese Society of Hypertension.

The JATOS study group consists of the Steering Committee, the Study Promoting Committee, the Endpoint Evaluation Committee, the Data and Safety Monitoring Board, and the Registration Office. The Steering Committee of the JATOS study group entrusted the sponsor with collection, monitoring, and management of the data, and set up the Central Administration and Monitoring Office in the Drug Safety Management Department and Biostatistics Department, Shionogi & Co., Ltd., which ensured that all data were analyzed in a blinded fashion. The Steering Committee wrote the paper.

The details of the JATOS study group are shown in the Appendix.

Results

Baseline Characteristics of the Subjects

By the entry deadline (December 31, 2002), 4,508 subjects were enrolled; 2,088 subjects (46.3%) by the members of Japan Physicians Association and 2,420 subjects (53.7%) by the members of the Japanese Society of Hypertension or other Physicians' Association. A total of 188 patients were excluded from analysis because of randomization errors, violation of Good Clinical Practice guidelines (*22*), or double registration. Of the remaining patients, 2,165 were assigned to the strict treatment group (group A) and 2,155 patients to the mild treatment group (group B). There were no significant differences between the treatment groups in sex, age, body-mass index (BMI), prior treatment, baseline BP (averaged BP in the run-in period), history of stroke or myocardial infarction (6 months or more before enrollment), cardiac hypertrophy, diabetes mellitus, or hyperlipidemia (Table 1).

Blood Pressure

The distribution of baseline SBP and that of DBP were similar between groups A and B (Fig. 2). BP decreased by 20.6/8.3 mmHg (systolic/diastolic) in group A and 18.2/7.4 mmHg in group B after 1 month of treatment. These changes in SBP and DBP from the baseline values were highly significant in both groups ($p < 0.0001$), and were significantly greater in

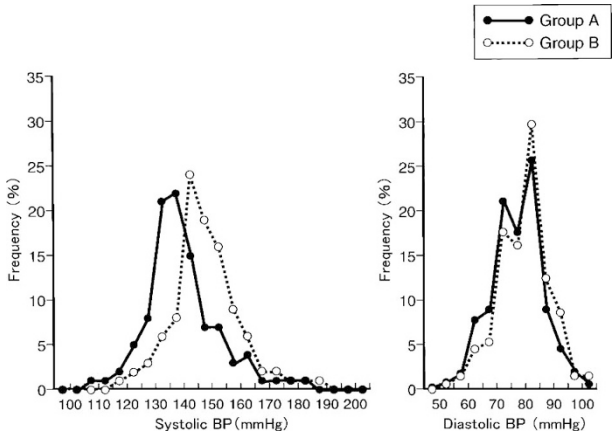

Fig. 4. *Frequency distributions of SBP and DBP in 12 months of treatment. The averaged BP was lower by 7.2 mmHg systolic and by 2.4 mmHg diastolic in group A than in group B after 12 months of treatment (both* $p < 0.0001$*).*

group A than in group B ($p=0.0002$ for SBP and $p=0.0284$ for DBP). The differences in BP between the treatment groups increased with time thereafter (Fig. 3). The BP (systolic/diastolic; mean±SD) in 12 months of treatment was 139.3±13.8/76.1±9.4 mmHg in group A and 146.5±14.6/78.5±10.0 mmHg in group B. SBP was thus 7.2 mmHg lower and DBP 2.4 mmHg lower in group A than group B after 12 months of treatment (both $p<0.0001$; Fig. 4). The percentage of the subjects who reached the target BP was 59.5% in group A and 67.4% in group B. This difference was significant ($p<0.001$).

Interim Analysis of Primary Endpoints

Interim analysis of primary endpoints was performed when the number of patient-years reached 4,164, approximately half of the target value. Primary endpoints had occurred in 87 patients by the interim analysis; stroke in 58 patients, heart disease in 27, occlusive arterial disease in 1, and renal failure in 1. As shown in Table 2, the incidence of stroke was twice as high as that of heart disease, and cerebral infarction was the major cause of stroke. Five patients with stroke and 2 patients with myocardial infarction died. Thus, primary-endpoint-related morbidity was 20.9/1,000 patient-years, and mortality was 1.7/1,000 patient-years.

Secondary endpoints are scheduled to be analyzed in the future.

Discussion

This study was designed to assess the optimal SBP in elderly hypertensive patients. Efonidipine, a dihydropiridine calcium antagonist widely used in Japan (*17*, *20*), was used as a baseline drug, because long-acting calcium antagonists are recommended as one of the first-choice drugs for the treatment of elderly hypertensive patients (*5–7*, *9*, *12*, *14*), and in fact are the most widely used drugs to manage hypertension in elderly patients in Japan (*23*).

Table 2. Primary Endpoints in 87 at the Interim Analysis (August 31, 2003)

Classification	Number of cases
Stroke	58
Cerebral infarction	(38)
Cerebral hemorrhage	(11)
Transient ischemic attack	(8)
Subarachnoid hemorrhage	(1)
Heart disease	27
Myocardial infarction	(7)
Angina pectoris	(13)
Congestive heart failure	(6)
Sudden death	(1)
Occlusive arterial disease	1
Renal failure	1

The target number of subjects was successfully recruited by the end of the registration period. There were no significant differences in sex, age, BMI, baseline BP, or other risk factors between the strict treatment group (group A) and the mild treatment group (group B), indicating that randomization of the treatment assignment was adequate. The only drawback of this study was that smoking status was not taken into account at the time of randomization.

BP reduction was significant in both groups 1 month after starting antihypertensive treatment, and BP continued to gradually decrease thereafter. Both SBP and DBP were significantly lower in group A than in group B after 1 or more months of treatment. SBP was lower by 7.2 mmHg and DBP by 2.4 mmHg in group A than in group B after 12 months of treatment (both $p<0.0001$). However, the respective treatment goals were achieved in significantly fewer subjects in group A than in group B. Whether this finding was simply due to the difficulty of reducing SBP below a critical level, or whether it may also have been related to other causes, such as the attitude of investigators toward less intensive treatment in elderly patients (*24*) or the poor adherence of patients to treatment (*4*), remains to be elucidated. It is expected, however, that BP differences between the two groups will increase towards the end of the treatment phase.

In the HOT study, designed to assess optimal BP in 18,790 hypertensive patients aged 50–80 years, the differences in the achieved BP reduction were 4.0 mmHg systolic and 4.1 mmHg diastolic even between patients with a target DBP of ≤90 mmHg and those with a target DBP of ≤80 mmHg (*12*). The difference between these groups in the achieved SBP was much smaller than the difference between groups A and B in our study. The ranges of the achieved SBP and DBP values, which were much smaller than expected, may have been one of the reasons for the lack of a clear-cut relation of the BP

Table 3. Incidence of Cardiovascular Disease in Patients Treated with Calcium Antagonists in Some of Recent Clinical Trials

Trial (*ref.*)	Drug	*n*	Age (years)	Morbidity (per 1,000 patient-years)
JATOS	Efonidipine	4,320	73.6	20.9
NICS-EH (*28*)	Nicardipine	204	69.7	27.8
Syst-Eur (*9*)	Nitrendipine	2,398	70.3	23.3
Syst-China (*29*)	Nitrendipine	1,253	66.4	21.4
INSIGHT (*30*)	Nifedipine	3,157	65.0	18.2
NORDIL (*31*)	Diltiazem	5,410	60.5	16.6
ALLHAT (*32*)	Amlodipine	9,048	66.9	56.8
VALUE (*33*)	Amlodipine	7,596	67.3	33.4

level to morbidity and mortality in the HOT study. In that study, patient inclusion and treatment assignments were based on DBP (*12*). Since SBP is more often and intimately related to target organ damage than DBP in elderly hypertensive patients (*4*), our study, which based patient enrollment and treatment on SBP, may provide practical and important information with regard to the treatment of elderly hypertensive patients.

As of this interim analysis, primary endpoints had occurred in 87 subjects, including 7 deaths. The morbidity rate was 20.9/1,000 patient-years, and the mortality rate was 1.7/1,000 patient-years. Similar to the findings of a recent international survey on the cardiovascular mortality in industrialized countries (*25*) and epidemiological studies of several regions in Japan (*26*, *27*), morbidity from stroke was approximately twice as high as morbidity from heart disease, and cerebral infarction was the major cause of stroke (*26*, *27*). Thus, the results of our interim analysis seem to be consistent with those of earlier studies showing that stroke is more frequent than heart disease in Japanese individuals with hypertension, while heart disease is more common than stroke in Western countries (*8*, *9*, *12*, *25*).

The effectiveness of calcium antagonists has attracted considerable attention, and large clinical trials comparing the long-term effects of calcium antagonists with those of placebo or conventional antihypertensive drugs have been recently reported. Table 3 summarizes some of these trials, showing the abbreviated trial names, calcium antagonists used, number of patients, mean age, and cardiovascular morbidity rate, expressed in terms of cases per 1,000 patient-years for patients treated with calcium antagonists. Although the mean age is much older in our study than in most other trials (*9*, *28–33*), the cardiovascular morbidity rate is lower in our study than in most other trials, excluding INSIGHT and NORDIL, in which the subjects were much younger than ours (*30*, *31*). Mortality from cardiovascular disease was also much lower in our study than in the previous trials that reported mortality (*9*, *29*, *31–33*). Thus, our study appears to have been safely conducted, at least judging from the cardiovascular disease.

To our knowledge, the present study is one of the first large clinical trials to assess optimal SBP in elderly hypertensive patients. Our study was completed as of the end of 2004, and we hope that the results of the final analysis will contribute to improved treatment for elderly hypertensive patients in Japan and other countries.

Appendix

JATOS Committees

Steering Committee: Yoshio Goto (Co-chair, Sendai), Masao Ishii (Co-chair, Yokohama), Takao Saruta (Tokyo), Tadashi Kawakami (Tokyo), Kanemi Kawabe (Tokyo), Toshio Ogihara (Osaka), Yuhei Kawano (Osaka).

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Data and Safety Monitoring Board: Naokata Shimizu (Chair, Yokohama), Chihiro Hirotsu (Tokyo), Hiroe Tsubaki (Tokyo), Ryozo Nagai (Tokyo), Iwao Kuwajima (Tokyo).

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Advisor: Yoshio Yazaki (Tokyo).

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