Original Article

Principal Results of the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS)

JATOS Study Group*

The benefits of lowering a systolic blood pressure below 140 mmHg in elderly hypertension remain controversial. This study is a prospective, randomized, open-label study with blinded assessment of endpoints to compare the 2-year effect of strict treatment to maintain systolic blood pressure below 140 mmHg with that of mild treatment to maintain systolic blood pressure below 160 but at or above 140 mmHg in elderly hypertensive patients. Patients with essential hypertension (65–85 years old, with a pretreatment systolic blood pressure of above 160 mmHg) were randomly assigned to receive strict treatment (n=2,212) or mild treatment (n=2,206). The baseline drug was efonidipine hydrochloride, a long-acting calcium antagonist. The primary endpoint was the combined incidence of cardiovascular disease and renal failure, and the secondary endpoints were total deaths and any safety problems. Although final blood pressures (systolic/diastolic) were significantly lower in the strict-treatment group compared with the mild-treatment group (135.9/74.8 *vs.* 145.6/78.1 mmHg; p<0.001), the incidence of the primary endpoint was similar in the two groups (86 patients in each group; p=0.99). Total deaths were 54 in the strict-treatment group *vs.* 42 in the mild-treatment group (p=0.22), and treatment was withdrawn because of adverse events in 36 patients in each group (p=0.99). An interaction between age and treatment for the primary endpoints (p=0.03) was seen. Complex clinical features associated with aging seem to have obscured the difference in effect between the two treatments. Further studies are needed to assess the optimal treatment strategy for hypertension in the elderly. (*Hypertens Res* 2008; 31: 2115–2127)

***Key Words*: essential hypertension, calcium antagonists, efonidipine hydrochloride, elderly patients**

Introduction

Systolic blood pressure (BP) increases steadily with age, whereas diastolic BP increases until 55 years of age and then declines (*1*). Thus, the relative importance of BP as a cardiovascular risk has been demonstrated to shift from diastolic BP to systolic BP with advancing age (*2*, *3*).

Recent guidelines for the management of hypertension recommend a target systolic BP of less than 140 mmHg and a target diastolic BP of less than 90 mmHg for elderly hypertensive patients (*4–7*). A further reduction in BP is recommended for hypertensive patients who have diabetes mellitus and kidney disease (*4–7*). However, the implication and the feasibility of maintaining systolic BP below 140 mmHg are poorly understood in elderly subjects, because this target level has been achieved in only a few interventional studies (*8*, *9*) and because no studies in which a pretreatment systolic BP of 160 mmHg or higher was reduced below 140 mmHg in a group average are available (*10*). Furthermore, the potential benefits of treating systolic hypertension may not be obtained in elderly patients (*11*, *12*) and, at the population level, favorable 5-year survival is associated with a high, but not a low, BP in subjects 75 years or older (*13*). Moreover, cardiovascular event rates increase in a curvilinear fashion after the age of 65 to 75 years (*14*). Thus, whether guidelines for the treat-

*Details of JATOS Study Group are shown in Appendix.

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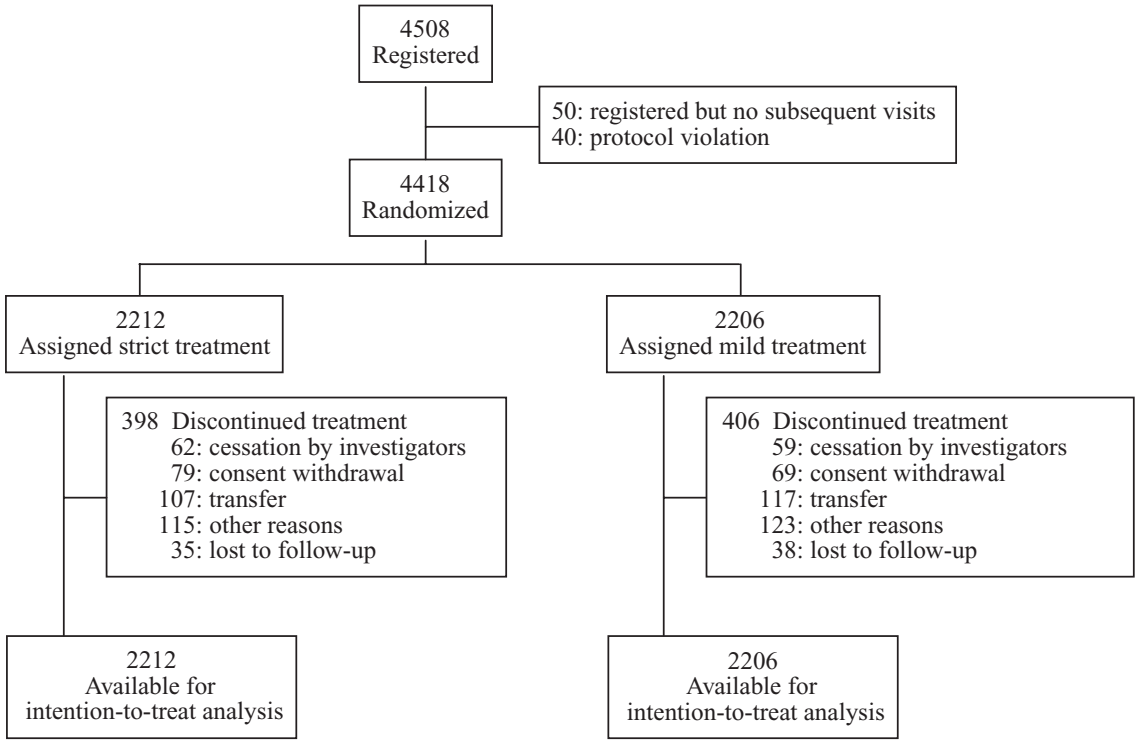

Fig. 1. *Flowchart of allocation of subjects. There was no significant difference between the two groups in the number of patients who withdrew from the study (p = 0.72). When follow-up inquiries were sent to the subjects who discontinued treatment, responses were not obtained from 35 subjects (1.6%) in the strict-treatment group and 38 (1.7%) in the mild-treatment group (p = 0.71).*

ment of hypertension in the general population can be applied to the elderly remains questionable.

To compare the effect of 2 years of strict antihypertensive treatment and that of mild treatment in elderly hypertensive patients, we organized the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS). The methods, protocol, and interim data monitoring of this trial have been reported elsewhere (*15*).

Methods

Purpose

The JATOS was a prospective, randomized, and open-label study with blinded assessment of endpoints. It was designed to compare the effects of 2 years of strict antihypertensive treatment to maintain systolic BP below 140 mmHg (strict-treatment group) with those of mild treatment to maintain systolic BP below 160 but at or above 140 mmHg (mild-treatment group). The baseline drug was efonidipine hydrochloride (efonidipine), a long-acting dihydropyridine calcium antagonist (*16*, *17*).

This study was registered at the UMIN Clinical Trial Registry with the trial number UMIN000001021.

Subjects

The subjects were male or female outpatients, 65 to 85 years of age, with essential hypertension who persistently had a systolic BP of 160 mmHg or higher during a run-in period while receiving no antihypertensive drugs or receiving the same drug(s) for at least 4 weeks. Individuals who received antihypertensive drugs were eligible if efonidipine could either be additionally given or substituted for one of the drugs received before study entry.

The exclusion criteria are reported in detail elsewhere (*15*); briefly, criteria included diastolic BP 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 New York Heart Association (NYHA) class II or higher, persistent arrhythmia such as atrial fibrillation, dissecting aneurysm of the aorta or occlusive arterial disease, hypertensive retinopathy, serum aspartate aminopeptidase 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 disease (serum crea-

Table 1. Baseline Characteristics of the Subjects

Variables	Strict treatment (n=2,212)	Mild treatment (n=2,206)
Sex		
Male, *n* (%)	874 (39.5)	843 (38.2)
Female, *n* (%)	1,338 (60.5)	1,363 (61.8)
Age, years	73.6±5.3	73.6±5.2
65–74 years, *n* (%)	1,277 (57.7)	1,272 (57.7)
75–85 years, *n* (%)	935 (42.3)	934 (42.3)
Body mass index, kg/m^2	23.6±3.4	23.6±3.5
Smoking status		
Current, *n* (%)	311 (14.1)	284 (12.9)
Previous, *n* (%)	102 (4.6)	101 (4.6)
Baseline blood pressure, mmHg		
Systolic	171.6±9.7	171.5±9.8
Diastolic	89.1±9.5	89.1±9.5
Enlarged heart or LVH,† *n* (%)	1,091 (49.3)	1,109 (50.3)
Past history of cerebrovascular disease, *n* (%)	92 (4.2)	100 (4.5)
Past history of cardiac and vascular disease, *n* (%)	76 (3.4)	58 (2.6)
Renal disease, *n* (%)	218 (9.8)	221 (10.0)
Diabetes mellitus, *n* (%)	264 (11.9)	257 (11.7)
Fasting serum glucose concentration, mg/dL	102.7±22.0	102.1±21.4
HbA1c, %	5.3±0.7	5.3±0.7
Hyperlipidemia, *n* (%)	1,162 (52.5)	1,139 (51.6)
Total cholesterol, mg/dL	205.1±35.4	206.0±35.4
HDL-cholesterol, mg/dL	56.4±15.0	56.7±15.3
Triglyceride, mg/dL	136.7±83.6	133.6±77.6
Prior antihypertensive drug treatment, *n* (%)	1,219 (55.1)	1,256 (56.9)
ACE inhibitors or ARBs, *n* (%)	747 (33.8)	756 (34.3)
Calcium antagonists except for efonidipine, *n* (%)	584 (26.4)	590 (26.7)
Adrenoceptor blocking drugs, *n* (%)	143 (6.5)	157 (7.1)
Diuretics, *n* (%)	80 (3.6)	76 (3.4)

Figures are number of subjects, percentages, or means±SD. LVH, left ventricular hypertrophy; HDL, high-density lipoprotein; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. †A cardiothoracic ratio of more than 50% on a chest X-ray film was defined as an enlarged heart, and LVH was diagnosed electrocardiographically.

tinine of 1.5 mg/dL or higher), 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 patients), patients were examined on at least two separate occasions, and BP was measured at least twice per visit by the auscultatory method, using a sphygmomanometer with the patients in the sitting position after 5 to 10 min of rest. BP measurements were averaged for each visit and the pulse rate was also recorded. Chest X-ray films and ECG were obtained, and routine laboratory examinations, including urinalysis, hematological examinations, and serum chemical analyses, were also performed during the run-in period. A cardiothoracic ratio of more than 50% on a chest X-ray film was defined as an enlarged heart, and left ventricular hypertrophy (LVH) was diagnosed according to the Sokolow-Lyon voltage criteria (*18*). Detailed examinations such as echocardiography were performed when a specific heart disease like valvular heart disease was suspected. Renal disease was diagnosed based on serum creatinine levels and the findings of urinalysis.

Diabetes mellitus was diagnosed according to the guidelines of the Japan Diabetes Society (*19*) and hyperlipidemia was diagnosed according to the guidelines of the Japan Atherosclerosis Society (*20*). Patients receiving treatment for diabetes mellitus or hyperlipidemia were considered to have these diseases.

Randomization

Written informed consent was obtained from all eligible subjects before or during the run-in period, after having confirmed the eligibility of subjects. The consent included the acceptance of follow-up inquiries by the administration office

Table 2. Number and Classification of Concurrently Used Antihypertensive Drugs at the End of Treatment

	Strict treatment (n=2,212)	Mild treatment (n=2,206)	p*
One drug, *n* (%)	1,054 (47.7)	1,280 (57.8)	<0.001
Two drugs, *n* (%)	698 (31.6)	604 (27.3)	0.002
Three drugs, *n* (%)	335 (15.1)	205 (9.3)	<0.001
Four drugs, *n* (%)	63 (2.9)	43 (1.9)	0.05
Five drugs, *n* (%)	1 (0.1)	1 (0.1)	1.00
Efonidipine monotherapy, *n* (%)	1,013 (45.8)	1,246 (56.5)	<0.001
ACE-inhibitors/ARBs, *n* (%)	901 (40.7)	684 (30.9)	<0.001
Ca antagonists,† *n* (%)	91 (4.1)	73 (3.3)	0.16
Adrenoceptor blocking drugs, *n* (%)	316 (14.3)	258 (11.6)	0.01
Diuretics, *n* (%)	339 (15.3)	197 (8.9)	<0.001
Others, *n* (%)	17 (0.8)	15 (0.7)	0.73
None, *n* (%)	61 (2.8)	73 (3.3)	0.29

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. *χ^2 test. †Other than efonidipine.

for patients who did not return to their physicians. The investigators sent a registration form describing the clinical characteristics of eligible patients to the registration office by facsimile. Immediately after registration, the registration office randomly assigned the subject to either treatment group using a computer-generated list and informed the investigators of the treatment assignments. The registration period was from April 1, 2001, through December 31, 2002. The treatment period ended on December 31, 2004.

Treatment

Untreated subjects initially received efonidipine at a daily dose of 20 to 40 mg (once daily). In subjects who were already receiving antihypertensive medications, a similar dose of efonidipine was added or substituted for one of the drugs being received before study entry without a washout period. The daily dose of efonidipine could be increased to 60 mg (once or twice daily) and antihypertensive drugs other than calcium antagonists were added, if needed. The subjects were instructed to visit their physicians every 2 or 4 weeks, and the investigators were asked to titrate the doses of the antihypertensive drugs so that the allocated target BP would be reached about 3 months after the start of treatment.

Endpoint Evaluation

Endpoints were evaluated by the members of the Endpoint Evaluation Committee, who were blinded to the treatment assignments and the time course of BP. The primary endpoint was the combined incidence of cerebrovascular disease (cerebral hemorrhage, cerebral infarction, transient ischemic attack, and subarachnoid hemorrhage), cardiac and vascular disease (myocardial infarction, angina pectoris requiring hospitalization, heart failure, sudden death, dissecting aneurysms of the aorta, and occlusive arterial disease), and renal failure (acute or chronic renal failure; doubling of the serum creatinine concentration to a value of 1.5 mg/dL or higher). Cerebrovascular disease was diagnosed based on neurological and radiological examinations. Cardiac and vascular diseases were diagnosed using radiographic, echocardiographic, and biochemical methods in addition to signs and symptoms. Sudden death, defined as death from instantaneous, unanticipated circulatory collapse within 1 h of initial symptoms, was also included in cardiac and vascular disease. Subjects who died within 28 d after the onset of any of the primary or secondary endpoints were considered to have died from these diseases. Arrhythmias such as atrial fibrillation were not included in the primary endpoint, but were considered adverse events. Secondary endpoints were deaths from any causes and any safety problems.

Statistical Analysis

In post-marketing studies of efonidipine, the incidence of cardiovascular events was approximately 4% in 2 years (*21*). Assuming that the difference in the incidence of primary endpoints between the strict-treatment group and the mild-treatment group would be 2 percentage points (3% in one and 5% in the other), we estimated that 1,605 subjects per group (3,210 subjects in total) would be required to detect a difference with a two-sided α level of 5% and 80% power (*22*). Because the dropout rate was estimated to be 20%, the target number of subjects was 2,000 per group (4,000 in total).

The effects of the two treatments were compared according to the intention to treat. Measured variables were expressed as percentages or means±SD. We compared the means of continuous variables using the *t*-test and their proportions using the χ^2 test (*23*). The cumulative incidence rates were estimated by the Kaplan-Meier method and compared using the log-rank test.

The contribution to the primary endpoint of risk factors

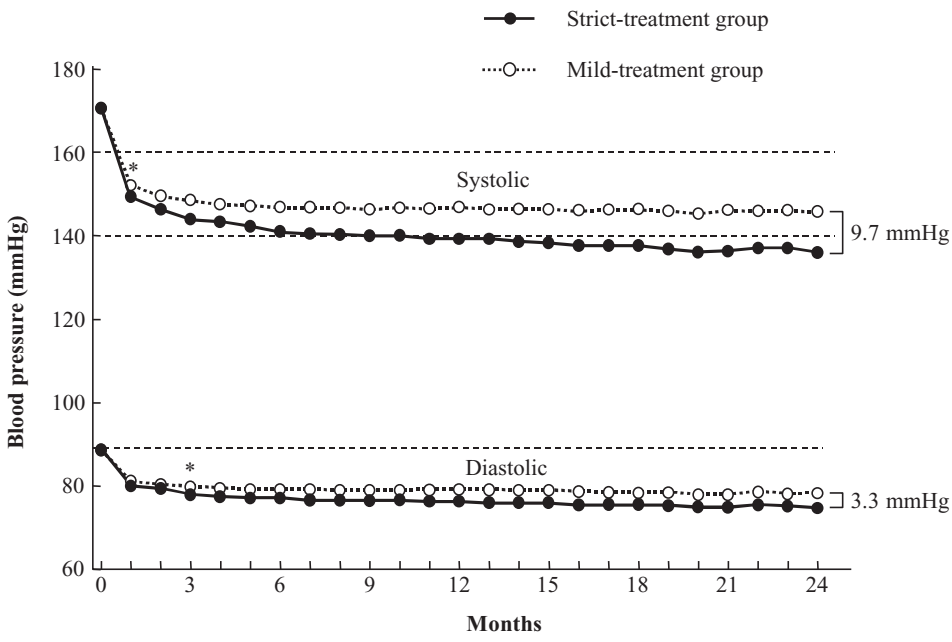

Fig. 2. *Blood pressure during treatment. *Intergroup differences were significant from this point ($p < 0.001$). Systolic and diastolic BPs were lower by 9.7 mmHg and 3.3 mmHg, respectively, in the strict-treatment group than in the mild-treatment group at the end of treatment (both $p < 0.001$).*

Table 3. Incidences of Nonfatal and Fatal Components of the Primary Endpoint

Events	Strict treatment (n=2,212)	Mild treatment (n=2,206)
Primary endpoint	86 (9)	86 (8)
Cerebrovascular disease	52 (3)	49 (3)
Cerebral infarction	36 (2)	30 (0)
Cerebral hemorrhage	7 (0)	8 (1)
Subarachnoid hemorrhage	1 (1)	4 (2)
Transient ischemic attack	8 (0)	7 (0)
Cardiac and vascular disease	26 (6)	28 (4)
Angina pectoris	9 (0)	10 (0)
Myocardial infarction	6 (1)	6 (0)
Congestive heart failure	8 (4)	7 (1)
Obstructive arterial disease	2 (0)	1 (0)
Abdominal aortic rupture	0 (0)	1 (1)
Aortic aneurysm enlargement	0 (0)	2 (1)
Sudden death	1 (1)	1 (1)
Renal failure	8 (0)	9 (1)

Numbers in the parentheses indicate the number of deaths.

such as age, sex, enlarged heart or LVH, prior cardiovascular disease, diabetes mellitus, hyperlipidemia, renal disease, or prior treatment was evaluated with the use of Cox's model. Because the subjects ranged in age from 65 to 85 years old and because the relation between the change in BP and survival may vary around 75 years of age (*24*), an age of 75 years was chosen as the cutoff point between younger patients and older patients.

All tests were two-sided, and the significance level was set at 5%.

Organization

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

Results

Study Profile

Although 4,508 subjects were registered, 50 were excluded because they did not return for follow-up appointments, and 40 were excluded because of violations of the study protocol (Fig. 1). Of the eligible 4,418 subjects, 2,212 were randomly assigned to the strict-treatment group and 2,206 to the mild-treatment group. After randomization, treatment was discontinued in 398 subjects in the strict-treatment group and in 406 in the mild-treatment group at the investigators' discretion or because of consent withdrawal, transfer, or other reasons (p=0.72). Follow-up inquiries were sent to the subjects who had discontinued treatment; responses were not obtained from 35 subjects (1.6%) in the strict-treatment group and 38 (1.7%) in the mild-treatment group (p=0.71; Fig. 1).

Table 4. Number of Events and Deaths from the Primary Endpoint and Its Components

Events	Morbidity			Mortality		
	Strict treatment (n=2,212)	Mild treatment (n=2,206)	p*	Strict treatment (n=2,212)	Mild treatment (n=2,206)	p*
Primary endpoint, *n* (%)	86 (3.89)	86 (3.90)	0.99	9 (0.41)	8 (0.36)	0.81
Per 1,000 patient-years (95% CI)	22.6 (18.1–27.9)	22.7 (18.2–28.1)	0.98	2.4 (1.1–4.5)	2.1 (0.9–4.2)	0.82
Cerebrovascular disease, *n* (%)	52 (2.35)	49 (2.22)	0.77	3 (0.14)	3 (0.14)	1.00
Per 1,000 patient-years (95% CI)	13.7 (10.2–17.9)	12.9 (9.6–17.1)	0.78	0.8 (0.2–2.3)	0.8 (0.2–2.3)	1.00
Cardiac and vascular disease, *n* (%)	26 (1.18)	28 (1.27)	0.78	6 (0.27)	4 (0.18)	0.53
Per 1,000 patient-years (95% CI)	6.8 (4.5–10.0)	7.4 (4.9–10.7)	0.77	1.6 (0.6–3.4)	1.1 (0.3–2.7)	0.53
Renal failure, *n* (%)	8 (0.36)	9 (0.41)	0.80	0 (0.00)	1 (0.05)	0.32
Per 1,000 patient-years (95% CI)	2.1 (0.9–4.1)	2.4 (1.1–4.5)	0.80	0.0 (0.0–0.8)	0.3 (0.0–1.5)	0.32

*χ^2 test.

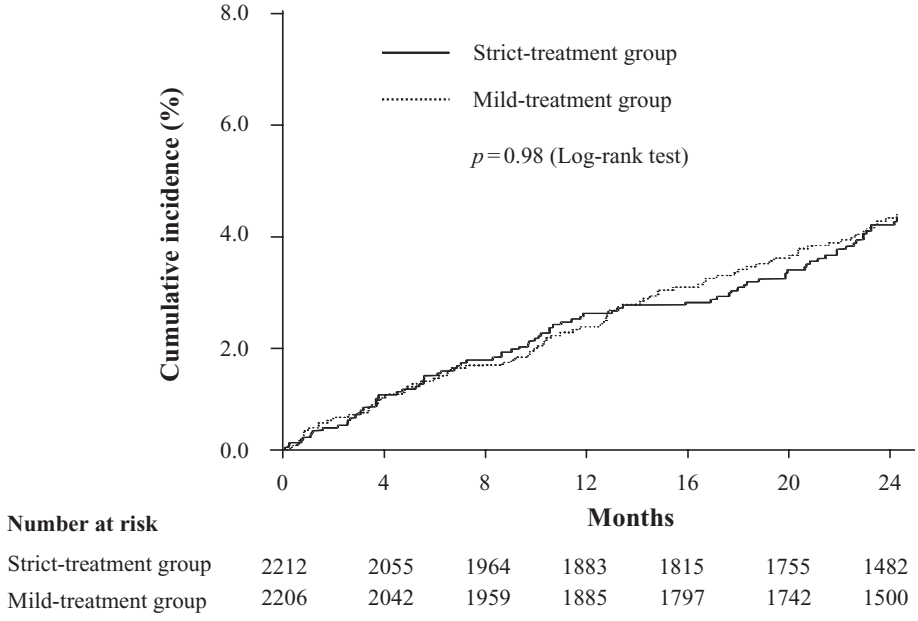

Fig. 3. *The Kaplan-Meier time-to-event analyses for the primary endpoint. The cumulative rates of morbidity from the primary endpoint were similar in the two groups. To estimate cumulative incidence rates of morbidity, data up to 2 years after administration were used. Data from more than 2 years after treatment were excluded.*

Baseline Characteristics

There were no significant differences between the two groups in sex, age, body mass index, smoking status, baseline BP, the prevalence of an enlarged heart or LVH, a past history (6 months or more before enrollment) of cerebrovascular disease or cardiac and vascular disease, prevalence of renal disease, diabetes mellitus or hyperlipidemia, or the proportion of patients who had received prior antihypertensive treatment (Table 1). The usage rates of various antihypertensive drugs did not differ significantly between the two groups.

Treatment

At the end of the study, 4,094 subjects (92.7%) were receiving efonidipine alone or in combination with other antihypertensive drugs. One thousand thirteen subjects (45.8%) in the strict-treatment group and 1,246 (56.5%) in the mild-treatment group were receiving monotherapy with efonidipine or another antihypertensive drug ($p<0.001$). As shown in Table 2, at the end of treatment, a combination of antihypertensive drugs was more frequently used in the strict-treatment group than in the mild-treatment group (40.7% *vs*. 30.9% for angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blockers, $p<0.001$; 14.3% *vs*. 11.6% for adrenocep-

Table 5. Adverse Events Which Necessitated Discontinuation of Treatment

Events	Strict treatment (n=2,212)	Mild treatment (n=2,206)	p*
Malignant disease	6	10	0.31
Psychoneurological symptom	4	5	0.74
Poor blood pressure control	4	5	0.74
Cardiac symptom or arrhythmias	7	4	0.37
Coronary bypass surgery	1	1	1.00
Hepatobiliary disease	2	3	0.65
Gastrointestinal symptom	2	0	0.16
Respiratory symptom or disease	4	2	0.42
Skin rash	1	0	0.32
Anemia	1	0	0.32
Traffic accident	1	0	0.32
Deterioration of diabetes mellitus	1	1	1.00
Other adverse events	2	5	0.25
Total	36	36	0.99

Figures are number of cases. *χ^2 test.

tor blockers, p=0.01; 15.3% *vs*. 8.9% for diuretics, p<0.001; 4.1% *vs*. 3.3% for calcium antagonists other than efonidipine, p=0.16; 0.8% *vs*. 0.7% for other drugs, p=0.73). No antihypertensive drugs were given to 61 subjects (2.8%) in the strict-treatment group and 73 (3.3%) in the mild-treatment group (p=0.29). The average number of drugs used at the end of the study was 1.7 in the strict-treatment group and 1.5 in the mild-treatment group (p<0.001).

Blood Pressure

BP decreased markedly after 1 month of treatment and then decreased gradually in both groups (Fig. 2). Systolic BP/diastolic BP (mean±SD) was 135.9±11.7/74.8±9.1 mmHg in the strict-treatment group and 145.6±11.1/78.1±8.9 mmHg in the mild-treatment group at the end of treatment; systolic and diastolic BPs were lower by 9.7 mmHg and 3.3 mmHg, respectively, in the strict-treatment group than in the mild-treatment group (both p<0.001). In the strict-treatment group, the average of the last two measurements of systolic BP was below 140 mmHg in 64.9% of the patients and below 130 mmHg in 19.4% of patients.

Primary Endpoint

The primary endpoint occurred in 86 patients in the strict-treatment group and in 86 patients in the mild-treatment group; among these patients, 9 and 8 died, respectively (Table 3). The incidence of cerebrovascular disease was approximately twice as high as that of cardiac and vascular events. The rates of morbidity and mortality from the primary endpoint and its components did not differ significantly between the two treatment groups (Table 4). The Kaplan-Meier time-to-event curves for the primary endpoint were similar in the two treatment groups (Fig. 3).

Secondary Endpoints

Fifty-four patients died of any cause in the strict-treatment group compared with 42 in the mild-treatment group (p=0.22). The main causes of death other than the primary endpoint were carcinoma, respiratory disease, and accidents. Treatment was discontinued because of adverse events in 36 patients in each of the treatment groups (p=0.99; Table 5). Adverse events such as gastrointestinal signs and symptoms or abnormal laboratory findings were reported for 550 patients in the strict-treatment group and 548 in the mild-treatment group (p=0.99).

Exploratory Data Analysis

We analyzed the contribution of risk factors such as age, sex, an enlarged heart or LVH, diabetes mellitus, prior cardiovascular disease, renal disease, or prior treatment to the primary endpoint. The age of the patients (younger or older than 75 years old) was also considered in the analysis.

As shown in Fig. 4, the primary endpoint was significantly related to age, sex, enlarged heart or LVH, past history of cerebrovascular disease, diabetes mellitus, renal diseases, and prior treatment. The hazard ratio of treatment (strict *vs*. mild) in younger patients was above 1.0, whereas it was below 1.0 in older patients. Therefore, to clarify treatment effects, the relation between these risk factors and outcomes was further analyzed. With respect to the primary endpoint, there was a significant interaction between age and treatment, but not between other variables, such as sex, body mass index, smoking status, family history, past history of cardiovascular disease, renal disease, diabetes mellitus, or hyperlipidemia. The incidence of the primary endpoint tended to be lower in the strict-treatment group than in the mild-treatment group in the younger patients, whereas the opposite trend was observed in the older patients (Table 6).

Discussion

The present study compared the occurrence of cardiovascular events between 2 years of strict antihypertensive treatment and 2 years of mild antihypertensive treatment in elderly hypertensive patients with a pretreatment systolic BP of 160 mmHg or higher. The baseline drug was efonidipine, a long-acting dihydropyridine calcium antagonist, and other types of antihypertensive drugs were given concomitantly as required to reach the assigned treatment goals. Although systolic and diastolic BPs were lower by 9.7 mmHg (p<0.001) and 3.3 mmHg (p<0.001), respectively, in the strict-treatment group than in the mild-treatment group at the end of treatment, the incidences of the primary endpoint and its components were

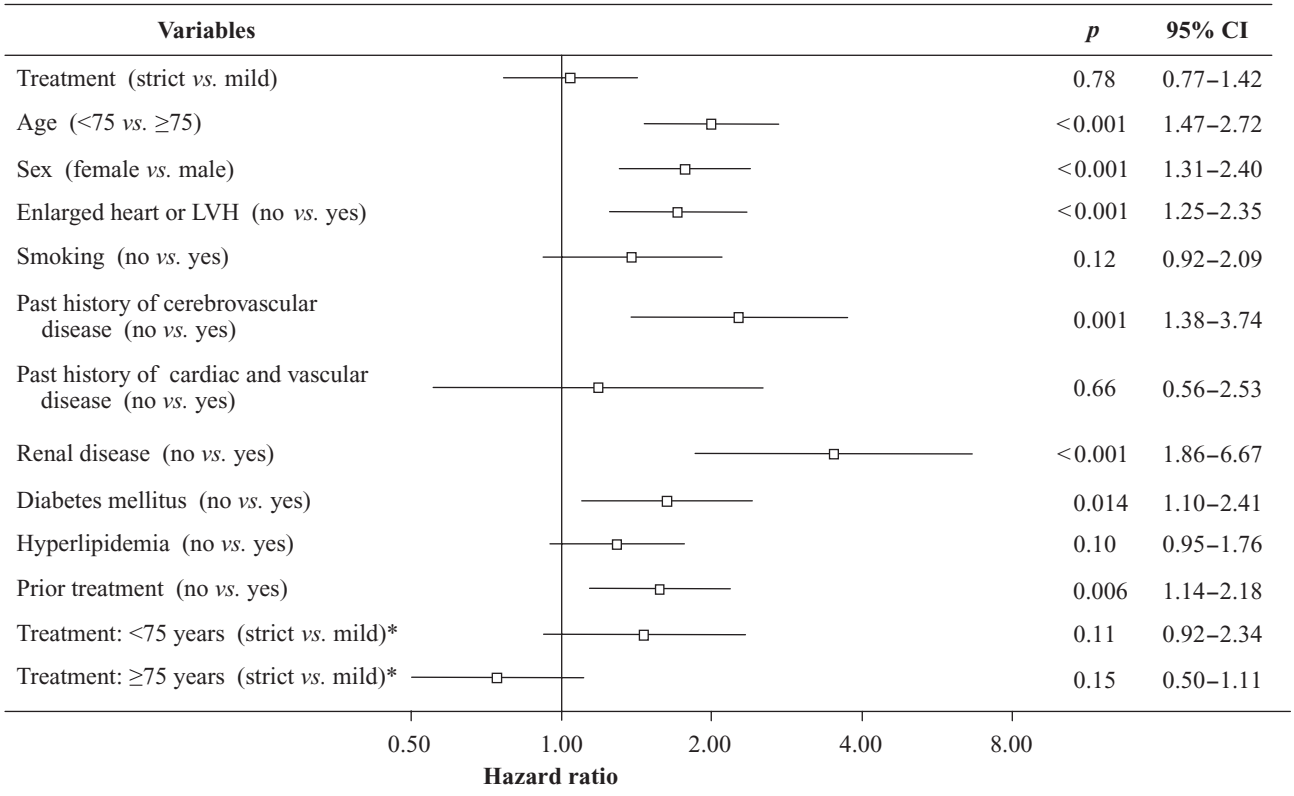

Fig. 4. *The involvement of risk factors in the incidence of the primary endpoint. The figure shows hazard ratios and their 95% confidence intervals (CI) as calculated with Cox's regression model. The involvement of age (75 years or older), sex (male), enlarged heart or LVH, a past history of cerebrovascular disease, diabetes mellitus, and prior antihypertensive treatment were significant. For age and sex, "75 years or older" and "male" showed higher risk, respectively. *In the comparison of "strict" vs. "mild" treatment, when the hazard ratio was smaller than 1, mild treatment was better than strict treatment.*

Table 6. Incidences of the Primary Endpoint and Its Components in Relation to Age and Treatment

Events and their incidence (%)	Below 75 years old (n=2,549)			75 years old or older (n=1,869)			p for the interaction†
	Strict treatment (n=1,277)	Mild treatment (n=1,272)	p*	Strict treatment (n=935)	Mild treatment (n=934)	p*	
Primary endpoint, n (%)	30 (2.35)	44 (3.46)	0.10	56 (5.99)	42 (4.50)	0.15	0.03
Cerebrovascular disease, n (%)	17 (1.33)	26 (2.04)	0.15	35 (3.74)	23 (2.46)	0.10	0.03
Cardiac and vascular disease, n (%)	10 (0.78)	13 (1.02)	0.49	16 (1.71)	15 (1.61)	0.80	0.50
Renal failure, n (%)	3 (0.23)	5 (0.39)	0.68	5 (0.53)	4 (0.43)	0.97	0.75

*Log-rank test. †Significance test of interaction term in Cox regression with treatment, age, sex, and interaction between treatment and age as covariates.

similar in the two groups. There were also no significant group differences in the secondary endpoints. These findings were in contrast to the results of meta-analyses of endpoint trials reporting that a reduction of 6.9 to 18.2 mmHg in systolic BP or of 2.3 to 8.3 mmHg in diastolic BP was associated with a considerably lower incidence of cardiovascular events (*25–27*). Thus, the lack of a significant intergroup difference in outcomes was unexpected.

The EWPHE trial reported that there was an interaction between age and treatment for cardiovascular death and that little or no benefit from treatment could be demonstrated in patients over 80 years old (*11*). A subgroup and per-protocol analysis of the Randomized European Trial on Isolated Systolic Hypertension in the Elderly also demonstrated that although stepwise antihypertensive drug treatment starting with a dihydropyridine calcium antagonist improved the

prognosis of elderly hypertensive patients, antihypertensive drug treatment had only a weak effect on total and cardiovascular mortality (*12*). Similar findings have been reported by several cohort studies focusing on the relationship between BP and total and cardiovascular mortality (*28–30*). A recent study by the EPOCH-JAPAN research group, which analyzed the relation of BP and all-cause mortality in 180,000 Japanese participants, showed that the effect of hypertension on multivariate-adjusted mortality gradually weakened with advancing age (*31*). Taken together, the relation between BP and cardiovascular events appears to become equivocal with advancing age. We thus attempted to clarify the relation between BP and cardiovascular events in the present study. However, as shown in Fig. 3, the cumulative event rates were so similar in the two groups that they most likely would not have differed from each other, even if the treatment had been prolonged.

In the present study, we performed an exploratory data analysis to assess the contribution of various risk factors to the primary endpoint. Analysis with Cox's model showed that age, sex, an enlarged heart or LVH, past history of cerebrovascular disease, diabetes mellitus, renal disease, and prior treatment were significantly related to the primary endpoint, consistent with the results of previous studies (*4–7*). An interesting finding was that the effect of strict treatment might be more favorable in younger patients (younger than 75 years old) than in older patients (75 years or older), whereas the opposite might be true for mild treatment. A further analysis demonstrated a significant interaction between age and treatment for the primary endpoint. The interaction between age and treatment for the primary endpoint seems to be one of the reasons for the lack of significant differences in outcomes between the two treatment groups, because event rates directed in opposite directions in the younger and older subjects in the two treatment groups offset each other when the two age groups were combined. The implication of the interaction between age and treatment in the present study should be further assessed in the future.

How far systolic BP should be reduced in elderly hypertensive patients remains controversial (*27*). The results of our study suggest that a reduction of mean systolic BP to 146 mmHg may be adequate in most elderly hypertensive patients, because that level was achieved in the mild-treatment group and because the outcomes did not significantly differ between the younger and the older subjects. On the other hand, more intensive treatment to reduce the systolic BP to less than 140 mmHg may be beneficial in younger patients able to tolerate such therapy. A recent study that examined the effects of indapamide (sustained release), with or without perindopril, in hypertensive patients 80 years or older showed that a target BP of 150/80 mmHg was beneficial (*32*). That study and ours offer important suggestions for setting treatment goals in hypertensive patients aged 75 years or older.

It is noteworthy that the mean number of antihypertensive drugs per patient in this study was much smaller than that reported by other studies (*33*). Integrated programs for patient education contributed to the effective management of hypertension (*34*). Although our study did not include special educational programs, patients were encouraged to comply with the scheduled visits, which were more frequent than in other similar clinical trials (*35–39*). This active follow-up may have contributed to the BP reduction.

In addition to the relatively low incidence of cardiovascular events, the mortality rates from the primary endpoint were surprisingly lower in the present study than in other similar clinical trials (*11*, *35–39*). These findings suggest that our treatment was appropriate as a whole and are consistent with the results of a recent epidemiological study showing that a marked decrease in mortality from stroke since 1970 has led to a longer life expectancy at birth in Japan than in any other country (*40*).

In summary, there was no significant difference in outcomes between strict treatment and mild treatment despite the significant difference in final BP. Complex clinical features associated with aging seem to have obscured the difference in effect between the two treatments. Further studies are needed to assess the treatment strategy for hypertension in the elderly.

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Appendix

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