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ORIGINAL ARTICLE

Comparison of strict- and mild-blood pressure control in elderly hypertensive patients: a per-protocol analysis of JATOS

Hiromi Rakugi[1], Toshio Ogihara[1], Yoshio Goto[2] and Masao Ishii[3], on behalf of the JATOS Study Group

We performed a per-protocol analysis of the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) to evaluate the optimal target blood pressure (BP) in elderly hypertensive patients. In JATOS, conducted in elderly (65–85 years) hypertensive patients treated with efonidipine hydrochloride, there were no differences between the strict-treatment group (systolic BP maintained at $<$140 mm Hg) and the mild-treatment group (systolic BP maintained at $\geqslant$140 mm Hg and $<$160 mm Hg) in the incidence of primary end points (cardiovascular disease and renal failure) for 2 years. The present study analyzed data in subgroups of JATOS in which the average systolic BP was within the range of target values. The average BP levels achieved in the strict-target BP achieved subgroup (n=1191) and the mild-target BP achieved subgroup (n=1531) were 132.3/74.0 mm Hg and 146.6/78.3 mm Hg, respectively. The incidences of primary end points were similar between these subgroups (11.1/1000 patients per year and 13.2/1000 patients per year, respectively, P=0.502), and there were also no differences in the incidences of adverse events. The incidences of cardiovascular events in patients who failed to achieve their respective treatment goals, on the other hand, were significantly higher than in patients who achieved them. These results indicate that strict treatment for elderly hypertensive patients may have little effect in enhancing the suppression of the onset of cardiovascular events as compared with mild treatment, although patients who have difficulties in achieving treatment goals should be given more aggressive treatment as a high-risk population.
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INTRODUCTION

Guidelines for the management of hypertension in the United States, Europe and Japan state that the treatment goal for blood pressure (BP) in elderly hypertensive patients should be below 140/90 mm Hg.[1–3] The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) was conducted because virtually no studies had been conducted previously to assess the benefits of maintaining BP below 140 mm Hg in these patients. JATOS was a prospective, randomized, open-label study with blinded assessment of end points. It was designed to compare the effects of 2 years of strict antihypertensive treatment to maintain systolic BP below 140 mm Hg (strict-treatment group) with those of mild treatment to maintain systolic BP at 140 to below 160 mm Hg (mild-treatment group) in elderly patients (65–85 years of age) with essential hypertension.[4] Final blood pressures (systolic/diastolic) were significantly lower in the strict-treatment group compared with the mild-treatment group (135.9/74.8 mm Hg *vs.* 145.6/78.1 mm Hg; $P<0.001$), but the incidences of the primary end point (combined incidence of cerebrovascular diseases, cardiac and vascular diseases, and renal failure) and secondary end points (total deaths and incidence of adverse events) were similar between the two groups, and the benefit of maintaining BP below 140 mm Hg in elderly hypertensive patients could not be demonstrated.[5] Intention-to-treat analysis of JATOS shows that the presence of patients in whom BP could not be maintained within the range of target values in each group may be one of the reasons for the lack of significant differences in outcomes between the two treatment groups. Therefore, the per-protocol analysis of JATOS was performed to evaluate the benefits of maintaining BP below 140 mm Hg in elderly hypertensive patients who could maintain BP within the range of target values.

METHODS

Study design

JATOS was a prospective, randomized, open-label study with blinded assessment of end points. It was designed to compare the effects of 2 years of strict antihypertensive treatment to maintain systolic BP below 140 mm Hg (strict-treatment group) with those of mild treatment to maintain systolic BP below 160 mm Hg but at $\geqslant$140 mm Hg (mild-treatment group) in elderly

[1]Department of Geriatric Medicine and Nephrology, Osaka University Graduate School of Medicine, Osaka, Japan; [2]Japan Physicians Association, Tokyo, Japan and [3]Yokohama City University and Yokohama Seamen's Insurance Hospital, Yokohama, Japan
Correspondence: Dr H Rakugi, Department of Geriatric Medicine and Nephrology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, B6, Suita, Osaka 565-0871, Japan.
E-mail: rakugi@geriat.med.osaka-u.ac.jp
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patients (65–85 years of age) with essential hypertension. The baseline drug was efonidipine hydrochloride (efonidipine), a long-acting dihydropyridine calcium antagonist.[6,7]

As the protocol of JATOS stipulated a period of about 3 months to lower BP to a desired level, patients in this study were followed up for the period from the fourth month of treatment to the end of the study, and those who completed the study before the fourth month were excluded. This study analyzed data of patients in whom the average of measurements of systolic BP (mean systolic BP) during the follow-up period from the fourth month of treatment to the end of the study was within the range of target values. The percentage of patients who achieved the treatment goal was 53.8% (1191 of 2212) in the strict-treatment group (strict-TA group, strict-target BP achieved group) and 69.4% (1531 of 2206) in the mild-treatment group (mild-TA group, mild-target BP achieved group) (Figure 1). The incidences of the primary end point in patients who failed to achieve the treatment goal were additionally analyzed.

The design and principal results of JATOS have been previously reported.[4,5] BP was measured at least twice per visit by the auscultatory method, using a sphygmomanometer with the patients in the sitting position after 5–10 min of rest. BP measurements were averaged for each visit and the pulse rate was also recorded. The primary end point was the combined incidence of cerebrovascular diseases (cerebral hemorrhage, cerebral infarction, transient ischemic attack and subarachnoid hemorrhage), cardiac and vascular diseases (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 per 100 ml or higher).

Statistical analysis

Measured variables were expressed as percentages or means ± s.d. We compared the means of continuous variables using Student's *t*-test and their proportions using a χ^2-test. The cumulative incidence rates were estimated by the Kaplan–Meier method and compared using a log-rank test. The contribution to the primary end point of risk factors, such as age, sex, enlarged heart or left ventricular hypertrophy, previous cardiovascular disease, diabetes mellitus, dyslipidemia, renal disease or previous treatment, was evaluated with the use of Cox proportional hazards regression model. All tests were two sided, and the significance level was set at 5%.

RESULTS

Baseline characteristics

As shown in Table 1, the mean ages of patients were 73.3 and 73.7 years, mean systolic/diastolic BPs at study entry were 170.5/89.2 mm Hg and 171.1/89.0 mm Hg, and mean pulse rates were 72.5 and 71.8 beats per minute in the strict-TA and mild-TA groups, respectively. There were no significant differences between the two groups. The percentages of patients with previous treatment for

Table 1 Baseline characteristics

n *(%)*	*Strict-TA* n=*1191*	*Mild-TA* n=*1531*	P-*value*
Male	455 (38.2)	575 (37.6)	0.73
Age (years)	73.3 ± 5.2	73.7 ± 5.2	0.06
Systolic blood pressure (mm Hg)	170.5 ± 9.0	171.1 ± 9.3	0.09
Diastolic blood pressure (mm Hg)	89.2 ± 9.1	89.0 ± 9.1	0.54
Heart rate (per min)	72.5 ± 10.4	71.8 ± 10.5	0.10
Current smoking	146 (12.3)	200 (13.1)	0.53
Diabetes mellitus	129 (10.8)	178 (11.6)	0.52
Dyslipidemia	617 (51.8)	782 (51.1)	0.701
Renal disease	89 (7.5)	136 (8.9)	0.19
Cardiomegaly[a]	544 (45.7)	777 (50.8)	0.01
Past history of cerebrovascular disease	49 (4.1)	61 (4.0)	0.87
Past history of cardiovascular disease	35 (2.9)	31 (2.0)	0.12
Past history of hypertensive treatment	655 (55.0)	987 (64.5)	<.0001
Previous antihypertensive drug treatment	583 (49.0)	876 (57.2)	<.0001
ACE inhibitors or ARBs	367 (30.8)	532 (34.7)	0.03
Ca antagonists except for efonidipine	256 (21.5)	415 (27.1)	0.001
Adrenoceptor-blocking drugs	61 (5.1)	114 (7.4)	0.01
Diuretics	42 (3.5)	54 (3.5)	1.00

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; mild-TA, mild-target BP achieved group; strict-TA, strict-target BP achieved group.
[a]Cardiac enlargement diagnosed with a cardiothoracic ratio of >50% on a chest X-ray film and/or left ventricular hypertrophy diagnosed with electrocardiography.

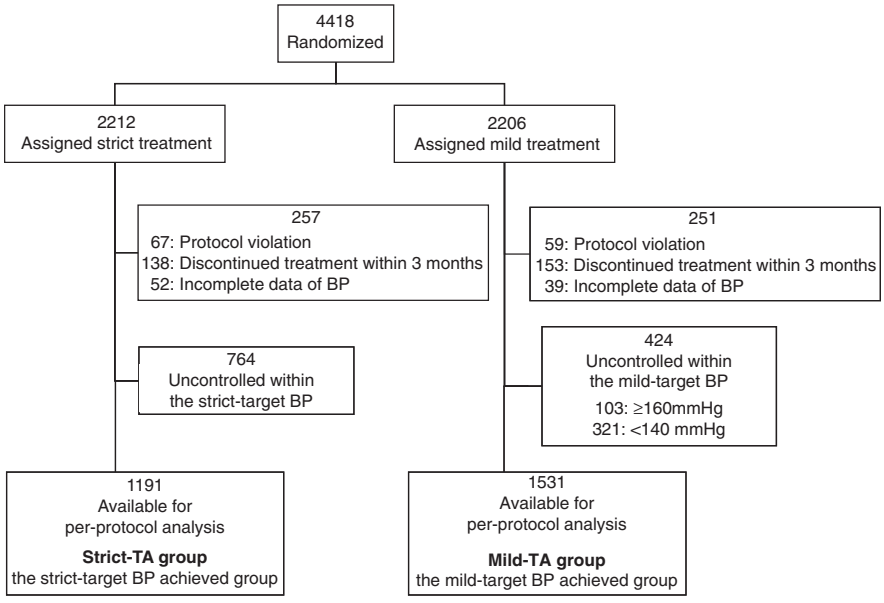

Figure 1 Allocation of subjects.

hypertension, enlarged heart or left ventricular hypertrophy, and previous antihypertensive treatment were higher in the mild-TA group.

BP and heart rate

As shown in Figure 2, BP decreased significantly after 1 month of treatment in both BP achieved groups. Systolic and diastolic BPs after 24 months were 132.3 ± 9.0 mm Hg and 74.0 ± 8.6 mm Hg in the strict-TA group, and 146.6 ± 9.6 mm Hg and 78.3 ± 8.6 mm Hg in the mild-TA group, respectively. That is, systolic and diastolic BPs were lower by 14.3 mm Hg and 4.3 mm Hg, respectively, in the strict-TA group than in the mild-TA group at the end of the study.

The heart rates at the start and end of the study were 72.5 ± 10.4 and 70.9 ± 9.2 ($P<0.0001$) in the strict-TA group and 71.8 ± 10.5 and 71.0 ± 9.4 ($P=0.096$) in the mild-TA group, respectively, indicating a significant decrease in the heart rate in the strict-TA group. Reflex tachycardia resulting from antihypertensive treatment was not noted in either group.

At the end of the study, a combination of antihypertensive drugs was used in 652 of 1191 patients (54.7%) in the strict-TA group and 821 of 1531 patients (53.6%) in the mild-TA group, and there were no significant differences between the two groups ($P=0.56$). Among concomitant drugs, those affecting the renin–angiotensin system (46.8 *vs.* 44.8%, $P=0.31$) and diuretics (17.5 *vs.* 14.9%, $P=0.07$) were most frequently used, and there were no significant differences between the two groups.

Incidence of primary end points and mortality

The incidence of the primary end points was similar between the two groups, with 2.10% ($n=25$, 11.1/1000 patients per year) in the strict-TA group and 2.48% ($n=38$, 13.2/1000 patients per year) in the mild-TA group (Table 2). The incidences of cerebrovascular events, cardiac and vascular events, and renal events were also similar between the groups. There was no difference in mortality between the strict-TA group (0.30%, $n=3$) and mild-TA group (0.20%, $n=3$). Heart disease was the most common cause of death. The cumulative incidence rates showed no difference between the strict-TA and mild-TA groups (Figure 3). The hazard ratio with Cox model, adjusted for age, sex, presence of previous treatment for hypertension, and presence of cardiomegaly, was 0.88 (95% confidence interval 0.53–1.46, $P=0.62$).

Comparison between target-unachieved and target-achieved patients

The incidence of primary composite end points in patients in whom levels of target-achieved BP were higher than the upper limit of the treatment goal was 4.97% (38/764) in the strict group and 8.74% (9/103) in the mild group. Although the number of patients in whom the levels of BP was ⩾160 mm Hg was small in the strict group, the incidence of primary end points was 14.29% (12/84). Primary events in target-unachieved patients were significantly higher than those in target-achieved patients in both strict-TA and mild-TA groups (both $P<0.0001$). These differences were still statistically significant even after adjustment with confounding factors: baseline BP, past history of hypertension, current smoking, dyslipidemia, diabetes mellitus, renal disease and cardiomegaly (both $P=0.002$). Basal characteristics of target-unachieved patients ($n=867$) compared with those in target-achieved patients ($n=2722$) showed higher level of systolic BP (173.9 ± 10.8 *vs.* 170.8 ± 9.2 mm Hg, $P<0.0001$), and higher prevalence of previous treatment of hypertension (71.2 *vs.* 60.3%, $P<0.0001$), dyslipidemia (55.2 *vs.* 51.4%, $P=0.048$), current smoking

Table 2 Number of events from the primary end point and its components

	Morbidity		
Events	*Strict-TA (n=1191)*	*Mild-TA (n=1531)*	*P-value*
Primary end point	25 (2.10)	38 (2.48)	0.56[a]
Per 1000 patient-years (95% CI)	11.1 (7.2–16.4)	13.2 (9.4–18.1)	0.50[b]
Cerebrovascular disease	14 (1.18)	19 (1.24)	0.86[a]
Per 1000 patient-years (95% CI)	6.2 (3.4–10.5)	6.6 (4.0–10.3)	0.87[b]
Cardiac and vascular disease	8 (0.67)	14 (0.91)	0.47[a]
Per 1000 patient-years (95% CI)	3.6 (1.5–7.0)	4.9 (2.7–8.2)	0.48[b]
Renal failure	3 (0.25)	5 (0.33)	0.92[a]
Per 1000 patient-years (95% CI)	1.3 (0.3–3.9)	1.7 (0.6–4.1)	0.72[b]

Abbreviations: BP, blood pressure; mild-TA, mild-target BP achieved group; strict-TA, strict-target BP achieved group.
[a]Log-rank test.
[b]χ^2-test.

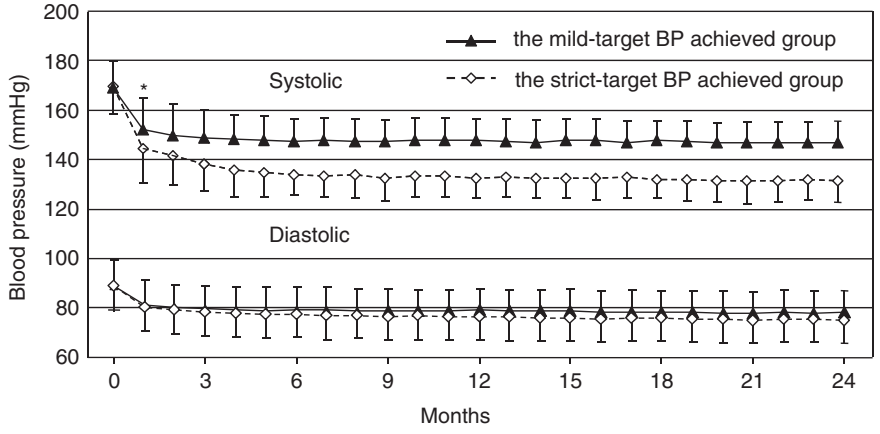

Figure 2 Blood pressure (BP) during treatment. *Intergroup differences were significant from this point ($P<0.0001$). The final achieved BP in the strict-TA group and that in the mild-TA group was 132.3 ± 9.0/74.0 ± 8.6 mm Hg and 146.6 ± 9.6/78.3 ± 8.6 mm Hg, respectively. Systolic and diastolic BP was reduced by a mean of 38.2/15.2 mm Hg in the strict-TA group and by 24.5/10.7 mm Hg in the mild-TA group. Between-group differences were 14.3 mm Hg systolic and 4.3 mm Hg diastolic (both $P<0.0001$). Strict-TA, strict-target BP achieved group; mild-TA, mild-target BP achieved group.

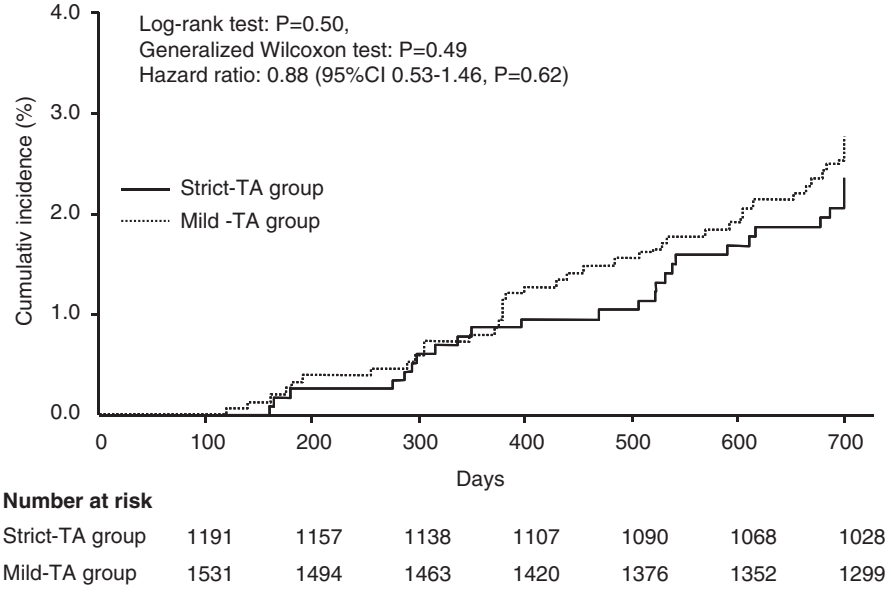

Figure 3 Kaplan–Meier time-to-event analyses for the primary end point. The cumulative rates of morbidity from the primary end point were similar in the two groups. To estimate cumulative incidence rates of morbidity, data up to 2 years after administration were used. Hazard ratio was calculated by Cox proportional hazards regression model with adjustment of age, sex, previous treatment for hypertension and cardiomegaly. Strict-TA, strict-target blood pressure (BP) achieved group; mild-TA, mild-target BP achieved group.

Table 3 Incidences of the primary end point and its components in relation to age and treatment

	Below 75 years old			*⩾75 years old*			
	Strict-TA (n=*710*)	*Mild-TA* (n=*875*)	P-*value*[a]	*Strict-TA* (n=*481*)	*Mild-TA* (n=*656*)	P-*value*[a]	P-*value for the interaction*[b]
Primary end point	11 (1.55)	19 (2.17)	0.43	14 (2.91)	19 (2.90)	0.86	0.66
Cerebrovascular disease	6 (0.85)	9 (1.03)	0.69	8 (1.66)	10 (1.52)	0.85	0.68
Cardiac and vascular disease	3 (0.42)	7 (0.80)	0.33	5 (1.04)	7 (1.07)	0.97	0.50
Renal disease	2 (0.28)	3 (0.34)	0.85	1 (0.21)	2 (0.30)	0.23	0.41

Abbreviations: BP, blood pressure; mild-TA, mild-target BP achieved group; strict-TA, strict-target BP achieved group.
[a]Log-rank test.
[b]Significance test of interaction term in Cox regression with treatment, age, sex, and interaction between treatment and age as covariates.

(16.4 *vs.* 12.7%, *P*=0.006), diabetes mellitus (13.8 *vs.* 11.3%, *P*=0.04), cardiomegaly (54.6 *vs.* 48.5%, *P*=0.002) and renal disease (11.9 *vs.* 8.3%, *P*=0.001).

Analysis of primary end points in elderly patients under and more than 75 years of age

In the strict-TA and mild-TA groups, the incidences of primary end point in elderly patients under 75 years of age were 1.55 and 2.17%, and those in patients more than 75 years of age were 2.91 and 2.90%, respectively. There were no interactions between age and treatment for the primary end points (Table 3). The hazard ratio of treatment (strict *vs.* mild) was 1.31 (*P*=0.48, 95% confidence interval: 0.62–2.78) in patients under 75 years of age, whereas it was 1.04 (*P*=0.91, 95% confidence interval: 0.52–2.09) in patients more than 75 years of age.

Incidence of adverse events

The incidence of adverse events was 19.8% (236/1191) in the strict-TA group and 20.8% (319/1531) in the mild-TA group, and there was no difference between the groups (*P*=0.51). The incidence of each adverse event was not more than 0.7%. In the strict-TA and mild-TA groups, the incidences of fracture, dizziness and light-headedness were 0.5 *vs.* 0.6%, 0.1 *vs.* 0.5%, and 0.3 *vs.* 0.3%, respectively, and there were no significant differences between the groups.

DISCUSSION

The present subanalysis of JATOS, per-protocol analysis, confirmed the result of intention-to-treat analysis, which showed that there was no significant difference in outcomes between strict treatment and mild treatment despite the significant difference in final BP. To be precise, the risk reduction in cardiovascular events by strict treatment compared with mild treatment was 12%, but it was not statistically significant. The final achieved BPs in the strict-TA and mild-TA groups were 132.3/74.0 and 146.6/78.3 mm Hg, respectively, and the differences were 14.3/4.3 mm Hg in the present per-protocol analysis. According to meta-analyses indicating that the risk reduction was associated with the BP reduction even in the elderly patients, this 14.3 mm Hg differences in systolic BP would cause more than 30% risk reduction in cardiovascular events.[8,9] Taken together, it may be suggested that once the systolic BP is reduced to the level of 147/78 mm Hg on average (achieved BP in the mild-TA group), lowering it further to below 140 mm Hg is of little clinical significance. It may be important that this BP level is compatible with the treatment goal,

<150/80 mm Hg, in the active treatment group of the Hypertension in the Very Elderly Trial, which clearly demonstrated the importance of lowering the systolic BP to at least below 150 mm Hg even in patients more than 80 years of age.[10]

Conversely, it is also necessary to consider the possibility that lowering BP further, to below levels in the strict-TA group, may be more effective in suppressing the onset of events. In the recently reported cardiovascular effects of systolic blood pressure control (Cardio-Sis) study, the rate of composite cardiovascular end points in nondiabetic patients with hypertension (average age: 67 years) was significantly lower in the tight control group (a treatment goal of <130 mm Hg) compared with that in the usual control group (a treatment goal of <140 mm Hg).[11] The achieved BP in the tight control group, however, was similar to that in the strict-TA group in the present per-protocol subanalysis of JATOS. Therefore, it cannot be concluded that lowering systolic pressure to <130 mm Hg is always beneficial.

Another important message of this subanalysis is the high incidence of cardiovascular events in patients who did not achieve the target BP in both strict-treatment and mild-treatment groups. In particular, patients in whom BP remained ⩾160 mm Hg after treatment demonstrated high incidence for cardiovascular diseases. Some of these target-unachieved patients may have presented more risk factors of cardiovascular diseases or have refractory hypertension due to advanced atherosclerosis at baseline. Therefore, it is emphasized that in the clinical setting, patients in whom BP does not respond well to the administration of recommended doses of antihypertensive agents need to be treated more aggressively and with greater care.

Study limitations

From the results of the per-protocol analysis of this study conducted as a subanalysis of JATOS, it cannot be concluded that the mild-treatment goal is simply the best choice for elderly hypertensive patients. One reason is that high-risk patients who could not achieve target BP were excluded from the study. Another reason is that the statistical power of the analysis is low. However, whether an extensive study should be conducted to solve this problem remains questionable. In this subanalysis, the difference in the incidence of events among patients who achieved the assigned treatment goal was 0.4%. To detect this level of difference statistically, 44 000 subjects (two-sided significance level: 0.05 with 80% power) are required. Even if a study with a sufficient sample size was to be conducted, a number needed to treat of 250 would be clinically of little meaning. Therefore, it is more practical to perform meta-analyses, including ongoing similar studies such as Valsartan in Elderly Isolated Systolic Hypertension (VALISH),[12] which compared groups of elderly hypertensive patients in terms of treatment goals.

The present per-protocol analysis excluded patients who completed the study within 3 months after randomization because the study protocol stipulated a period of about 3 months to lower BP to a desired level. Number of excluded patients because of this reason was 138 in the strict-treatment group and 153 in the mild-treatment group. There was no statistical difference in event rates between two groups (13.8% in the strict-treatment group, 12.4% in the mild-treatment group). Therefore, our conclusion would be affected not so much by control status of BP within 3 months after randomization.

In conclusion, for the treatment of elderly hypertensive patients, a reduction of at least 25/10 mm Hg from about 170/90 mm Hg seems very likely to result in an improvement in prognosis. In patients who easily achieved a goal of below 140 mm Hg in accordance with the guidelines, BP should be controlled to between 132 mm Hg (achieved BP in the strict-TA group) and 147 mm Hg (achieved BP in the mild-TA group), taking into account the instability of BP, adverse reactions of drugs and the cost. Patients who have difficulties in achieving treatment goals should be treated as a high-risk population and should be given more aggressive treatment.

CONFLICT OF INTEREST

Drs Ogihara, Goto and Ishii report receiving advisory board fees from Shionogi Co. Ltd, Osaka. The remaining authors declare no conflict of interest.

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