Original Article

Impact of Blood Pressure Control on Cardiovascular Events in 26,512 Japanese Hypertensive Patients: The Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) Study, a Prospective Nationwide Observational Study

Kazuaki SHIMAMOTO[1)], Toshiro FUJITA[2)], Sadayoshi ITO[3)], Hiroaki NARITOMI[4)], Toshio OGIHARA[5)], Kazuyuki SHIMADA[6)], Heizo TANAKA[7)], and Nobuo YOSHIIKE[8)]

The Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study was performed to investigate the relationship between blood pressure (BP) and development of stroke or myocardial infarction (MI) in Japanese hypertensive patients. A total of 26,512 hypertensive patients (mean age: 62.2 years, 43.9% men) were analyzed. All patients received open-labelled losartan for a maximum of 5 years. Endpoints were stroke, MI including sudden cardiac death, and all cardiovascular (CV) events (stroke and MI). The mean observation period was 3.0 years. The mean baseline systolic/diastolic BP was 165.8/94.8 mmHg and decreased to 141.6/82.0 mmHg during treatment. The incidences of stroke, MI, and total CV events were 3.90, 1.02, and 4.92 per 1,000 patient-years, respectively. Aging, diabetes, a history of CV disease, and smoking were independent risk factors for CV events. The risk of all CV events was positively related to BP level during treatment, and increased significantly when the BP exceeded 140/90 mmHg. Age was a strong contributor to CV events, but about a half of the very elderly patients (≥85 years, *n*=692) had a BP below 140/90 mmHg during treatment and significantly fewer events occurred in these patients than in those with a BP of 140/90 mmHg or higher. These results suggest that BP should be below 140/90 mmHg in Japanese patients with hypertension for reducing the risk of CV events. BP was controlled below 140/90 mmHg in a half of the very elderly hypertensive patients in this study, and these patients also had a lower incidence of CV events. (*Hypertens Res* 2008; 31: 469–478)

***Key Words*: losartan, hypertension, blood pressure, cardiovascular disease, observational study**

From the [1)]Sapporo Medical University School of Medicine, Sapporo, Japan; [2)]University of Tokyo, Graduate School of Medicine, Tokyo, Japan; [3)]Tohoku University, Graduate School of Medicine, Sendai, Japan; [4)]National Cardiovascular Center, Suita, Japan; [5)]Osaka University, Graduate School of Medicine, Suita, Japan; [6)]Jichi Medical University School of Medicine, Shimotsuke, Japan; [7)]Koshien University, Takarazuka, Japan; and [8)]National Institute of Health and Nutrition, Tokyo, Japan.

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Address for Reprints: Kazuaki Shimamoto, M.D., Sapporo Medical University School of Medicine, 16, Minamiichijo Nishi, Chuo-ku, Sapporo 060–0061, Japan. E-mail: simamoto@sapmed.ac.jp

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Introduction

Antihypertensive therapy is essential to reduce the occurrence of cardiovascular (CV) events and mortality. Many large-scale studies of various antihypertensive medications, such as Ca channel blockers (CCBs), angiotensin receptor antagonists (ARBs) and diuretics, have shown that reduction of the blood pressure (BP) is essential to prevent CV events (*1–4*). Based on these results, guidelines for the clinical management of hypertension such as Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004) (*5*) and the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (*6*) have been established and are being used in the daily management of hypertension. According to these guidelines, the optimal target BP level for uncomplicated hypertension is defined as lower than 140/90 mmHg regardless of age, although an interim level of 150/90 mmHg for elderly patients aged 75 or older is recommended for the purpose of careful and gradual reduction to the optimal target level in the Japanese guidelines.

The optimal target BP levels based on the risk factors are also established in these guidelines, but these levels are mainly derived from studies performed in Western countries, which enrolled patients who met the various inclusion and exclusion criteria. In clinical practice, clinicians prescribe antihypertensive medications daily for patients with various background factors, such as age, complications, and history of CV events that differ from those of the subjects in controlled clinical trials. Therefore, it is very important to assess the influence of various backgrounds as risk factors on antihypertensive therapy and the risk of future CV events. Several studies of Japanese hypertensive patients have already been conducted, but these studies have mainly assessed small cohorts in specific rural areas. Information from large-scale studies under daily clinical practice is limited.

The Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study was initiated in 2000 as a large-scale observational study of losartan therapy. This study was designed to enroll 30,000 patients with hypertension throughout Japan, and the subjects were treated with losartan on an open-label basis mainly at a daily dose of 50 mg under common clinical management for a maximum of 5 years (*7*). The present study focuses on the relation between BP control and the incidence of CV events in not only the overall patient group but also elderly or diabetic patients of the J-HEALTH cohort.

Methods

Subjects

The eligible patients were hypertensive men or women aged 20 years or older who had not taken any antihypertensive agents within the previous 1 month. Patients who had previously been treated with losartan were excluded. Each patient was informed of the purpose and methods of the study, as well as the measures taken for protection of privacy, before they were enrolled. Patients gave verbal informed consent and then underwent a complete review of their medical history, as well as physical examination and laboratory evaluation. The methods were previously reported in detail (*7*).

Treatment and Monitoring

The patients were initially treated with losartan at a dose of 25–50 mg once daily, which was increased up to 100 mg once daily if necessary. Addition of other antihypertensive agents was allowed from 3 months after the start of losartan therapy, if required. No restrictions were placed on the treatment of complications.

The clinic BP was measured by the usual method at each institution. At each time of measurement, one clinic BP value was reported at the discretion of the physician. After starting losartan therapy, the clinic BP value was measured every 3 months for analysis of the clinic BP values during treatment. Standard laboratory tests were performed every 6 months with the routine methods used at each institution. To assess complications and the medical history, physicians judged the existence of disease indicated in the registration form at their discretion.

In addition, the patients who were on drug treatment for hyperlipidemia or diabetes mellitus and met the definition of either disease indicated in the relevant guidelines were defined as having hyperlipidemia or diabetes. Hyperlipidemia also included at least one of the dyslipidemic constituents, such as total cholesterol (TC) $\geq$220 mg/dL, low-density lipoprotein-cholesterol (LDL-C) $\geq$140 mg/dL, high-density lipoprotein-cholesterol (HDL-C) $<$40 mg/dL, and triglycerides (TG) $\geq$150 mg/dL. Diabetes mellitus was defined as a history of diabetes mellitus, or fasting blood glucose (FBG) $>$126 mg/dL and/or HbA1c $>$6.5%.

Evaluation of Endpoints

The primary endpoint of the study was a composite of CV events including fatal or non-fatal stroke (new occurrence or recurrence of cerebral hemorrhage, cerebral infarction, or subarachnoid hemorrhage diagnosed on the basis of typical clinical symptoms persisting for more than 24 h and/or computerized tomography/magnetic resonance imaging findings), transient ischemic attack (TIA) defined as a focal neurological deficit presumed to be vascular in origin persisting for less than 24 h, fatal or non-fatal myocardial infarction (MI) (new occurrence or recurrence) diagnosed on the basis of typical clinical symptoms, electrocardiogram changes and elevation of cardiac enzymes, or sudden cardiac death. In addition, the independent event classification committee reviewed adjudi-

Table 1. Baseline Characteristics of the Patients

	Total (n=26,512)	Male (n=11,638)	Female (n=14,874)
Age (years)	62.2±12.0	59.9±12.0	64.0±11.8
Clinic SBP (mmHg)	165.8±17.1	165.0±16.8	166.5±17.2
Clinic DBP (mmHg)	94.8±11.5	96.7±11.4	93.3±11.4
BMI (kg/m^2)	24.1±3.5	24.3±3.3	23.9±3.7
Alcohol drinking (%)	38.8	68.1	16.0
Smoking habit (%)	25.1	44.9	9.7
Complications			
Hyperlipidemia (%)	38.3	36.0	40.2
Diabetes mellitus (%)	12.6	15.3	10.5
Hyperuricemia/Gout (%)	10.6	19.8	3.5
Cardio-/cerebrovascular disease (%)	10.5	10.9	10.2

Data are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index. Alcohol drinking: ≥3 times/week and ≥200 mL/time (1 middle-size bottle of beer or 2 glasses of diluted whiskey with water).

cated endpoint events on the basis of all available information documented in the case report form by the physicians.

Statistical Analysis

For the present analysis, variables were compared using the *t*-test, the χ^2 test, or analysis of variance (ANOVA). Results were expressed as the mean±SD, and differences were considered statistically significant at $p<0.05$. Analysis of the overall results was based on survival analysis. Subgroups were stratified by BP values measured during treatment. Relationships between the endpoints and BP values or prognostic factors were assessed by using the Cox proportional hazards model. Statistical analyses were conducted with the SAS package (Version 8.02; SAS Institute Inc., Cary, USA).

Results

Subjects and Follow-Up

Out of 31,048 patients enrolled in the study, 4,536 patients were excluded because of protocol violations or lack of data, and thus a total of 26,512 patients were used to investigate the relationship between BP and stroke or MI. The mean follow-up period was 3.0 years. The clinical characteristics of the 31,048 enrolled patients at baseline have already been reported (*7*), and the characteristics of the 26,512 patients analyzed in the present study are shown in Table 1. The profile of these patients was similar to that of the total group of all enrolled patients. Their mean age was 62.2±12.0 years and the mean baseline BP was 165.8±17.1/94.8±11.5 mmHg. Major complications were hyperlipidemia (38.3%) and diabetes (12.6%). The concomitant antihypertensive medications have been described elsewhere (*8*). In brief, 41% of the subjects were taking two or more antihypertensive medications. Their BP decreased to 136.9±13.2/79.2±9.6 mmHg after 60 months.

Table 2. Incidence of Stroke and MI during Treatment

Events	No. of events	Incidence
Stroke	307	3.90
Cerebral infarction	205	
Transient ischemic attack	19	
Cerebral hemorrhage	55	
Subarachnoid hemorrhage	20	
Unclassified stroke	8	
MI	80	1.02
Total	387	4.92

No. of patients: 26,512. Incidence: events/1,000 patient-years. MI, myocardial infarction including sudden cardiac death.

Incidence of Stroke and MI, and Risk Factors for Stroke and MI

During the follow-up period, cerebrovascular events (stroke or TIA) and MI occurred in 307 and 80 patients, respectively. The incidences of stroke or TIA and MI during treatment were 3.90 and 1.02 per 1,000 patient-years, respectively (Table 2). The incidence of stroke was 4-fold higher than that of MI.

Next, we identified risk factors contributing to CV events by using the Cox proportional hazards model. The relative risk of CV events was highest at an age over 75 years (3.81), while current smoker status (1.88), CV disease (1.97), diabetes mellitus (1.51), and hyperuricemia (1.37) were also significant risk factors for the occurrence of CV events (Table 3).

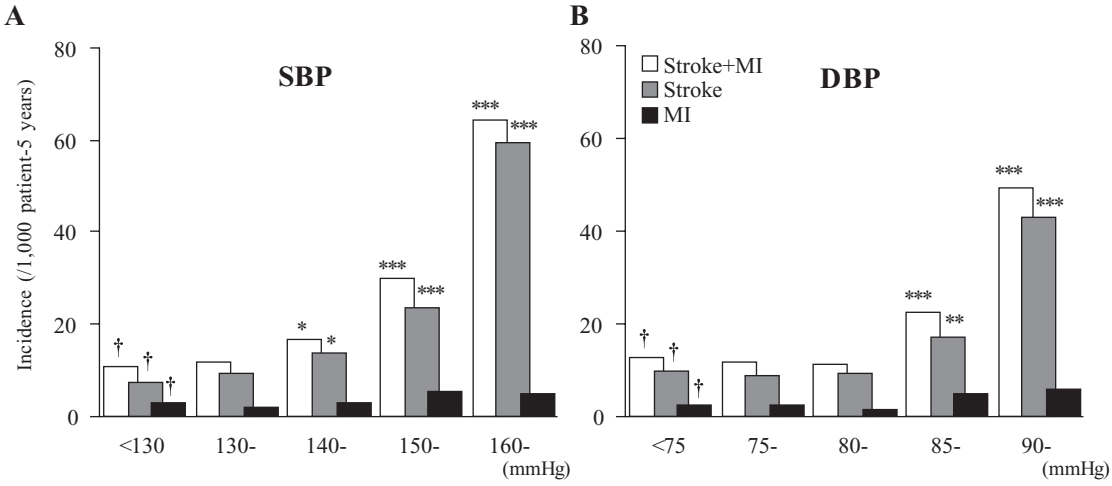
Relationship between BP and CV Events

The relationship between BP during treatment and the incidence of CV events is shown in Fig. 1. The incidence of CV events increased along with the BP and was significantly higher when the systolic BP (SBP) was higher than 140

Table 3. Relative Risk of Stroke and MI for Baseline Characteristics

	No. of patients	No. of events	RR (95% CI)	*p* value
Male	11,638	194	1.36 (1.07–1.73)	0.013
Age (years)				
<65	14,646	121	1.00 (Reference)	
65–74	7,690	131	1.93 (1.50–2.49)	<0.001
≥75	4,176	135	3.81 (2.92–4.97)	<0.001
Obesity (BMI ≥25 kg/m^2)	7,452	105	1.06 (0.84–1.35)	0.621
Smoking habit	6,666	128	1.88 (1.45–2.45)	<0.001
Alcohol drinking	10,295	149	0.85 (0.65–1.12)	0.247
Cardio-/cerebrovascular disease	2,793	97	1.97 (1.55–2.50)	<0.001
Hyperlipidemia	10,163	163	1.10 (0.89–1.35)	0.375
Diabetes mellitus	3,345	76	1.51 (1.17–1.94)	0.001
Hyperuricemia	2,812	55	1.37 (1.02–1.84)	0.036
Urinary protein ≥ +	1,390	32	1.46 (1.00–2.13)	0.053

RR, relative risk; MI, myocardial infarction including sudden cardiac death; BMI, body mass index; CI, confidence interval. Alcohol drinking: ≥3 times/week and ≥200 mL/time (1 middle-size bottle of beer or 2 glasses of diluted whiskey with water). Adjusted for sex, age, diabetes mellitus, cerebrovascular disease, cardiovascular disease, smoking habit and alcohol drinking.



Stroke + MI	31	100	125	77	54	91	77	71	71	77
Stroke	21	78	99	60	49	68	59	59	54	67
MI	10	22	26	17	5	23	18	12	17	10
No. of patients	3,263	9,401	8,645	3,442	1,761	4,803	5,535	7,269	4,726	4,179

Fig. 1. *Relationship between the incidence of cardiovascular events and (A) SBP or (B) DBP level during antihypertensive treatment. SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction including sudden cardiac death. The results were adjusted for sex, age, diabetes mellitus, cerebrovascular disease, cardiovascular disease, smoking habit and alcohol drinking. *p < 0.05, **p < 0.01, ***p < 0.001 vs. †reference category.*

mmHg and the diastolic BP (DBP) was higher than 85 mmHg than when BP was lower than 130/75 mmHg. The relationship between MI and BP was not clearly shown because of the low incidence of MI in the J-HEALTH cohort (Table 2). The incidence of stroke was strongly correlated with BP, and similar results were also observed when stroke was separated into cerebral hemorrhage and infarction (data not shown).

The relationship between BP and the incidence of CV events with and without various complications is shown in Table 4. In diabetic patients, the risk was increased at 130/85 mmHg or higher. In patients with a history of cerebrovascular or cardiovascular diseases, the incidence of stroke and MI

Table 4. Relationship between Blood Pressure during Treatment and Incidence of Stroke or MI in Patients with/without DM or CVD

	Non-DM				DM				Non-CVD				CVD			
	n	Events	Incidence	*p*	*n*	Events	Incidence	*p*	*n*	Events	Incidence	*p*	*n*	Events	Incidence	*p*
SBP (mmHg)																
<130	2,898	25	10.0	†	365	6	18.2	0.189	2,787	20	10.1	†	476	11	22.2	0.034
130–139	8,302	79	11.1	0.659	1,099	21	19.3	0.027	8,399	68	10.4	0.910	1,002	32	28.0	<0.001
140–149	7,559	99	15.9	0.04	1,086	26	25.3	<0.001	7,817	97	16.0	0.059	828	28	31.3	<0.001
150–159	2,923	60	28.5	<0.001	519	17	40.5	<0.001	3,110	61	29.1	<0.001	332	16	48.8	<0.001
≥160	1,485	48	74.8	<0.001	276	6	35.5	0.005	1,606	44	61.1	<0.001	155	10	111.4	<0.001
DBP (mmHg)																
<75	4,035	71	12.6	†	768	20	17.7	0.173	3,955	60	12.4	†	848	31	23.0	0.005
75–79	4,800	63	11.4	0.564	735	14	16.4	0.357	4,879	59	11.7	0.769	656	18	18.7	0.121
80–84	6,387	56	10.1	0.231	882	15	18.7	0.163	6,606	55	10.5	0.375	663	16	20.1	0.085
85–90	4,230	56	20.5	0.008	496	15	39.9	<0.001	4,359	50	18.6	0.038	367	21	60.4	<0.001
≥90	3,715	65	49.2	<0.001	464	12	56.7	<0.001	3,920	66	47.1	<0.001	259	11	79.6	<0.001
Total	23,167	311	16.6		3,345	76	24.9		23,719	290	16.3		2,793	97	31.7	

Incidence: events/1,000 patient-years. MI, myocardial infarction including sudden cardiac death; DM, diabetes mellitus; CVD, cardio-/cerebrovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure. Adjusted for sex, age, cerebrovascular disease, cardiovascular disease, smoking habit and alcohol drinking in non-DM and DM. Adjusted for sex, age, diabetes mellitus, smoking habit and alcohol drinking in non-CVD and CVD. †Reference category.

increased significantly at a much lower level of SBP than in those without a history of these diseases.

BP and CV Events in Elderly Patients

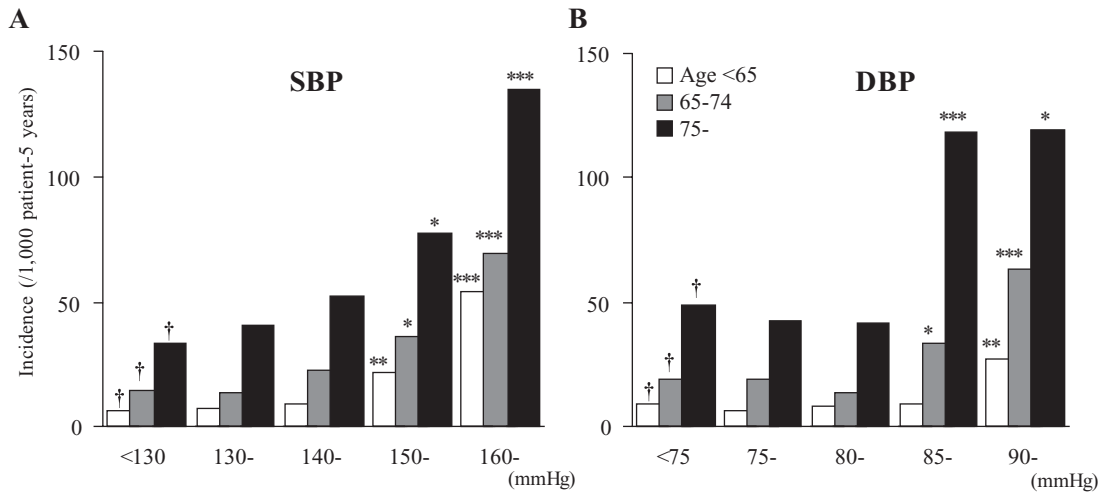
We also analyzed the relationship between BP during treatment and CV events in elderly patients. Patients were divided into three age groups, which were ≥75 years (oldest, $n=4,176$), 65 to 74 years (older, $n=7,690$), and <65 years (middle-aged, $n=14,646$) according to the age classification of the JSH guidelines. All CV events occurred in 121 patients of the middle-aged group, in 131 patients of the older group, and in 135 patients of the oldest group.

As shown in Fig. 2, the incidence of CV events was strongly related to BP in all three age groups. Compared with the DBP, control of the SBP had more influence on the increase of CV events. Figure 2 also demonstrates that the BP during treatment was more strongly related with the incidence of CV events in younger patients than in older patients. In patients under 65 years old, the incidence of CV events was 9-fold higher at an SBP >160 mmHg than at an SBP <130 mmHg. In contrast, the incidence was only 4 times higher in patients over 75 years old in the same comparison. However, the absolute incidence of CV events was much higher in the older age groups. The incidences of CV events per 1,000 patient-years during 5 years of follow-up at an SBP of less than 130 mmHg were 5.8 for the middle-aged (<65 years old), 14.4 for the older (≥65 to <75 years old) and 32.8 for the oldest group (≥75 years old).

A few clinical data in very elderly patients were available; however, we had 692 patients aged 85 or older in the present study. So we analyzed the incidence of CV events in this very elderly subset. BP was well-controlled below 140/90 mmHg in about half of these very elderly Japanese patients with hypertension, and the incidence of CV events was 2-fold higher in the group with a BP ≥140/90 mmHg (96.8 per 1,000 patient-years for 5 years of follow-up) than in those with a BP <140/90 mmHg (42.4 per 1,000 patient-years for 5 years of follow-up) (Fig. 3). As shown in Table 5, the baseline characteristics in these two groups were similar except for BP levels.

BP and Mortality

All-cause mortality was 5.67/1,000 patient-years (446/26,512), while cardiovascular morality (death from stroke, TIA, MI, or cardiac sudden death) was 0.8/1,000 patient-years (63/26,512). A J-shaped curve was observed between total mortality and SBP or DBP level. Cardiovascular mortality increased with an elevation of SBP, but a J-shaped relationship was observed between DBP and cardiovascular mortality (Table 6). Neither SBP nor DBP affected cancer mortality in this study (data not shown). Total mortality in patients with SBP <130 mmHg was significantly higher than that in patients with SBP 130–139 ($p<0.05$) and 140–149 ($p<0.05$) mmHg. No significant difference in total mortality was seen among patients with SBP <130, 150–159, and ≥160 mmHg. Cardiovascular mortality in patients with SBP ≥160 mmHg was 6-fold higher ($p<0.001$) than that in patients with SBP <130 mmHg. Total mortality was significantly lower in patients with DBP 75–79 mmHg ($p<0.01$), and significantly higher in patients with DBP ≥90 mmHg ($p<0.01$) than that in patients with DBP <75 mmHg. A similar pattern was



<65	Events	8	30	32	25	26	10	13	25	22	51
	Patients	1,836	5,222	4,709	1,849	1,030	1,302	2,375	4,206	3,553	3,410
65-74	Events	11	33	48	26	13	31	34	22	26	18
	Patients	898	2,810	2,579	978	425	1,928	2,069	2,100	1,029	564
≥75	Events	12	37	45	26	15	50	30	24	23	8
	Patients	529	1,369	1,357	615	306	1,573	1,091	963	344	205

Fig. 2. *Relationship between the incidence of cardiovascular events and (A) SBP or (B) DBP level during antihypertensive treatment in 3 different age groups. SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction including sudden cardiac death. The results were adjusted for sex, diabetes mellitus, cerebrovascular disease, cardiovascular disease, smoking habit and alcohol drinking. *p < 0.05, **p < 0.01, ***p < 0.001 vs. †reference category.*

observed between cardiovascular mortality and DBP levels. Most notably, the mean age in patients with DBP < 75 mmHg was approximately 15 years older than that in patients with DBP ≥ 90 mmHg (69.6 *vs*. 54.7 years old) (Table 6).

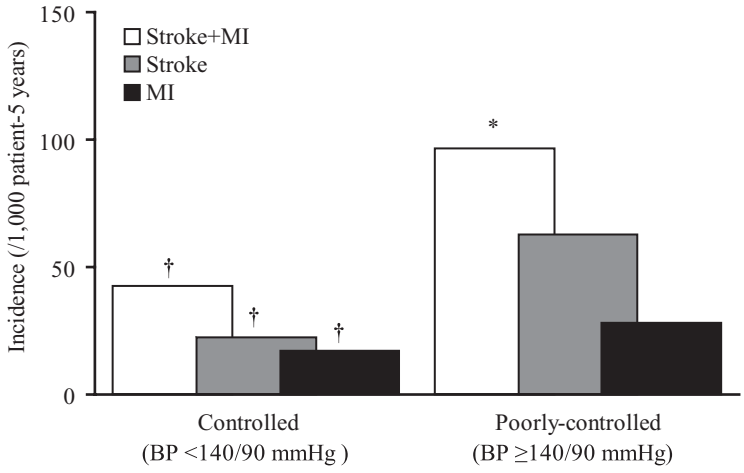
Discussion

The J-HEALTH study is a large-scale (30,000 patients) nationwide multicenter observational study that is providing valuable epidemiological information about Japanese patients with hypertension. We have previously reported on the clinical characteristics of the J-HEALTH cohort (*7*), which is a relatively young population with mild hypertension and few complications. Because our cohort was enrolled all over Japan (data not shown), the subjects are thought to be representative of the actual patients treated in daily Japanese clinical practice.

Staessen *et al*. performed a meta-analysis and concluded that lowering of the BP was needed for the prevention of CV events (*4*). Therefore, it is important to assess not only the BP at baseline, but also the mean reduction of BP during observation. Overall BP control in the J-HEALTH cohort ($n = 26,512$) has been described in detail elsewhere (*8*). We summarized the BP status at baseline and during observation for these patients in the present study. The baseline BP and the reduction of BP during losartan-based antihypertensive treatment were 165.8/94.8 mmHg and 24.4/13.9 mmHg, respectively. Baseline BP and the reduction of BP during the Losartan Intervention For Endpoint reduction (LIFE) (*2*), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (*1*), and the Controlled Onset Verapamil Intervention of Cardiovascular End Points studies (*9*) were, respectively, 174.3/97.9 and 30.2/16.8; 142/84 and 12.3/8.6; and 150.1/86.8 and 13.6/7.8 mmHg. Compared with these trials, our data suggest that the reduction of BP achieved by current clinical management in Japan is comparable with the results of other randomized controlled trials.

We investigated the incidence of CV events (stroke and MI). As shown in Table 2, CV events occurred in 387 patients (4.92/1,000 patient-years). Tanizaki *et al*. reported that the incidence of cerebral infarction was 6.4/1,000 patient-years for men and 3.4 for women in the Hisayama study (*10*). The incidence of stroke in the J-HEALTH study was similar to that in the Hisayama study. Regarding MI, its incidence in patients with hypercholesterolemia was 0.91/1,000 patient-years in the Japan Lipid Intervention Trial (J-LIT) study (*11*), and the incidence of MI was similar in the present study.

We also investigated the relative risk of CV events for each baseline characteristic. The results clearly demonstrated that well-known risk factors, such as age, smoking, a history of CV disease, diabetes mellitus, and hyperuricemia, were independent contributors to the development of CV events during



Stroke + MI	9		18	
Stroke	5		12	
MI	4		6	
No. of patients	310		382	

Fig. 3. *Incidence of cardiovascular events in patients aged 85 years or older. BP, blood pressure; MI, myocardial infarction including sudden cardiac death. The results were adjusted for sex, diabetes mellitus, cerebrovascular disease, cardiovascular disease, smoking habit and alcohol drinking. *p < 0.05 vs. †reference category.*

Table 5. Characteristics of Patients Aged 85 Years or Older

	Controlled BP <140/90 mmHg (*n*=310)	Poorly controlled BP≥140/90 mmHg (*n*=382)	*p* value
Baseline			
Male (%)	28.1	23.6	0.177
Age (years)	87.8±2.8	87.7±2.9	0.646
BMI (kg/m^2)	21.6±3.6	21.5±3.2	0.743
Smoking habit (%)	11.3	8.4	0.226
Alcohol drinking (%)	12.5	12.1	0.882
SBP (mmHg)	162.9±17.0	172.1±17.8	<0.001
DBP (mmHg)	85.7±12.2	86.9±12.4	0.231
Cardio-/cerebrovascular disease (%)	40.3	23.3	<0.001
Diabetes mellitus (%)	13.6	8.6	0.039
Hyperlipidemia (%)	28.7	27.8	0.780
During treatment			
SBP (mmHg)	131.3±6.8	151.5±10.3	<0.001
DBP (mmHg)	72.8±6.6	78.9±8.5	<0.001
Concomitant antihypertensive drugs (%)	42.9	49.0	0.113

Data are expressed as mean±SD. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index. Alcohol drinking: ≥3 times/week and ≥200 mL/time (1 middle-size bottle of beer or 2 glasses of diluted whiskey with water).

daily clinical practice in Japan. We could not demonstrate that hyperlipidemia was a significant independent risk factor for CV events. Although the J-HEALTH cohort had a high percentage of hyperlipidemic patients (38.3%), their mean serum TC level was not particularly high, possibly because lipid levels in the majority of patients were relatively low. This could be one of the reasons why we could not detect an influence of hyperlipidemia on CV events.

Although several interventional studies (*1*, *2*, *9*) have shown that BP control is beneficial for hypertensive patients, it is also valuable to demonstrate the influence of BP on CV events in actual clinical practice. The Hisayama study is a

Table 6. Incidence of Total and Cardiovascular Deaths in Patients Stratified with Blood Pressure during Treatment

	All patients (n=26,512)		Total death					Cardiovascular death (stroke and MI)				
	n	Age (years old)	Events	Incidence	Age (years old)	SBP/DBP (mmHg) (mean values during treatment)	PP (mmHg) (mean values during treatment)	Events	Incidence	Age (years old)	SBP/DBP (mmHg) (mean values during treatment)	PP (mmHg) (mean values during treatment)
SBP (mmHg)												
<130	3,263	61.9±12.4	67	45.4†	77.1±10.6	123.1/72.4	50.8	6	1.4†	71.3±11.0	126.0/76.7	49.3
130–139	9,401	62.0±11.8	143	33.7*	73.7±11.2	135.2/77.0	58.2	21	1.8	71.3±10.7	135.2/78.0	57.2
140–149	8,645	62.4±11.9	127	33.1*	74.1±11.0	144.4/78.0	66.4	12	1.2	77.1±8.5	145.7/77.8	67.9
150–159	3,442	62.6±12.4	85	61.0	75.1±12.3	154.3/81.6	72.7	14	3.8*	77.5±12.3	154.3/82.3	72.0
≥160	1,761	62.0±12.4	24	56.5	73.3±14.1	167.9/88.3	79.6	10	8.9***	67.4±15.7	167.6/89.7	77.9
DBP (mmHg)												
<75	4,803	69.6±10.5	160	38.1†	78.9±9.2	136.5/68.9	67.6	23	1.9†	77.0±8.9	140.3/69.9	70.4
75–79	5,535	65.4±11.0	92	26.0**	74.2±10.3	141.0/77.4	63.6	7	0.7*	76.0±9.6	143.8/78.4	65.4
80–84	7,269	61.8±11.4	100	31.1	73.4±10.9	141.7/82.2	59.5	8	0.9	73.3±13.1	149.0/83.4	65.6
85–90	4,726	58.3±11.0	58	42.0	72.0±13.4	146.8/86.9	59.9	14	3.5	73.9±13.2	147.0/86.9	60.1
≥90	4,179	54.7±11.1	36	62.8**	63.7±12.2	154.8/94.6	60.2	11	6.5**	62.5±11.6	154.2/94.8	59.4

Data are expressed as mean±SD. Incidence: events/1,000 patient-5 years. MI, myocardial infarction including sudden cardiac death; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure. Adjusted for sex, age, diabetes mellitus, cerebrovascular disease, cardiovascular disease, smoking habit and alcohol drinking. *p<0.05, **p<0.01, ***p<0.001 *vs.* †reference category.

long-term observational study of Japanese patients. It has demonstrated that a SBP >140 mmHg leads to a higher mortality rate compared with a BP ≤140 mmHg (*12*). Figure 1 indicates that there was a clear relation between BP during treatment and CV events, especially stroke, suggesting that the BP level should be less than 140/85 mmHg in Japanese with hypertension treated clinically. The lack of any association between BP and the incidence of MI may have been related to the low incidence of MI in our present population.

The target BP was examined in hypertensive patients with diabetes in the Hypertension Optimal Treatment study. The risk of CV events was significantly lower in patients with DBP ≤80 mmHg than in those with ≤85 mmHg or ≤90 mmHg (*13*). It was recently reported for Japanese patients that the risk of CV events was significantly decreased at BP ≤130/80 mmHg in hypertensive patients with diabetes in the J-LIT sub-analysis (*14*). As previously reported, the risk of CV events was lower at BP <130/85 mmHg in hypertensive patients with diabetes in the J-HEALTH cohort. These findings from J-HEALTH data support the JSH 2004 (*5*), the JNC 7 (*6*), the American Diabetes Association (*15*) and the European Society of Hypertension/European Society of Cardiovascular (ESH/ESC) (*16*) guidelines for treatment of hypertension accompanied with diabetes mellitus, which recommended that the target SBP/DBP be lower than 130/80 mmHg.

In the stratified analysis by age, the incidence of CV events in younger patients was more strongly influenced by BP elevation than that in elderly patients (Fig. 2). The Prospective Studies Collaboration has published a meta-analysis of individual data on BP and mortality for one million adults taken from 61 prospective observational studies (*17*). Although they analyzed mortality, BP was linearly related to vascular mortality without any evidence of a threshold. The American Heart Association Stroke Council has also stated that the contribution of BP to ischemic stroke decreases with age (*18*).

Although the reduction of relative risk by lowering BP was smaller in elderly patients than in younger patients in the present study, BP control remains very important for older patients because absolute incidence of CV events is much higher in the older age groups. Ferrucci *et al*. demonstrated the importance of treating isolated systolic hypertension in older patients with a high-risk profile in the Systolic Hypertension in the Elderly Program (SHEP) study, with the number of patients who need to be treated to prevent one CV event becoming progressively smaller for each higher CV risk quartile (*19*). Like the present study, other large-scale clinical trials have demonstrated the benefit of antihypertensive therapy in elderly patients (*20–23*). In addition, clinical guidelines for management of hypertension such as the JNC 7 (*6*) and ESH/ESC (*16*) state that the target BP should be below 140/90 mmHg regardless of age. However, there is little compelling evidence on which to base an optimal target BP for elderly persons (*24*). Detailed analysis of the Hisayama study has demonstrated that the incidence of vascular events increases with rising BP in each risk stratum among younger elderly subjects, but a similar relationship was not observed among the older elderly subjects (*25*). In the SHEP sub-analysis,

reduction of BP to lower than 140 mmHg increased events in elderly hypertensive patients whose BP at entry was higher than 160 mmHg (*26*).

It is still controversial whether BP control for very elderly patients is beneficial as indicated for middle-aged patients. Interestingly, BP was controlled below 140/90 mmHg in about half of our very elderly Japanese hypertensive patients (aged ≥85 years), and they had a low incidence of CV events even after adjustment for other risk factors such as diabetes and a history of cardio-/cerebrovascular disease. However, the baseline SBP was 10 mmHg lower in the BP-controlled group than in the BP-uncontrolled group. This difference of baseline BP may account in part for the difference in the incidence of CV events. The Hypertension in the Very Elderly Trial is ongoing as a prospective randomized open blinded end-points investigation of elderly (>80 years old) hypertensive patients with a target BP <150/80 mmHg (*27*). Preliminary results have demonstrated a reduction of stroke events and stroke mortality (*28*). In Japan, some intervention trials, such as the Japan Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients and the Valsartan in Elderly Isolated Systolic Hypertension study, have been conducted to assess optimal BP for the Japanese elderly patients with hypertension, and these results are expected to provide further information for the management of elderly patients with hypertension (*29, 30*). It will be necessary to investigate and discuss such findings from those interventional studies further before setting an optimal treatment for hypertension in elderly patients.

A J-shaped curve was observed between total mortality and SBP or DBP level in the J-HEALTH study. Death from stroke and MI increased with an elevation of SBP, but a J-shaped relationship was observed between DBP and cardiovascular mortality. Neither SBP nor DBP affected cancer mortality in this study. Boutitie *et al*. reported a J-shaped relationship between risk for death and SBP or DBP in their meta-analysis of seven randomized clinical trials (*31*). They concluded that the increased risk for death observed in patients with low BP was not related to antihypertensive treatment and was not specific to BP-related events. They speculated that the J-shaped curve was probably attributable to poor health conditions that led to low BP and an increased risk for death, and we tend to agree with this assessment. In addition, the mean age was higher in the group of patients with DBP <75 mmHg compared to those with DBP ≥75 mmHg in the present study. Elderly patients were frequently associated with low DBP and poor health conditions, probably resulting in an increased risk for death, although mortality was adjusted for age. We should note that one important limitation of this study was that it was not an intervention trial, so it was difficult to set an optimal BP level.

In summary, we demonstrated that classical risk factors, such as male gender, aging, diabetes mellitus, a history of cardio-/cerebrovascular disease, and smoking, are independent risk factors for future vascular events in daily clinical practice in Japan. After adjustment for these factors, there was a clear relation between BP control and CV events. The incidence of CV events was significantly increased in patients with BP ≥140/85 mmHg and in diabetic patients with BP ≥130/85 mmHg during treatment, suggesting the validity of adopting current clinical guidelines for Japanese hypertensive patients. Furthermore, about half of our very elderly patients with hypertension had a BP below 140/90 mmHg on losartan-based treatment, and these well-controlled very elderly patients had significantly fewer CV events than uncontrolled patients. In conclusion, there was a clear impact of BP during treatment on CV events in our Japanese hypertensive patients.

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Appendix

J-HEALTH Study Committees

Monitoring Committee: Takenori Yamaguchi (Chair), Tanenao Eto, Toshiharu Furukawa, Katsumi Yoshida.
Event Assessment Committee: Hiroaki Naritomi (Chair), Yoichiro Hashimoto, Uichi Ikeda, Mitsuaki Isobe, Toshio Kushiro, Ken Nagata, Kazuyuki Shimada, Takemori Yamawaki.
Safety Assessment Committee: Kendo Kiyosawa (Chair), Hiroshi Hirose, Sadayoshi Ito, Akinori Kasahara, Hiroshi Kawabe, Genjiro Kimura, Hirofumi Makino, Mitsuhiko Moriyama, Ikuo Saito, Hiromichi Suzuki, Eiji Tanaka.
Medical Expert Advisory and Publication Committee: Hiroaki Naritomi (Chair), Toshiro Fujita, Sadayoshi Ito, Toshio Ogihara, Kazuyuki Shimada, Kazuaki Shimamoto, Heizo Tanaka, Nobuo Yoshiike.
The Administrative Office: The Post-Marketing Surveillance Department of Banyu Pharmaceutical Co., Ltd. (Tokyo, Japan).

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