

*Original Article*

## Continued High Risk of Stroke in Treated Hypertensives in a General Population: The Jichi Medical School Cohort Study

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Although it is confirmed that antihypertensive treatment for hypertension (HT) reduces stroke, it is uncertain whether the risk of stroke in controlled hypertensives is as low as that in normotensives. To address this question, we examined the risk of stroke in hypertensives with or without antihypertensive treatment in the general population. A total of 11,103 men and women were enrolled in for this multi-center, population-based cohort study. Subjects were divided into three categories: normotensives (blood pressure <140/90 mmHg), treated hypertensives, and non-treated hypertensives (blood pressure  $\geq$ 140/90 mmHg without antihypertensive treatment). The treated hypertensives were divided into controlled and uncontrolled HT groups. The non-treated hypertensives were also divided into two groups: mild HT, and moderate or severe HT. The mean follow-up duration was 10.7 years. Risk of all stroke was significantly higher in the hypertensives than in the normotensives (treated HT: hazard ratio=3.00 in men and 3.34 in women, 95% confidence interval=2.00–4.51 in men and 2.29–4.87 in women; non-treated HT: 2.56, 1.83–3.57 in men and 1.93, 1.35–2.76 in women). Risk of stroke in controlled treated hypertensives was about three times as high as that in normotensives (2.96, 1.66–5.26 in men and 3.69, 2.20–6.17 in women). Risk of stroke was about 2.5 times higher in individuals with hyperglycemia than in those with normoglycemia among both treated hypertensive men and women. In conclusion, compared with normotensives, hypertensives of all categories had a significantly higher risk of stroke. Residual confounding might have affected the result that risk of stroke was higher in controlled treated HT than in non-treated mild HT. Moreover, it is important to control blood pressure and blood glucose in hypertensives in order to reduce the risk of stroke. (*Hypertens Res* 2008; 31: 1125–1133)

**Key Words:** hypertension, stroke, treatment, risk factor, cohort study

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This study was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by grants from the Foundation for the Development of the Community, Tochigi, Japan.

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Received August 10, 2007; Accepted in revised form January 30, 2008.

## Introduction

Hypertension (HT) is an important contributor to stroke risk. Many prospective studies of the association between blood pressure (BP) and stroke have been conducted in recent years. Lawes *et al.* (1) found that the association between BP and risk of stroke was continuous and log linear, and the same in five meta-analyses (2–6). The risk of stroke increased continuously above BP levels of approximately 115/75 mmHg. There is also extensive evidence of reduction in stroke risk with BP lowering in randomized controlled trials (RCTs) comparing antihypertensive drugs to a placebo or no treatment. However, BP control among hypertensive patients is often insufficient, and a considerable proportion of treated hypertensive patients do not achieve the target BP (7–13). Tight control of BP has been reported to reduce the risk of stroke and other cardiovascular diseases (CVD) in patients with HT and diabetes mellitus (DM) in an RCT (14). These findings showed that BP control is important in attempts to reduce the risk of stroke. Almgren *et al.* reported in their cohort of men that total incidence of stroke was double in treated HT compared with non-HT, and the incidence of stroke was not related to achieved BP (15). In their cohort study, Li *et al.* reported that the risk of stroke was higher in treated hypertensives than normotensives, and the additional impact of diabetes on the risk of stroke was greater in women than in men (16).

We reported BP categories and CVD risk factors in our previous cross-sectional analysis (17). Using the same Japanese population-based cohort, we here examined the risk of stroke with or without hypertensive treatment and with or without BP control, and the effect of various comorbidities on stroke in those under hypertensive treatment. We also examined the association between BP categories and risk of stroke, and examined differences in stroke risk between men and women with hyperglycemia, which was the only comorbidity found to have a significant effect on stroke.

## Methods

### Subjects

Data were obtained between April 1992 and July 1995 in 12 districts in rural areas of Japan as part of the Jichi Medical School (JMS) Cohort Study. Details of the JMS Cohort Study, which was a population-based prospective cohort study begun in 1992 to clarify the risk factors of CVD, have been reported elsewhere (18, 19). The total number of participants in the JMS Cohort Study was 12,490 (including both men and women). Subjects who declined to be followed-up ( $n=6$ ), or those who were unable to provide sufficient information about their BP and past medical history of hypertension were excluded. A total of 11,103 subjects were thus enrolled in for the present study (4,318 men and 6,785 women).

The normotensives were defined as subjects with systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg. Treated hypertensives were defined as subjects receiving antihypertensive treatment irrespective of their current BP levels, and non-treated hypertensives were defined as subjects with SBP  $\geq$ 140 mmHg and/or DBP  $\geq$ 90 mmHg without antihypertensive treatment. Controlled treated HT (controlled HT) subjects were defined as those with SBP <140 mmHg and DBP <90 mmHg who were receiving antihypertensive treatment, and uncontrolled treated HT (uncontrolled HT) subjects were defined as those with SBP  $\geq$ 140 mmHg and/or DBP  $\geq$ 90 mmHg without antihypertensive treatment. Mild HT was defined as SBP of 140–159 mmHg or DBP of 90–99 mmHg, and moderate or severe HT was defined as SBP  $\geq$ 160 mmHg and/or DBP  $\geq$ 100 mmHg (20). Hyperglycemia, which was assessed in reference to both impaired glucose tolerance (IGT) and DM, was defined as a fasting blood glucose  $\geq$ 110 mg/dL with no caloric intake for at least 3 h, or as casual blood glucose  $\geq$ 140 mg/dL in those who had eaten less than 3 h before measurement (or who were unsure of their last meal time; or in cases in which meal time was not considered). Dyslipidemia was defined as total cholesterol  $\geq$ 220 mg/dL and/or triglycerides  $\geq$ 150 mg/dL. Obesity as defined as a body mass index (BMI)  $\geq$ 25 kg/m<sup>2</sup> according to the Japanese criteria.

The SBP and DBP were measured with a fully automated sphygmomanometer, BP203RV-II (Nippon Colin, Komaki, Japan), placed on the right arm of a seated subject who had rested in the sitting position for 5 min before the measurement. BMI was calculated as weight (kg)/height (m)<sup>2</sup>. Information about medical history and lifestyle was gathered by questionnaire.

Total cholesterol and triglycerides were measured by an enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation (CV): 1.5% for total cholesterol and 1.7% for triglycerides). High-density lipoprotein (HDL)-cholesterol was measured using the phosphotungstate precipitation method (Wako; interassay CV: 1.9%). Blood glucose was measured *via* an enzymatic method (Kanto Chemistry, Tokyo, Japan; interassay CV: 1.9%).

### Follow-Up System

A routine mass screening examination system for CVD for the aged held throughout Japan by law was utilized to obtain the baseline data for the cohort study. Repeat examinations were used to follow most subjects every year. Those examined were asked whether they had any history of stroke and CVD. Those with such a history were asked for the time of these incidents and the names of the hospitals where they were treated. Subjects who did not come to the screening examination were contacted by mail or phone. Medical records at hospitals in the area were also checked to determine if these subjects had been hospitalized. Public health nurses also visited the subjects to obtain additional information.

**Table 1. Age-Adjusted Means of Risk Factors by 3 Blood Pressure Categories**

	Men									
	Normotensives			Hypertensives						
	n	Mean	SEM	Treated			Non-treated			
				n	Mean	SEM	n	Mean	SEM	p <sup>#</sup>
Age (years)	2,725	52.8	12.3	422	63.0	8.0*	1,171	57.7	10.8 <sup>†,‡</sup>	<0.01
Systolic blood pressure (mmHg)	2,725	119.6	12.2	422	146.2	19.5*	1,171	153.2	14.2 <sup>†,‡</sup>	<0.01
Diastolic blood pressure (mmHg)	2,725	72.8	8.5	422	87.4	12.3*	1,171	90.7	9.4 <sup>†,‡</sup>	<0.01
Total cholesterol (mg/dL)	2,701	183.5	33.8	420	185.7	33.6	1,167	188.1	35.1 <sup>†</sup>	<0.01
HDL-cholesterol (mg/dL)	2,702	48.7	13.2	420	48.9	14.0	1,167	49.4	13.8	0.46
Triglyceride (mg/dL) <sup>§</sup>	2,701	104.8	(61.3–179.1)	420	115.0	(68.4–193.3)*	1,167	115.0	(64.9–203.9) <sup>†</sup>	<0.01
Blood glucose (mg/dL)	2,704	102.6	28.1	419	110.9	37.8*	1,166	110.6	33.9	<0.01
Body mass index (kg/m <sup>2</sup> )	2,697	22.5	2.7	420	23.9	3.1*	1,159	23.7	3.0 <sup>†,‡</sup>	<0.01

	Women									
	Normotensives			Hypertensives						
	n	Mean	SEM	Treated			Non-treated			
				n	Mean	SEM	n	Mean	SEM	p <sup>#</sup>
Age (years)	4,575	52.9	11.6	826	62.0	6.9*	1,384	59.0	9.5 <sup>†,‡</sup>	<0.01
Systolic blood pressure (mmHg)	4,575	117.1	13.0	826	147.5	20.8*	1,384	152.6	12.2 <sup>†,‡</sup>	<0.01
Diastolic blood pressure (mmHg)	4,575	70.7	8.8	826	87.0	11.5*	1,384	88.1	8.9 <sup>†,‡</sup>	<0.01
Total cholesterol (mg/dL)	4,551	192.2	34.4	821	207.0	31.4*	1,375	206.4	34.7 <sup>†</sup>	<0.01
HDL-cholesterol (mg/dL)	4,551	53.3	12.4	821	51.6	12.0*	1,375	51.5	12.8 <sup>†</sup>	<0.01
Triglyceride (mg/dL) <sup>§</sup>	4,550	88.4	(54.3–143.8)	821	114.6	(70.5–186.3)*	1,375	108.1	(65.0–179.9) <sup>†</sup>	<0.01
Blood glucose (mg/dL)	4,545	98.3	20.1	820	107.3	28.6*	1,371	104.4	24.9 <sup>†</sup>	<0.01
Body mass index (kg/m <sup>2</sup> )	4,525	22.6	3.0	819	24.8	3.6*	1,374	23.9	3.2 <sup>†,‡</sup>	<0.01

HDL, high-density lipoprotein. <sup>§</sup>Geometric mean ( $\pm$ SEM). <sup>#</sup>Calculated using ANOVA adjusted for age except age. \* $p < 0.05$ , normotensives vs. treated hypertensives. <sup>†</sup> $p < 0.05$ , normotensives vs. non-treated hypertensives. <sup>‡</sup> $p < 0.05$ , treated hypertensives vs. non-treated hypertensives. \*, <sup>†</sup> and <sup>‡</sup>: using Scheffe's test.

If an incident case was suspected, forms for stroke incidence were filled out and duplicate computer tomography films or magnetic resonance imaging films for strokes were obtained.

### Diagnostic Criteria

The diagnosis was determined independently by a diagnosis committee, composed of one radiologist, one neurologist and two cardiologists. Diagnosis of stroke was determined by the presence of a focal and nonconvulsive neurological deficit lasting for 24 h or longer with a clear onset. Stroke subtype was determined by the criteria of the National Institute of Neurological Disorder and Stroke (21).

### Statistical Analysis

Analysis of variance was used for calculating the variance among BP categories, and mean values of lipids and BMI are shown after age adjustment in each sex. Scheffe's test was used to compare variables and values of  $p < 0.05$  were considered to indicate statistical significance (Tables 1, 2). Hazard

ratios (HR) for all stroke or stroke subtypes were calculated using Cox's proportional hazard model with normotensives as a reference in three BP categories (Table 3), and five BP categories (Table 4). In the calculation of HR, three kinds of adjustments were used: adjustment for age; adjustment for age, smoking status and drinking status; and adjustment for age, smoking status, drinking status, total cholesterol, and BMI. Multivariate analysis with Cox's proportional hazard model was used to calculate each relative risk of other risk factors in treated hypertensive men and women (Tables 3, 4). These analyses were done using SAS software version 8.2 (SAS Institute Inc., Cary, USA).

### Results

Subjects with treated HT included 422 men (9.8%) and 826 women (12.2%). Those with non-treated HT included 1,171 men (27.1%) and 1,384 women (20.4%) (Table 1). Subjects with treated DM and hyperlipidemia accounted for 2.4% and 1.3% of men and 1.6% and 2.0% of women, respectively. As shown in Table 2, the mean age of non-treated mild HT subjects was lower than that in the other three hypertensive cate-

**Table 2. General Characteristics of Treated Hypertensives**

	Men												
	Treated HT						Non-treated HT						
	Controlled			Uncontrolled			Mild HT			Moderate-severe HT			
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	
Age (years)	151	63.6	8.1	271	62.6	7.9	835	57.1	11.1	336	59.1	9.8	
Systolic blood pressure (mmHg)	151	126.0	10.2	271	157.4	13.5	835	146.6	6.9	336	169.6	14.4	
Diastolic blood pressure (mmHg)	151	76.4	8.3	271	93.6	9.6	835	87.3	6.5	336	99.3	10.0	
Total cholesterol (mg/dL)	151	180.9	34.4	269	188.4	32.9	833	188.7	34.6	334	186.5	36.1	
HDL-cholesterol (mg/dL)	151	46.7	13.5	269	50.2	14.2	833	49.2	13.8	334	49.9	13.7	
Triglyceride (mg/dL) <sup>§</sup>	151	117.7 (66.3–208.9)		163	113.4 (69.7–184.6)		833	115.0 (64.3–205.8)			334	114.9 (66.3–199.2)	
Blood glucose (mg/dL)	151	111.4	43.1	268	110.7	34.5	832	109.3	31.7	334	113.9	38.9	
Body mass index (kg/m <sup>2</sup> )	150	23.6	3.2	270	24.0	3.0	828	23.5	3.0	331	24.0	2.9	

	Women												
	Treated HT						Non-treated HT						
	Controlled			Uncontrolled			Mild HT			Moderate-severe HT			
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	
Age (years)	283	62.3	6.9	543	61.8	7.0	1,043	58.6	9.5	341	60.1	9.5	
Systolic blood pressure (mmHg)	283	126.7	10.0	543	158.4	16.1	1,043	147.3	6.2	341	168.7	11.7	
Diastolic blood pressure (mmHg)	283	77.1	7.4	543	92.2	9.6	1,043	85.4	7.0	341	96.2	9.0	
Total cholesterol (mg/dL)	281	203.0	32.7	540	209.1	30.5	1,035	206.2	35.3	340	206.9	33.1	
HDL-cholesterol (mg/dL)	281	51.6	12.4	540	51.5	11.8	1,035	51.5	13.0	340	51.2	12.1	
Triglyceride (mg/dL) <sup>§</sup>	281	117.2 (69.7–196.9)		163	113.3 (71.0–180.8)		1,035	106.3 (64.4–175.4)			340	113.8 (66.9–193.7)	
Blood glucose (mg/dL)	280	109.7	34.0	540	106.0	25.3	1,031	104.5	24.8	340	104.1	24.9	
Body mass index (kg/m <sup>2</sup> )	282	24.8	3.8	537	24.9	3.4	1,038	23.8	3.1	336	24.2	3.5	

HT, hypertension; HDL, high-density lipoprotein. <sup>§</sup>Geometric mean (±SD).

gories in both men and women. SBP and DBP were higher in uncontrolled treated hypertensives than in the subjects with non-treated mild HT in both men and women.

The mean follow-up duration was 10.7 years, and a total of 412 stroke cases were identified during the follow-up period (210 cases in men and 202 cases in women). Risk of all stroke was significantly higher in both treated and non-treated hypertensives than in the normotensives after adjusting for multiple risk factors using Cox’s proportional hazard model (treated HT: hazard ratio=3.00 in men and 3.34 in women, 95% confidence interval [CI]=2.00–4.51 in men and 2.29–4.87 in women; non-treated HT: 2.56, 1.83–3.57 in men and 1.93, 1.35–2.76 in women). A similar tendency was seen for cerebral infarction in both men and women (treated HT: 3.49, 2.21–5.49 in men and 4.06, 2.41–6.84 in women; non-treated HT: 2.13, 1.43–3.18 in men and 2.27, 1.37–3.75 in women). Risk of cerebral hemorrhage was higher in the non-treated hypertensives in men and was higher in the treated hypertensives in women compared to normotensives. Risks of subarachnoid hemorrhage in the treated and non-treated

hypertensives were about three times higher than those in the normotensives in women (treated HT: 2.93, 1.23–7.03; non-treated HT: 2.57, 1.24–5.33) (Table 3).

Subjects were divided into five BP categories: normotensives, controlled hypertensives; uncontrolled hypertensives; non-treated hypertensives with mild hypertension; and non-treated hypertensives with moderate or severe hypertension (Table 4). Risk for stroke was significantly higher in the subjects in all four hypertensive categories than in the normotensives in both men and women. Even in the controlled treated hypertensives the risk was about three times higher than that in the normotensives in both men and women (controlled HT: 2.96, 1.66–5.26 in men and 3.69, 2.20–6.17 in women). Uncontrolled treated hypertensives had the highest risk of cerebral infarction of the four hypertensive categories in both men and women (uncontrolled HT: 4.00, 2.43–6.58 in men and 3.67, 2.03–6.62 in women).

Figure 1 shows the proportion of subjects with or without stroke by health condition. The proportion with hyperglycemia among those with stroke was higher than the proportion

**Table 3. Hazard Ratio for All Stroke and Stroke Subtypes by 3 Blood Pressure Categories**

		Men								
		Normotension (n=2,725)		Treated HT (n=422)			Non-treated HT (n=1,171)			
		Case	HR	Case	HR	95% CI	Case	HR	95% CI	
All stroke	Age-adjusted	68	1.00	47	2.84	1.95–4.15	95	2.65	1.94–3.62	
	Multi-adjusted <sup>†</sup>		1.00		3.00	2.00–4.51		2.56	1.83–3.57	
Cerebral hemorrhage	Age-adjusted	12	1.00	5	1.81	0.63–5.21	30	4.59	2.34–9.00	
	Multi-adjusted <sup>†</sup>		1.00		1.55	0.48–5.04		4.97	2.41–10.28	
Cerebral infarction	Age-adjusted	51	1.00	39	3.10	2.01–4.77	60	2.12	1.46–3.08	
	Multi-adjusted <sup>†</sup>		1.00		3.49	2.21–5.49		2.13	1.43–3.18	
Subarachnoid hemorrhage	Age-adjusted	5	1.00	3	2.92	0.67–12.81	5	1.98	0.57–6.89	
	Multi-adjusted <sup>†</sup>		1.00		1.90	0.34–10.50		1.77	0.49–6.43	

		Women								
		Normotension (n=4,574)		Treated HT (n=826)			Non-treated HT (n=1,384)			
		Case	HR	Case	HR	95% CI	Case	HR	95% CI	
All stroke	Age-adjusted	71	1.00	63	3.15	2.23–4.45	68	2.17	1.55–3.05	
	Multi-adjusted <sup>†</sup>		1.00		3.34	2.29–4.87		1.93	1.35–2.76	
Cerebral hemorrhage	Age-adjusted	21	1.00	14	2.73	1.36–5.47	12	1.19	0.58–2.46	
	Multi-adjusted <sup>†</sup>		1.00		2.67	1.26–5.64		1.10	0.51–2.36	
Cerebral infarction	Age-adjusted	32	1.00	39	4.58	2.84–7.39	41	2.35	1.46–3.77	
	Multi-adjusted <sup>†</sup>		1.00		4.06	2.41–6.84		2.27	1.37–3.75	
Subarachnoid hemorrhage	Age-adjusted	17	1.00	10	3.00	1.33–6.79	15	2.43	1.19–4.96	
	Multi-adjusted <sup>†</sup>		1.00		2.93	1.23–7.03		2.57	1.24–5.33	

HT, hypertension; HR and 95% CI, hazard ratio and 95% confidence interval, calculated using Cox's proportional hazard model.

<sup>†</sup>Adjusted for age, smoking status, drinking status, hyperglycemia, total cholesterol and body mass index.

in those without stroke in the normotensives for men, and in women, the proportion of hyperglycemia among those with stroke was greater than that without stroke in the controlled HT and uncontrolled HT groups. The proportion of subjects with obesity was significantly higher in those without stroke than among those with stroke in the male subjects with mild HT without treatment (data not shown). In multivariate analysis with Cox's proportional hazard model, the risk of stroke in hyperglycemic subjects was 2.35 (95% CI: 1.21–4.54) and 2.52 (1.37–4.64) in treated hypertensive men and women, respectively. No significant difference was seen in other components of metabolic syndrome among treated hypertensives (Table 5).

## Discussion

The incidence rate of stroke was previously about two times higher in Japan than in Western countries (22–25). Due to an emphasis on BP control, stroke incidence has been declining since 1970 in Japan (26, 27). However, in the present study, we show that the risk of stroke is significantly higher in treated hypertensives than in normotensives, even among those with controlled HT (<140/90 mmHg). We also showed

that risk of stroke was about 2.5 times higher in hyperglycemic subjects than in normoglycemic subjects among treated hypertensives. Hyperglycemia was found to be a more important contributor to stroke risk than any other comorbidity, including obesity and dyslipidemia.

A linear relationship between BP and CVD mortality and CVD incidence has been consistently observed in numerous cohort studies (2–6). Most of these studies were carried out in Western countries, but the same tendency has been observed in Asian countries, including Japan (28). These findings support the general attitude of “the lower, the better” with respect to BP control in patients at risk for CVD. However, a considerable number of hypertensives did not receive treatment in these studies, and half of those who were treated were not sufficiently controlled.

In the present study, we found that the risk was higher among treated hypertensives than among non-treated hypertensives for all stroke and for cerebral infarction in both sexes. Risk of stroke was about 3 times higher in both controlled and uncontrolled hypertensives than in normotensives in men and women. Furthermore, risk of stroke in controlled hypertensives was higher than that in non-treated mild hypertensives. Some case-control studies and cohort studies have



**Table 4. Hazard Ratio for All Stroke and Stroke Subtypes by 5 Blood Pressure Categories**

		Men														
		Normotension (n=2,725)			Treated HT						Non-treated HT					
				Controlled (n=151)			Uncontrolled (n=271)			Mild HT (n=835)			Moderate-severe HT (n=336)			
		Case	HR	Case	HR	95% CI	Case	HR	95% CI	Case	HR	95% CI	Case	HR	95% CI	
All stroke	Age-adjusted	68	1.00	16	2.66	1.53-4.61	31	2.96	1.92-4.54	59	2.34	1.65-3.32	36	3.38	2.25-5.07	
	Multi-adjusted <sup>‡</sup>		1.00		2.96	1.66-5.26		3.05	1.92-4.85		2.34	1.62-3.37		3.17	2.02-4.97	
Cerebral hemorrhage	Age-adjusted	12	1.00	3	3.10	0.86-11.16	2	1.12	0.25-5.07	17	3.64	1.73-7.64	13	7.01	3.19-15.44	
	Multi-adjusted <sup>‡</sup>		1.00		3.36	0.91-12.43		0.60	0.08-4.75		4.27	1.96-9.29		7.11	2.92-17.32	
Cerebral infarction	Age-adjusted	51	1.00	10	2.37	1.19-4.70	29	3.48	2.17-5.59	38	1.87	1.22-2.84	22	2.77	1.68-4.57	
	Multi-adjusted <sup>‡</sup>		1.00		2.64	1.31-5.29		4.00	2.43-6.58		1.98	1.27-3.07		2.59	1.49-4.49	
Subarachnoid hemorrhage	Age-adjusted	5	1.00	3	8.17	1.85-36.03	0	0.00	—	4	2.20	0.59-8.27	1	1.41	0.16-12.16	
	Multi-adjusted <sup>‡</sup>		1.00		5.55	1.00-30.73		0.00	—		1.92	0.49-7.47		1.25	0.14-11.26	

		Women													
		Normotension (n=4,575)		Treated HT						Non-treated HT					
				Controlled (n=283)			Uncontrolled (n=543)			Mild HT (n=1,043)			Moderate-severe HT (n=341)		
		Case	HR	Case	HR	95% CI	Case	HR	95% CI	Case	HR	95% CI	Case	HR	95% CI
All stroke	Age-adjusted	71	1.00	21	3.02	1.85-4.94	42	3.23	2.19-4.75	48	2.08	1.44-3.02	20	2.44	1.48-4.03
	Multi-adjusted <sup>‡</sup>		1.00		3.69	2.20-6.17		3.16	2.06-4.85		1.95	1.32-2.87		1.87	1.08-3.24
Cerebral hemorrhage	Age-adjusted	21	1.00	4	2.47	0.83-7.32	10	2.85	1.32-6.15	8	1.09	0.48-2.49	4	1.46	0.49-4.32
	Multi-adjusted <sup>‡</sup>		1.00		2.63	0.87-7.95		2.68	1.16-6.21		1.09	0.47-2.54		1.11	0.32-3.87
Cerebral infarction	Age-adjusted	32	1.00	14	4.96	2.62-9.39	25	4.38	2.57-7.45	32	2.54	1.54-4.19	9	1.83	0.86-3.88
	Multi-adjusted <sup>‡</sup>		1.00		4.74	2.42-9.26		3.67	2.03-6.62		2.59	1.53-4.38		1.44	0.62-3.35
Subarachnoid hemorrhage	Age-adjusted	17	1.00	3	2.80	0.80-9.81	7	3.14	1.27-7.80	8	1.73	0.73-4.06	7	4.63	1.87-11.42
	Multi-adjusted <sup>‡</sup>		1.00		3.10	0.87-11.09		2.90	1.08-7.82		1.86	0.78-4.45		4.63	1.84-11.65

HT, hypertension (controlled: < 140/90 mmHg, mild HT: 140-159/90-99 mmHg, moderate-severe HT: ≥ 160/100 mmHg); HR and 95% CI, hazard ratio and 95% confidence interval, calculated using Cox's proportional hazard model. <sup>‡</sup>Adjusted for age, smoking status, drinking status, hyperglycemia, total cholesterol and body mass index.

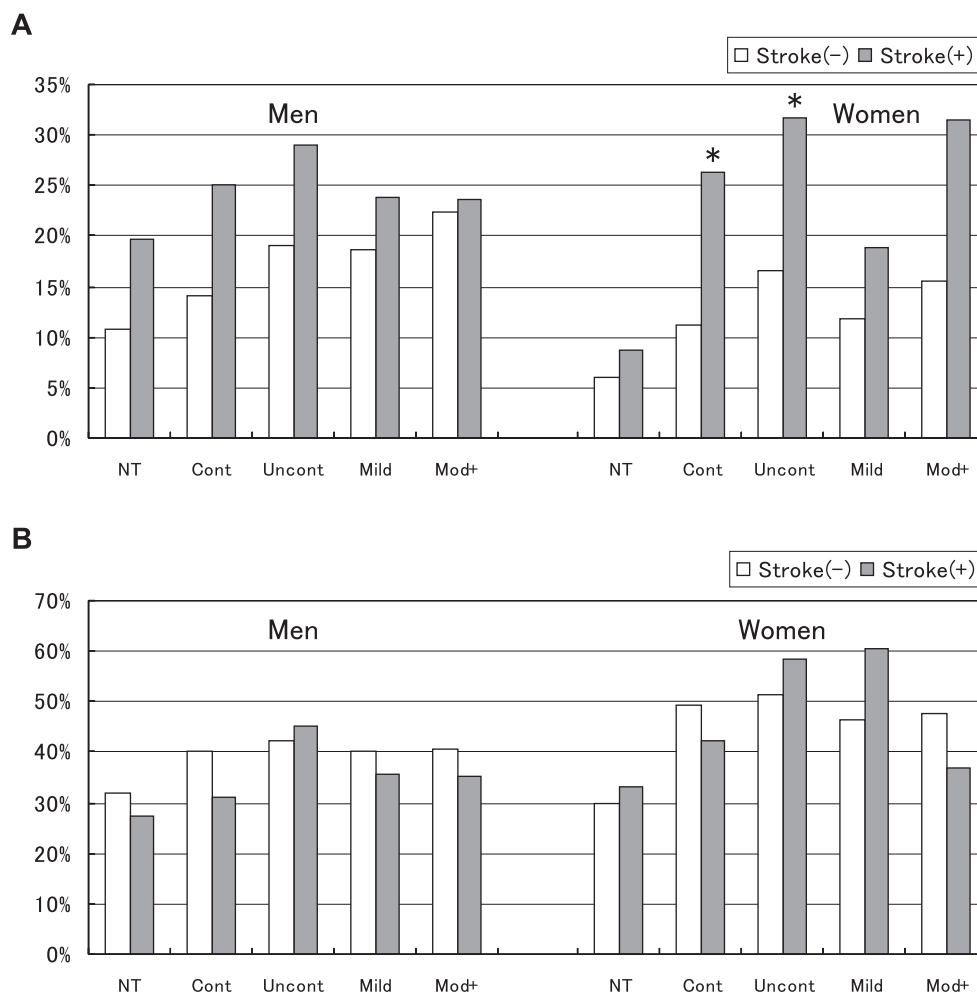
shown that treated hypertensives were still at risk of stroke (15, 29-33). Almgren *et al.* reported in their cohort study of men that total incidence of stroke was almost doubled for treated hypertensive men compared with nonhypertensive men. The relative risk was 1.75, and the incidence of stroke was not related to achieved SBP or DBP (15). The same tendency was seen in our results. Possible explanations as to why treated hypertensives have a higher risk of stroke include the possibility that physicians might start antihypertensive medication at BP levels well above that considered normal, *i.e.*, more than 160/100 mmHg, because of the patient's reticence to start medication or because of adherence to the older HT criterion of 160/95 mmHg.

Not only high BP, but also the duration of HT proceeding atherosclerosis or other comorbidity may affect the risk of stroke. Furthermore, factors might elevate the risk of stroke in controlled treated hypertensives more than in individuals with untreated mild HT. Untreated hypertensives may have a shorter period of HT and thus have a lower risk of stroke than controlled hypertensives. Furthermore, some untreated

hypertensives might have white coat hypertension, which carries a lower risk for stroke than essential hypertension (34).

Many clinical trials, including RCTs (35, 36), have demonstrated that BP lowering in hypertensives reduces the risk of stroke mortality and incidence. Lawes *et al.* reported that pooled relative risks of stroke were approximately 0.6-0.7 among those treated with different kinds of drugs in a meta-analysis of RCTs comparing antihypertensive drugs to a placebo or no treatment (1). Another meta-analysis in the same review showed that an intensive antihypertensive treatment regimen reduces the risk of stroke by about 20% compared with a less intensive regimen.

Some studies have demonstrated sex differences in the risk of all-cause or stroke mortality in diabetic patients, with the risk being higher in women than in men (37, 38). However, the existence of a sex difference in the risk of stroke and stroke mortality in hypertensive subjects with DM is controversial. In their meta-analysis of RCTs, Gueyffier *et al.* found that there was no difference in the risk of CVD between men and women under hypertensive treatment (39). However, the



**Fig. 1.** A: Proportion of impaired glucose tolerance (IGT) or diabetes mellitus (DM) by blood pressure categories. B: Proportion of dyslipidemia by blood pressure categories. A  $\chi^2$  test was performed to compare subjects with and without stroke in each blood pressure category. \* $p < 0.05$ ; otherwise: not significant. NT, normotension; Cont, controlled treated hypertension; Uncont, uncontrolled treated hypertension; Mild, mild hypertension; Mod+, moderate to severe hypertension. IGT or DM: fasting blood glucose  $\geq 110$  mg/dL or casual blood glucose  $\geq 140$  mg/dL or treated DM. Dyslipidemia: total cholesterol  $\geq 220$  mg/dL and/or triglycerides  $\geq 150$  mg/dL.

**Table 5. Impact of Baseline Characteristics for Stroke Risk in Treated Hypertensive Men and Women**

	Men		Women	
	HR	95% CI	HR	95% CI
Age (10 years)	1.11	1.06–1.17	1.08	1.03–1.13
SBP (20 mmHg)	0.99	0.72–1.38	0.90	0.67–1.20
Smoking (yes vs. no)	0.88	0.45–1.71	2.14	0.84–5.46
Alcohol (yes vs. no)	1.75	0.77–3.96	1.33	0.70–2.53
Obesity (yes vs. no)	1.32	0.66–2.64	0.96	0.54–1.70
Lipid component (yes vs. no)	1.24	0.66–2.31	0.64	0.35–1.19
Hyperglycemia (yes vs. no)	2.35	1.21–4.54	2.52	1.37–4.64

HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; HDL, high-density lipoprotein; Obesity: body mass index  $\geq 25$  kg/m<sup>2</sup>. Lipid component: triglycerides  $\geq 150$  mg/dL and/or HDL cholesterol  $< 40$  mg/dL. Hyperglycemia: fasting blood glucose  $\geq 110$  mg/dL or casual blood glucose  $\geq 140$  mg/dL. Cox's proportional hazard model was used to calculate HR with including variables simultaneously.

Framingham Study and the Hoorn study showed there was no difference in the risk of stroke between women and men with DM (40, 41). The DAI Study showed that age and previous stroke are the main predictors of stroke in diabetes. However, antihypertensive treatment was not a predictor of stroke in diabetes (42). A large collaborative cohort study showed that SBP is an important risk factor for CVD with or without DM, but there is no evidence that SBP constitutes a more important risk of CVD among people with diabetes (43). New-onset diabetes was associated with a significantly increased risk for CVD in a 28-year follow-up cohort study (44). In our data, the risk was about 2.5 times higher for those with hyperglycemia than those with normoglycemia after adjustment for potential risk factors in both male and female treated hypertensives.

The present study has some limitations. First, although the cohort was population-based, it was not randomized. We previously reported the standardized mortality ratios (SMRs) of these same subjects, and the SMRs were about 0.7 in both men and women (19). To gather this sample, we used the health check-up system that is applied throughout Japan by law, and that includes check-ups for CVD. The follow-up rate was quite high but the eligible subjects were on average healthier than the general population, and the proportions with treated HT, DM or hyperlipidemia were low. We did not estimate the effect of the study subjects being healthier than the general population, but we did adjust for potential risk factors to reduce the possibility of bias. Second, we defined hyperglycemia as an IGT  $\geq 140$  mg/dL or DM  $\geq 200$  mg/dL in the subjects less than 3 h after a meal or without information about the time of the last meal. Single point data collection will result in some misclassification, especially in the diagnosis of HT. In consideration of the white coat effect, non-treated hypertensives may have been overestimated, and thus the risk of stroke in non-treated hypertensives may have been underestimated. The present study had a number of strengths; it was a large-scale multi-center cohort study, and data, including BP data, were also obtained in a standardized fashion. The subjects were followed more than 10 years and the follow-up rate was quite high. Diagnosis of stroke was made by an independent committee using accepted diagnostic criteria.

In conclusion, we found that the risk of stroke was about 3 times higher in treated hypertensives than in normotensives. The risk was still high in controlled HT as well as uncontrolled or non-treated HT. In treated hypertensives, hyperglycemia constituted a similar risk for stroke, being about 2.5 times higher in both sexes. Thus it is important to control BP and blood glucose in hypertensives in order to reduce the risk of stroke.

### Acknowledgements

The authors thank Dr. J.D. Curb, and Dr. K. Yano for their comments on the manuscript.

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