Original Article

The Risk of Cardiovascular Events in Japanese Hypertensive Patients with Hypercholesterolemia: Sub-Analysis of the Japan Lipid Intervention Trial (J-LIT) Study, a Large-Scale Observational Cohort Study

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Coronary events and stroke are leading causes of death in Japan. However, the effects of hypertension on the risk of coronary events and stroke have not been well established in Japanese hypercholesterolemic patients. This study aimed to determine the relationship between the risk of coronary events or stroke and blood pressure and cholesterol levels during low-dose simvastatin treatment using data from the Japan Lipid Intervention Trial (J-LIT) study (a large scale nationwide cohort study). In the present study, 47,294 hypercholesterolemic patients were treated with open-labeled simvastatin (5 to 10 mg/day) for 6 years by a large number of physicians in a clinical setting. The adjusted incidence rates of coronary events in males and females were 8.9 and 2.3 and those of stroke were 17.6 and 11.3/1,000 patients during the 6-year period, respectively. The incidence rate of stroke was higher than that of coronary events in both males and females. An obvious sex difference was observed in terms of the incidence of coronary events. The risk of coronary events, stroke, and total cardiovascular events were increased, with elevations in blood pressure observed in patients treated for hypercholesterolemia. The risk of total cardiovascular events in the groups exhibiting less lipid control increased, with lower blood pressure levels than those of the well-controlled group. For patients with hypercholesterolemia and hypertension, blood pressure should be strictly controlled in order to prevent both coronary events and stroke, and the serum total cholesterol levels should be maintained at low levels as well. (*Hypertens Res* 2005; 28: 879–887)

***Key Words*: hypertension, hyperlipidemia, lipid-lowering agents, myocardial infarction, cerebrovascular disease**

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Introduction

Myocardial infarction and stroke are major causes of death in Japan (*1*). We have already demonstrated that high levels of total cholesterol (TC), as well as high levels of low-density lipoprotein cholesterol (LDL-C), increased the risk of coronary events, and high levels of high-density lipoprotein cholesterol (HDL-C) reduced this risk in Japanese hypercholesterolemic patients (*2*, *3*). Many epidemiological studies have demonstrated a relationship between blood pressure and the risk of coronary events and stroke in Western countries (*4*–*7*). Recently, the Japanese Coronary Intervention Study (JCIS) Group (*8*) reported that the incidence of coronary events in Japan was approximately 25% of that in the United States. Takeya *et al*. (*9*) reported that the incidence of stroke in Japan was about three times as great as in Hawaii. Fujisawa *et al*. (*10*) reported that hypertension, diabetes, obesity, and smoking were risk factors, although hypercholesterolemia was not included among the risk factors for coronary events in Japanese. Arima *et al*. (*11*) reported that the age- and sex-adjusted incidence of cardiovascular disease significantly increased with elevated blood pressure in patients enrolled in the Hisayama Study. The Eastern Stroke and Coronary Heart Disease Collaborative Research Group (*12*) reported a strong, continuous association between diastolic blood pressure (DBP) and the risk of both hemorrhagic and non-hemorrhagic stroke in eastern Asian people, including Japanese. Matsubara *et al*. (*13*) reported that in hypertensives requiring lipid management, the lipid-lowering approach appeared to be insufficient, as the target achievement rate was relatively low, despite the high treatment rate. However, the combined effects of hypertension and hypercholesterolemia on the risk of coronary events and stroke have not been well established in Japan.

The Japan Lipid Intervention Trial (J-LIT) study is a nationwide cohort study including a large number of hypercholesterolemic patients treated with open-labeled simvastatin (5 to 10 mg/day); the J-LIT study was carried out for 6 years by a large number of physicians using standard clinical practices to evaluate the relationship between cardiovascular disease and lipid levels (*2*, *3*, *14*). In the present study, we analyzed the relationship between the risk of coronary events or stroke and blood pressure and cholesterol levels under low-dose simvastatin therapy.

Methods

Subjects

The J-LIT study enrolled 52,421 patients (males: 12,587, females: 27,634) with serum TC levels of ≥220 mg/dl (males: 35–70 years old; post-menopausal females: <70 years old). The patients had been treated with a lipid-lowering agent, and were screened for eligibility after a washout period of at least 4 weeks; this washout period lasted for at least 12 weeks in the case of patients previously treated with probucol. The exclusion criteria included a recent coronary events or stroke, uncontrolled diabetes mellitus, serious concomitant hepatic or renal disease, secondary hypercholesterolemia, malignancy, or any other illness with a poor prognosis. Patients lacking a history of the following at the time of enrollment were included in the analysis of this cohort: documented coronary heart disease (CHD), any coronary intervention, or stroke.

Table 1. Baseline Characteristics of the Patients

	Males (n=12,587)	Females (n=27,634)
Age (years old)	53.9±9.1	59.4±6.5
BMI (kg/m^2)	24.3±2.9	23.9±3.3
Hypertension (%)	63.3	63.8
Diabetes mellitus (%)	19.1	13.3
ECG abnormality (%)	13.0	12.6
CHD familial history (%)	5.1	4.7
Smoking habit (%)	43.9	4.0
Alcohol consumption (%)	73.7	8.5
Lipid profile		
TC (mg/dl)	267.9±40.9	270.8±31.0
LDL-C (mg/dl)	178.2±34.3	184.2±32.9
TG (mg/dl)	251.3±243.3	169.4±111.7
HDL-C (mg/dl)	48.9±14.7	54.8±14.9
Blood pressure profile		
SBP (mmHg)	139.1±18.7	139.5±19.0
DBP (mmHg)	83.7±11.7	81.4±11.0

BMI, body mass index; CHD, coronary heart disease; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Treatment and Endpoints

The design of the J-LIT study has been described previously (*15*). Patients were treated with open-labeled simvastatin at a dose of 5 to 10 mg/day. All patients, including those who had discontinued simvastatin for any reason, were monitored for 6 years. Their lipid levels, adverse events, and coronary and stroke events were documented in the medical records. Cholesterol levels were determined locally at the participating institutions. Dietary and exercise therapies were recommended to patients by the investigators. Additional lipid-lowering agents were allowed only when the serum TC level did not respond adequately to treatment by simvastatin alone. No restrictions were placed on the administration of medical treatment for complications. Sitting blood pressure was measured using a sphygmomanometer. Body weight, blood pressure, and the serum lipid levels were measured every 6 months after enrollment, and the patients were interviewed

Table 2. Incidence Rate of Coronary Events and Stroke during the Treatment Periods According to TC Group

	Males (n=12,587)		Females (n=27,634)	
	Number of events	Incidence rate	Number of events	Incidence rate
Coronary events				
All	99	(8.9)	89	(2.3)
<220*	45	(7.0)	35	(1.7)
≥220*	54	(12.2)	54	(3.3)
p value**		0.006		0.002
Stroke				
All	205	(17.6)	321	(11.3)
<220*	124	(17.3)	157	(10.1)
≥220*	81	(17.9)	164	(12.7)
p value**		0.836		0.042
Total cardiovascular events				
All	304	(27.0)	410	(13.6)
<220*	169	(24.6)	192	(11.6)
≥220*	135	(30.2)	218	(16.0)
p value**		0.074		0.001

Incidence rate: No. of events/1,000 patients for the 6-year period. Incidence rate and p value were adjusted for age, diabetes mellitus, hypertension, alcohol consumption and smoking habit. *TC during treatment (mg/dl). **TC <220 mg/dl *vs*. TC ≥220 mg/dl. TC, total cholesterol. Coronary events: acute myocardial infarction and sudden cardiac death; total cardiovascular events: coronary events and stroke.

about drug compliance, number of cigarettes smoked, and alcohol consumption. Every 12 months, hepatic and renal function was monitored, and an electrocardiogram test was performed.

The primary endpoints of the present analysis were coronary events and stroke. All coronary events and stroke that occurred during the study period were reviewed and evaluated by the Endpoint Classification Committee. Each patient was informed about the study purpose, as well as about drug efficacy and the need for long-term treatment. Written informed consent was not obtained from the patients, because commercially available simvastatin preparations were used for this open-labeled study.

Statistical Analysis

All data, including those obtained after the termination of simvastatin therapy, were analyzed by survival analysis. The blood pressure was calculated using data obtained throughout the study period. The TC levels were calculated using data obtained during the treatment period. The data regarding blood pressure and TC levels that were acquired after the onset of any disease (including the primary endpoints) were excluded from the present analysis. For the analysis of baseline patient age and lipid profiles, continuous variables within and between subgroups were assessed using the paired or unpaired t-test or the analysis of variance using a trend test. Patients were classified into 3 and 5 subgroups, as based on the mean DBP and systolic blood pressure (SBP) levels, respectively. The reference categories were set based on the subgroup exhibiting the lowest blood pressure. We calculated the relative risks using 95% confidence intervals for each endpoint of each subgroup relative to the reference category; for this analysis, the Cox proportional-hazards model was used with adjustments made for age at baseline (as a continuous variable), diabetes mellitus, smoking habit, and alcohol consumption. The effects of each baseline characteristic at each endpoint were assessed. The data are expressed as the mean±SD. For all of the statistical analyses, a p value of <0.05 was considered to be significant. All statistical calculations were performed using the SAS software package (version 6.12, SAS Institute Inc., Cary, USA).

Results

Subjects

A total of 42,360 patients from among the 52,421 patients enrolled in the J-LIT study were analyzed as the primary prevention cohort. The clinical characteristics of this cohort have been reported previously (*15*). In the present analysis, data collected from 40,221 patients were analyzed, and the data from 1,255 patients and 884 patients were excluded due to a history of vascular disease or incomplete covariance, respectively. The baseline characteristics of the patients are shown in Table 1. The ratios of male and female patients with hyper-

Table 3. Correlation between Cardiovascular Events and Blood Pressure during the Treatment Period

	Population	Coronary events				Stroke				Total cardiovascular events			
		Event	RR	95% CI	*p*	Event	RR	95% CI	*p*	Event	RR	95% CI	*p*
Males													
SBP (mmHg)													
<130	3,692	18	1.00			32	1.00			50	1.00		
130–139	3,759	22	1.19	(0.64–2.23)	0.581	48	1.28	(0.82–2.01)	0.280	70	1.25	(0.87–1.80)	0.232
140–149	3,318	32	1.95	(1.08–3.52)	0.026	70	1.95	(1.28–2.98)	0.002	102	1.95	(1.38–2.75)	<0.001
150–159	1,357	12	1.81	(0.86–3.81)	0.117	32	2.17	(1.32–3.57)	0.002	44	2.06	(1.36–3.10)	0.001
≥160	461	15	6.79	(3.38–13.68)	<0.001	23	4.67	(2.71–8.04)	<0.001	38	5.39	(3.51–8.27)	<0.001
DBP (mmHg)													
<80	5,112	25	1.00			63	1.00			88	1.00		
80–89	5,676	45	1.71	(1.05–2.80)	0.032	101	1.50	(1.09–2.05)	0.013	146	1.56	(1.19–2.03)	0.001
≥90	1,799	29	3.85	(2.24–6.63)	<0.001	41	2.34	(1.57–3.48)	<0.001	70	2.79	(2.02–3.83)	<0.001
Total	12,587	99				205				304			
Females													
SBP (mmHg)													
<130	7,698	10	1.00			48	1.00			58	1.00		
130–139	8,508	17	1.31	(0.60–2.87)	0.499	97	1.64	(1.16–2.32)	0.005	114	1.58	(1.15–2.17)	0.005
140–149	7,431	34	2.88	(1.42–5.86)	0.003	85	1.60	(1.12–2.29)	0.009	119	1.83	(1.34–2.51)	<0.001
150–159	2,968	12	2.46	(1.06–5.71)	0.037	64	3.03	(2.08–4.41)	<0.001	76	2.91	(2.06–4.11)	<0.001
≥160	1,029	16	9.31	(4.20–20.65)	<0.001	27	3.79	(2.36–6.10)	<0.001	43	4.86	(3.27–7.23)	<0.001
DBP (mmHg)													
<80	14,247	38	1.00			130	1.00			168	1.00		
80–89	11,389	43	1.66	(1.07–2.57)	0.025	145	1.52	(1.20–1.93)	<0.001	188	1.55	(1.26–1.91)	<0.001
≥90	1,998	8	2.21	(1.02–4.77)	0.043	46	3.36	(2.39–4.72)	<0.001	54	3.12	(2.29–4.26)	<0.001
Total	27,634	89				321				410			

Total cardiovascular events: coronary events and stroke. RR, relative risk; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure.

tension, based on the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines (*16*), were 63.3 and 63.8%, respectively. The serum levels of TC, LDL-C, triglycerides (TG), and HDL-C in males were 267.9±40.9, 178.2±34.3, 251.3±243.3, and 48.9±14.7 mg/dl, respectively; the corresponding serum levels in females were 270.8±31.0, 184.2±32.9, 169.4±111.7, and 54.8±14.9 mg/dl, respectively. SBP and DBP in males were 139.1±18.7 and 83.7±11.7 mmHg, respectively; the corresponding values for females were 139.5±19.0 and 81.4±11.0 mmHg, respectively. The ratios for smoking and alcohol consumption in males were much greater than those for females.

Changes in Blood Pressure during the Study Period

Baseline SBP and DBP values in the male patients were 139.1±18.7 and 83.7±11.7 mmHg, and in females, the corresponding values were 139.5±19.0 and 81.4±11.0 mmHg, respectively. Approximate blood pressure decreases of 3 mmHg (SBP) and 2 mmHg (DBP) were observed during the first 6 months of treatment in both males and females. Sex differences were not observed in terms of the changes in SBP and DBP. Hypertension was classified according to the JNC 7 guidelines (*16*). The ratios of normal, pre-hypertension, hypertension stage 1, and hypertension stage 2 in males were 9.3, 35.7, 36.8, and 18.2% at baseline, respectively; the corresponding values for females were 9.9, 35.8, 37.4, and 16.9%, respectively. The ratios of hypertension stage 2 in males and females decreased from 18.2 and 16.9% at baseline to 10.7 and 10.2% at 6 months, respectively. After 6 months, the ratios of hypertension, as classified by the JNC 7, were almost identical during the study period in males and females. No remarkable changes in SBP or DBP were observed across the entire study period. About 36% of the hypertensive patients were treated with antihypertensive agents, and 64% of the patients were not treated. Sixty percent of the treated patients were treated with Ca^{2+} antagonists, and 30% were treated with angiotensin-converting enzyme (ACE) inhibitors.

Incidence of Coronary Events or Stroke during the Study Period

The incidence of coronary events or stroke was analyzed in each group, each of which was stratified according to TC

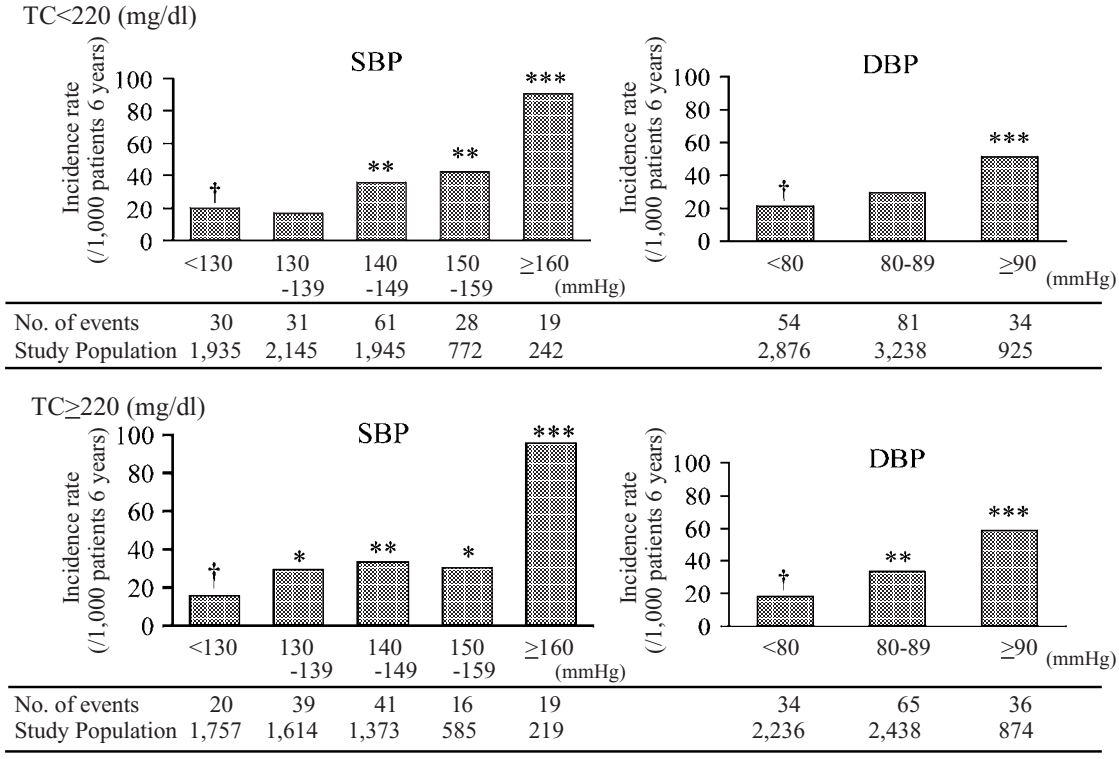

Fig. 1. *Correlation between total cardiovascular events and blood pressure in subgroups stratified by total cholesterol levels in male patients. Incidence rate: No. of events/1,000 patient for the 6-year period. The SBP < 130 mmHg group and the DBP < 80 mmHg group were used as reference categories.* *p < *0.05,* **p < *0.01,* ***p < *0.001* vs. *reference category (†). Adjustments were made for age, diabetes mellitus, smoking habit, and alcohol consumption.*

level during the treatment period; the results are shown in Table 2. The respective incidence rates of coronary events in males and females were 8.9 and 2.3, and those of stroke were 17.6 and 11.3/1,000 patients during the 6-year period. The respective incidence of cerebral infarction in males and females was 103 and 137, and that of cerebral hemorrhage was 40 and 60; in addition, the incidence for non-classified stroke was 62 and 124 for males and females, respectively. The incidence of stroke was higher than that of coronary events among both males and females. Obvious sex differences were observed in terms of the incidence of coronary events. The incidence rates of coronary events among male patients whose TC levels were less than 220 mg/dl and greater than or equal to 220 mg/dl were 7.0 and 12.2/1,000 patients for the 6-year period, and the corresponding values obtained for female patients were 1.7 and 3.3/1,000 patients for the 6-year period, respectively. The incidence rates of stroke in male patients whose TC levels were less than 220 mg/dl and greater than or equal to 220 mg/dl were 17.3 and 17.9/1,000 patients for the 6-year period, and those of female patients were 10.1 and 12.7/1,000 patients for the 6-year period, respectively. The incidence rates of total cardiovascular events in male patients whose TC levels were less than 220 mg/dl and greater than or equal to 220 mg/dl were 24.6 and 30.2/1,000 patients for the 6-year period, and those of female patients were 11.6 and 16.0/1,000 patients for the 6-year period, respectively. The incidence of coronary events was approximately 2 times higher among the male and female patients whose TC levels were greater than or equal to 220 mg/dl than that among both male and female patients whose TC levels were less than 220 mg/dl.

Relationships between the Relative Risk of Coronary Events or Stroke and Blood Pressure during the Study Period

The relationships between the relative risk of coronary events or stroke and blood pressure during the study period are shown in Table 3. The relative risk of coronary events was significantly higher in male patients whose SBP was 140–149 mmHg and greater than or equal to 160 mmHg, as compared to that of male patients whose SBP was less than 130 mmHg; moreover, the relative risk of coronary events was significantly higher in female patients whose SBP was greater than or equal to 140 mmHg, as compared to that of the female patients whose SBP was less than 130 mmHg. A significant increase in the relative risk of coronary events was observed in both male and female patients whose DBP was greater than

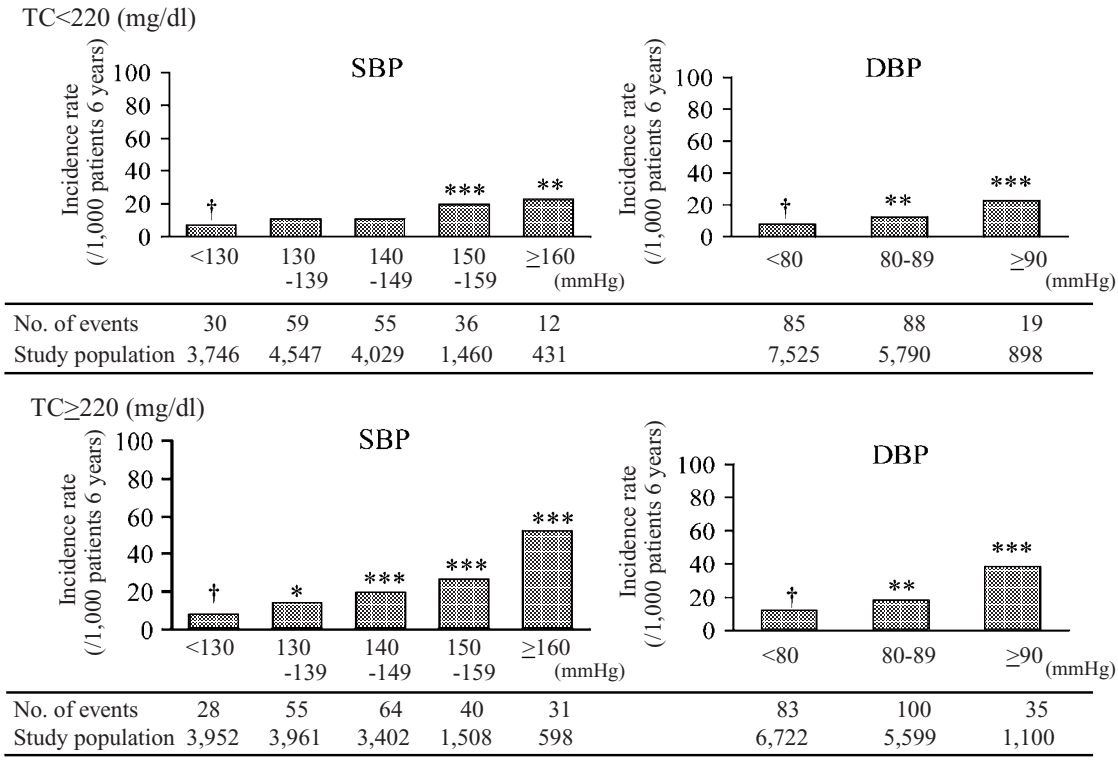

Fig. 2. *Correlation between total cardiovascular events and blood pressure in subgroups stratified by total cholesterol levels in female patients. Incidence rate: No. of events/1,000 patient for the 6-year period. The SBP < 130 mmHg group and the DBP < 80 mmHg group were used as reference categories.* *p < *0.05,* **p < *0.01,* ***p < *0.001* vs. *reference category (†). Adjustments were made for age, diabetes mellitus, smoking habit, and alcohol consumption.*

or equal to 80 mmHg, as compared to that of male and female patients whose DBP was less than 80 mmHg.

Male patients whose SBP was greater than or equal to 140 mmHg had a significantly higher risk of stroke compared to that of those patients whose SBP was less than 130 mmHg; moreover, males whose DBP was greater than or equal to 80 mmHg had a higher risk than that of male patients whose DBP was less than 80 mmHg. Female patients whose SBP was greater than or equal to 130 mmHg had a significantly higher risk of stroke than that of the female patients whose SBP was less than 130 mmHg; moreover, the female participants whose DBP was greater than or equal to 80 mmHg had a higher risk of stroke than that of female patients whose DBP less than 80 mmHg.

The relative risk of total cardiovascular events was significantly higher in male patients whose SBP was greater than or equal to 140 mmHg, as compared to that of male patients whose SBP less than 130 mmHg; moreover, this risk was higher in male patients whose DBP was greater than or equal to 80 mmHg than that of the male patients whose DBP was less than 80 mmHg. The relative risk of total cardiovascular events was significantly higher in female patients whose SBP was greater than or equal to 130 mmHg than that of female patients whose SBP was less than 130 mmHg, and the relative risk of total cardiovascular events was significantly higher in female patients whose DBP was greater than or equal to 80 mmHg than that of female patients whose DBP was less than 80 mmHg.

Relative Risk of Coronary Events or Stroke in Subgroups Stratified by TC Levels during the Treatment Period

The correlation between the incidence of total cardiovascular events and blood pressure was analyzed in subgroups stratified by TC levels, and the results are shown in Figs. 1 and 2. Baseline TC levels in the group of male patients whose lipid levels were well-controlled (TC levels <220 mg/dl) and those of the group of male patients with less well-controlled lipid levels (TC levels ≥220 mg/dl) were 258.3±40.1 and 280.1±38.6, mg/dl, respectively. The corresponding values for females in the well-controlled lipid group and those of the less well-controlled lipid group were 260.7±23.8 and 281.4±34.0 mg/dl, respectively. Baseline SBP in the well-controlled male group and that of the less well-controlled male group, *i.e.*, the insufficiently treated males, were 140.1±18.7 and 137.7±18.6 mmHg, respectively. The corresponding values for females in the well-controlled lipid group

and for females in the less well-controlled lipid group were 140.1±18.9 and 138.7±19.1 mmHg, respectively. In the well-controlled male patients, the incidence rate of total cardiovascular events was higher among those whose SBP was greater than or equal to 140 mmHg than among those whose SBP was less than 130 mmHg; in addition, the rate was higher in those whose DBP was greater than or equal to 90 mmHg than among those whose DBP was less than 80 mmHg. In the group of males with less well-controlled lipid levels, the incidence rate of total cardiovascular events was higher in those whose SBP was greater than or equal to 130 mmHg than in those whose SBP was less than 130 mmHg, and the rate was higher in those whose DBP was greater than or equal to 80 mmHg than in those whose DBP was less than 80 mmHg. As regards the corresponding rates for females with well-controlled lipid levels (TC levels <220 mg/dl), the incidence rate of total cardiovascular events was higher in female patients whose SBP was greater than or equal to 150 mmHg than in those whose SBP was less than 130 mmHg, and the rate was higher in those whose DBP was greater than or equal to 80 mmHg than in those whose DBP was less than 80 mmHg. In the group of females with less well-controlled lipids (TC levels ≥220 mg/dl), the incidence rate of total cardiovascular events was higher in those female patients whose SBP was greater than or equal to 130 mmHg than in those whose SBP was less than 130 mmHg, and the rate was higher in those whose DBP was greater than or equal to 80 mmHg than in those whose DBP was less than 80 mmHg. As regards both male and female patients with less well-controlled lipid levels, the incidence rate of coronary events and stroke tended to increase with blood pressure.

Discussion

The J-LIT study was the first successful nationwide cohort study to include 47,294 hypercholesterolemic patients treated with open-labeled simvastatin (5 to 10 mg/day); the J-LIT study was carried out for 6 years by a large number of physicians in a standard clinical setting. This study aimed to determine the relationship between the risk of coronary events or stroke and blood pressure and hypercholesterolemia during low-dose simvastatin treatment.

SBP (−3 mmHg) and DBP (−2 mmHg) values in both males and females showed slight decreases during the first 6 months of treatment. The respective ratios of hypertension stage 2 in male and female patients decreased from 18.2 and 16.9% at baseline to 10.7 and 10.2% at 6 months, respectively. This decrease in blood pressure might have been the result of the strict control of hypertension in cases of moderate and severe hypertension, together with the control of hyperlipidemia.

The respective incidence rates of coronary events in males and females were 8.9 and 2.3, and those of stroke were 17.6 and 11.3/1,000 patients in the 6-year period of the study. As expected from a national survey conducted by the Ministry of Health, Labor and Welfare (*17*), the incidence of stroke was higher than that of coronary events in both males and females. Obvious sex differences were observed in the incidence of coronary events. The incidence rates of coronary events in male and female patients whose TC levels were greater than or equal to 220 mg/dl were approximately two times higher than those of patients whose TC levels were less than 220 mg/dl. However, the incidence rates of stroke in male and female patients, the cholesterol levels of whom were greater than or equal to 220 mg/dl, were almost identical to that of patients whose cholesterol levels were less than 220 mg/dl. In our subanalysis published in a related paper (*18*), we previously reported that high TC and LDL-C levels and low HDL-C levels were greater risk factors for coronary events than for stroke. In the case of stroke, these levels were risk factors for ischemic stroke, but not for hemorrhagic stroke. In this subanalysis, the definition of stroke included both ischemic and hemorrhagic stroke, which may account for why the TC levels did not affect the incidence of stroke.

The risks for coronary events, stroke, and total cardiovascular events were increased with elevations in blood pressure among patients treated for hypercholesterolemia. The relative risk of a coronary events was higher in male and female patients whose SBP was greater than or equal to 140 mmHg, as compared to that of patients whose SBP was less than 130 mmHg. Male patients whose SBP was greater than or equal to 140 mmHg and female patients whose SBP was greater than or equal to 130 mmHg had a significantly higher risk of stroke than did the patients whose SBP was less than 130 mmHg. The relative risk of total cardiovascular events was significantly higher in male patients whose SBP was greater than or equal to 140 mmHg and in female patients whose SBP was greater than or equal to 130 mmHg, as compared to that of patients whose SBP less than 130 mmHg. The Asia Pacific Cohort Studies Collaboration study revealed that blood pressure was strongly associated with cardiovascular events in Asian populations (*19*). Our results also demonstrated that blood pressure was strongly associated with cardiovascular events in Japanese patients treated for hypercholesterolemia. In the analysis which classified the type of stroke as either cerebral infarction or cerebral hemorrhage, a strong correlation with blood pressure was observed in both analyses (data, not shown). However, a stronger correlation was observed in the case of cerebral hemorrhage.

The risk of total cardiovascular events in groups with less well-controlled lipid levels increased from lower blood pressure level than that of the well-controlled groups. As regards the groups with well-controlled lipid levels, the relative risk of total cardiovascular events was significantly higher in male patients whose SBP was greater than or equal to 140 mmHg and in female patients whose SBP was greater than or equal to 150 mmHg than that of patients whose SBP was less than 130 mmHg. However, in the groups with less well-controlled lipid levels, the relative risk of total cardiovascular events was higher in male and female patients whose SBP was greater

than or equal to 130 mmHg than that of patients whose SBP was less than 130 mmHg. Therefore, it appears that blood pressure should be controlled more strictly in groups with less well-controlled lipid levels than in the well-controlled groups. In the Hisayama study (*11*), the risk of cardiovascular events was reported to increase with SBP values of greater than or equal to 140 mmHg in Japanese ranging in age from 60 to 79 years old. In our J-LIT study, the risk of total cardiovascular events increased with SBP values of greater than or equal to 140 mmHg in the groups with well-controlled lipid levels. However, the relative risk of total cardiovascular events among those with less well-controlled lipid levels was higher in patients whose SBP was greater than or equal to 130 mmHg. The present results of both analyses were thus in good agreement, with the exception that in the group with less well-controlled lipid levels, the relative risk of total cardiovascular events was higher in patients whose SBP was greater than or equal to 130 mmHg. This difference may reflect the difference in TC levels in both studies. According to the results of the Kyushu Lipid Intervention Study (KLIS) (*20*), the risk of CHD events was approximately 50% lower and that of cerebral infarction was 70% lower at TC levels below 220 mg/dl than the corresponding risk values observed at TC levels 240 mg/dl or higher. Thus, achieving a decrease in TC levels to below 220 mg/dl appears desirable for the prevention of cardiovascular disease, according to the results of both the KLIS and the J-LIT studies. The Eastern Stroke and Coronary Heart Disease Collaborative Research Group (*12*) reported a strong, continuous association between DBP and the risk of both hemorrhagic and non-hemorrhagic stroke in eastern Asian people. They also reported that there were trends towards a decrease in the risk of non-hemorrhagic stroke and an increase in the risk of hemorrhagic stroke with decreasing cholesterol levels. A reduction of 3 mmHg in DBP was associated with a decrease in the number of strokes by about a third. In that study, it was concluded that blood pressure was an important determinant of stroke risk in eastern Asian populations, whereas the serum cholesterol level was less important, *i.e.*, it appeared to affect the proportions of stroke subtypes more than overall stroke numbers. Green *et al*. (*21*) reported that the reduction of stroke risk was greater with antihypertensive therapy, whereas the decrease in coronary events risk was greater with cholesterol-lowering therapy. Cholesterol-reducing therapy combined with an antihypertensive regimen is of significantly greater benefit in terms of reducing overall cardiovascular risk. Our results also demonstrated that the control of blood pressure and lipid levels was necessary to reduce the total cardiovascular risk. Our results regarding the effects of blood pressure and TC levels on cardiovascular events are consistent with the findings of these previous reports (*11*, *12*, *19*, *21*). Therefore, the control of hypercholesterolemia, as well as that of hypertension, is essential for the prevention of cardiovascular events.

For patients with hypercholesterolemia and hypertension, blood pressure should be strictly controlled to help prevent both coronary events and stroke, and the serum TC levels should be maintained at low levels as well.

Study Limitation

Although we designated this study as the "Japan Lipid Intervention Trial," it was in fact a cohort and observational study, rather than an intervention study.

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