

*Original Article*

## Effects of Hypertension and Type 2 Diabetes Mellitus on the Risk of Total Cardiovascular Events in Japanese Patients with Hypercholesterolemia: Implications from the Japan Lipid Intervention Trial (J-LIT)

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**Hyperlipidemia, hypertension, and diabetes mellitus (DM) are well-established risk factors for cardiovascular disease. We analyzed the cardiovascular events in hyperlipidemic patients with or without DM who were administered open-labeled simvastatin in groups stratified by blood pressure level using data from the Japan Lipid Intervention Trial (J-LIT). Hyperlipidemic patients with DM ( $n=6,288$ ) had significantly more cardiovascular events than those without DM ( $n=33,933$ ). The incidence rates of total cardiovascular events in the Non-DM and DM groups were 15.40 and 25.76 per 1,000 patients for the 6-year period, respectively. The relative risk of total cardiovascular events in the DM vs. the Non-DM group was 1.68, and the relative risk was significantly higher in the DM than in the Non-DM group. The relative risks of total cardiovascular events were significantly higher in DM and Non-DM patients whose systolic blood pressure (SBP) was greater than or equal to 130 mmHg compared to that of Non-DM patients whose SBP was less than 130 mmHg, and in DM and Non-DM patients whose diastolic blood pressure (DBP) was greater than or equal to 80 mmHg compared to that of Non-DM patients whose DBP was less than 80 mmHg. In all groups stratified by SBP and DBP, relative risks of total cardiovascular events were higher in DM patients than in Non-DM patients. For patients with hypercholesterolemia and DM, blood pressure should be strictly controlled in order to prevent both coronary events and stroke. These results are in good agreement with the JNC 7 and the ESH/ESC guidelines for DM patients, which recommended that the SBP and DBP be less than 130 and 80 mmHg, respectively. (*Hypertens Res* 2007; 30: 119–123)**

**Key Words:** hyperlipidemia, diabetes mellitus, hypertension, simvastatin, cardiovascular events

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## Introduction

Cardiovascular and cerebrovascular complications are the leading causes of death and disability in patients with diabetes mellitus (DM) (1, 2). DM is associated with a marked increase (by a factor of two to four) in the risk of coronary heart disease (CHD) (3). Prospective epidemiological studies have confirmed DM as an independent risk factor of stroke with an increased relative risk ranging from 2-fold to 5-fold (2). Fujishima *et al.* (4) reported that DM was a significant risk factor for both CHD and stroke in Japanese people. Many epidemiological studies have demonstrated that lowering blood pressure reduced the risk of coronary events and stroke (5–8). According to both the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 6) and the World Health Organization–International Society of Hypertension (WHO-ISH) 1999 report (9, 10), the recommended systolic blood pressure (SBP) and diastolic blood pressure (DBP) in DM patients were 130 and 85 mmHg, respectively. In the Hypertension Optimal Treatment (HOT) Study (11), the risk of major cardiovascular events in DM patients whose DBP was greater than or equal to 80 mmHg was found to be one-half of the risk in DM patients whose DBP was greater than or equal to 90 mmHg. In the UK Prospective Diabetes Study (UKPDS), tight blood pressure control in patients with hypertension and type 2 diabetes improved both cardiovascular disease and diabetes-related outcomes (12). In step with these results, the recommended SBP/DBP in DM patients have been changed to 130/80 mmHg in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (13).

The Japan Lipid Intervention Trial (J-LIT) study was the first and largest nationwide cohort study involving more than 50,000 hypercholesterolemic patients under the conditions of ordinary clinical practice to evaluate the relationship between lipid levels and the incidence of CHD (14–17) or cerebrovascular disease (18). Using the J-LIT database, we examined the relationship between the incidence of cardiovascular events and both blood pressure level and target blood pressure level in DM patients stratified by SBP and DBP.

## Methods

### Subject

The J-LIT study enrolled 52,421 patients with serum total cholesterol (TC) levels of  $\geq 220$  mg/dl: men aged 35 to 70 years and postmenopausal women under 70 years old between 1992 and 1993. When the patients had been treated with lipid-lowering agents, they were screened for eligibility after a washout period of at least 4 weeks; the washout lasted for at least 12 weeks in patients previously treated with probucol. The exclusion criteria included a recent coronary

event or stroke, uncontrolled DM, serious concomitant hepatic or renal disease, secondary hypercholesterolemia, malignancy or any other illness with a poor prognosis. Patients without documented CHD and without any history of coronary intervention or stroke at the time of enrollment were analyzed in this report.

### Treatment and Endpoints

The design of the J-LIT study has been described previously (14). Patients were treated with open-labeled simvastatin at a dose of 5 to 10 mg/day. All patients were monitored for 6 years from 1993 to June 1999. Their lipid levels, adverse events, coronary events and stroke were documented in the medical records. No restrictions were placed on the medical treatment for complications. Sitting blood pressure was measured using a sphygmomanometer. Body weight, blood pressure, and the fasting serum lipid levels were measured every 6 months after enrollment and patients were interviewed about drug compliance, number of cigarettes smoked, alcohol consumption, and amount of exercise. Every 12 months, hepatic and renal functions were monitored, and an electrocardiogram test was performed. DM was diagnosed as a fasting blood glucose level of  $\geq 126$  mg/dl (19).

The primary endpoints of the present analysis were coronary events (myocardial infarction and sudden cardiac death) and stroke. All coronary events and stroke that occurred during the study period were evaluated by the Endpoint Classification Committee. Each patient was informed of the study purpose, as well as the 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 mean blood pressure was calculated using the data obtained throughout the study period. The mean TC level was calculated using the same data set excluding the baseline values. The values of blood pressure and TC level 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 4 and 5 subgroups based on the mean DBP and SBP levels, respectively. The reference values were taken as the mean from subjects in the Non-DM subgroup exhibiting the lowest blood pressure. We calculated the relative risks using 95% confidence intervals (CI) for each endpoint of each subgroup relative to the reference value; for this analysis, the Cox proportional-hazards model was used with adjustments for gender and age at baseline (as a continu-

ous variable), smoking habit and drinking habit (as a categorized data). The data are expressed as the mean $\pm$ 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 8.02; SAS Institute Inc., Cary, USA).

## Results

### Characteristics of the Study Patients

The characteristics of the patients' backgrounds are shown in Table 1. Among the 40,221 patients screened for this analysis, 6,288 (15.6%) hypercholesterolemic patients had type 2 diabetes as well. The ratio of males to females in the DM group was higher than that in the Non-DM group. The rates of drinkers and smokers in the DM group were higher than those in the Non-DM group. Fasting blood glucose levels in the DM group were significantly higher than those in the Non-DM group. Serum triglyceride levels in the DM group were higher than those in the Non-DM group, but not significantly so. Other lipid parameters were not different between the DM and Non-DM groups. TC levels during the study period in DM and Non-DM patients were  $218.5\pm 31.3$  and  $220.8\pm 29.1$  mg/dl, respectively. SBP and DBP at baseline in Non-DM patients were  $139.1\pm 18.9$  and  $82.2\pm 11.3$  mmHg, respectively; and the corresponding values for DM patients were  $140.6\pm 18.8$  and  $81.6\pm 11.0$  mmHg, respectively. No remarkable changes in SBP or DBP were observed during the entire study period.

### Incidence of Cardiovascular Events

The crude incidence of coronary events in Non-DM and DM has been already reported (17). The adjusted incidence of coronary events and/or stroke was analyzed in the Non-DM and DM groups and the results are shown in Table 2. The incidence rates of coronary events in the Non-DM and DM groups were 3.50 and 7.39, and those of stroke were 11.85 and 18.10 per 1,000 patients for the 6-year period, respectively. The respective incidence rates of coronary events and stroke in the DM group were higher than those in the Non-DM group. The incidence rates of total cardiovascular events in the Non-DM and DM groups were 15.40 and 25.76 per 1,000 patients for the 6-year period, respectively. The respective relative risks of coronary events, stroke and total cardiovascular events in the DM vs. the Non-DM group were 2.12 (95% CI, 1.55 to 2.89), 1.53 (95% CI, 1.25 to 1.88) and 1.68 (95% CI, 1.42 to 2.00).

### Relationships between the Relative Risk of Total Cardiovascular Events and Blood Pressure during the Study Period

The relative risk of total cardiovascular events was signifi-

**Table 1. Baseline Characteristics of the Subjects, Risk Factors, Lipid and Blood Pressure Profiles**

	Non-DM ( <i>n</i> =33,933)	DM ( <i>n</i> =6,288)
Male (%)	29.7	39.7
Age (years old)	57.7 $\pm$ 7.9	57.8 $\pm$ 7.8
BMI (kg/m <sup>2</sup> )	23.9 $\pm$ 3.1	24.4 $\pm$ 3.4
Hypertension (%)	63.1	66.4
ECG abnormality* (%)	12.3	15.0
CHD familial history (%)	4.8	4.6
Smoking habit (%)	15.6	21.2
Drinking habit (%)	28.0	33.9
Lipid		
TC (mg/dl)	269.8 $\pm$ 34.4	270.1 $\pm$ 34.7
LDL-C (mg/dl)	182.7 $\pm$ 33.6	181.0 $\pm$ 32.9
TG (mg/dl)	189.1 $\pm$ 156.2	226.9 $\pm$ 222.7
HDL-C (mg/dl)	53.3 $\pm$ 15.0	51.3 $\pm$ 15.3
FBG (mg/dl)	95.6 $\pm$ 21.1	153.8 $\pm$ 56.1
Blood pressure		
SBP (mmHg)	139.1 $\pm$ 18.9	140.6 $\pm$ 18.8
DBP (mmHg)	82.2 $\pm$ 11.3	81.6 $\pm$ 11.0

BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure. \*Study physician's diagnosis.

cantly higher in DM and Non-DM patients whose SBP was greater than or equal to 130 mmHg compared to that of Non-DM patients with SBP of less than 130 mmHg. The relative risk was significantly higher in DM and Non-DM patients whose DBP was greater than or equal to 80 mmHg compared to that of Non-DM patients with DBP of less than 80 mmHg (Fig. 1). However, in all groups stratified by SBP and DBP, relative risks of total cardiovascular events were higher in DM patients than those in Non-DM.

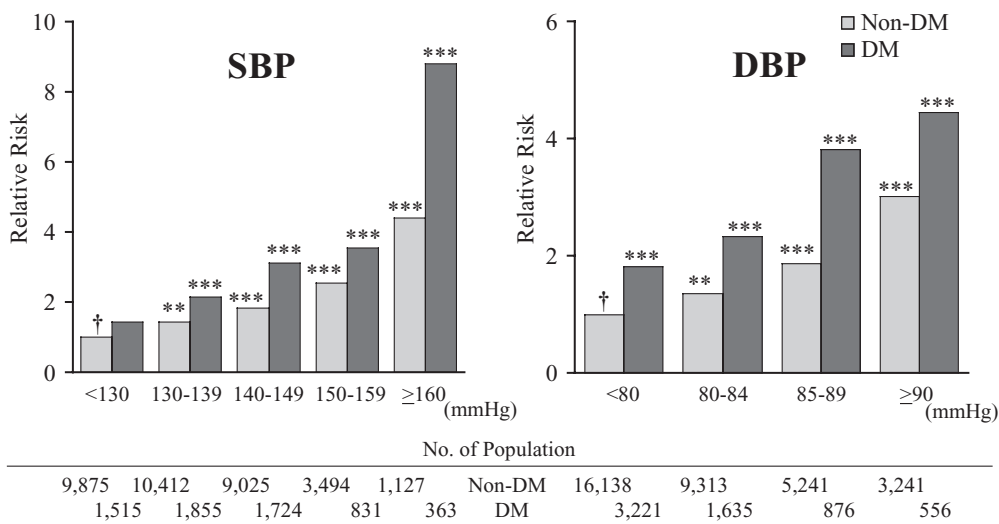
## Discussion

The J-LIT study was the first and largest epidemiological study in Japan to demonstrate a relationship between serum lipid levels and the incidence of CHD or total mortality in Japanese patients with hypercholesterolemia (16). Since the J-LIT study was conducted under a common clinical environment in a target population of hypercholesterolemic patients throughout the country, the findings could be reasonably extrapolated to the general Japanese hypercholesterolemic population. The J-LIT study was thought to be a good model system to elucidate the influence of having multiple risk factors on the cardiovascular events. Although the J-LIT study enrolled hypercholesterolemic patients, the results could be used for epidemiological purposes, because lipid levels were well controlled in many patients throughout the study period

**Table 2. Adjusted Incidence\* of Coronary Events and Stroke during the Treatment Periods**

	Non-DM (n=33,933)		DM (n=6,288)		p value
	Number of events	Incidence rate	Number of events	Incidence rate	
Coronary events	131	3.50	57	7.39	<0.001
Stroke	405	11.85	121	18.10	<0.001
Total cardiovascular events	536	15.40	178	25.76	<0.001

Coronary events: acute myocardial infarction and sudden cardiac death. Total cardiovascular events: coronary events and stroke. Incidence rate: number of incidence per 1,000 patients for the 6 years period. DM, diabetes mellitus.\*Adjusted for age, gender, hypertension, total cholesterol, smoking habit and drinking habit.



**Fig. 1.** Relationships between the relative risk of total cardiovascular events and blood pressure during the study period. †Data in the groups of non-diabetic patients with SBP <130 mmHg and DBP <80 mmHg were used as reference values. \*\*p < 0.01, \*\*\*p < 0.001 vs. the reference values. All data were adjusted for gender, age, total cholesterol, smoking habit, and drinking habit.

and the results were adjusted using TC levels.

In our previous study (16), we reported that the serum TC and low-density lipoprotein cholesterol levels were positively correlated and the serum high-density lipoprotein cholesterol level was inversely correlated with the risk of CHD in patients without a history of CHD. We have also reported that the risk of total cardiovascular events increased at lower blood pressure level in the group with poorer lipid control than in the well-controlled group, and concluded that blood pressure should be strictly controlled for the prevention of both coronary events and stroke in addition to lowering the serum TC level in patients with hypercholesterolemia and hypertension (20). It should be considered that the outcomes of this study were limited, because all patients were treated with simvastatin, which has pleiotropic effects. The blood pressure level posing a significant risk might be lower in patients without statin treatment than in the patients studied here.

In the present study, we analyzed the effects of hyperten-

sion and DM on the risk of cardiovascular events using the J-LIT data. The relative risk of total cardiovascular events in the DM vs. the Non-DM group was 1.68, and the risk was significantly higher in the DM group. In all groups stratified by SBP or DBP, the relative risks of total cardiovascular events were higher in DM than in Non-DM patients. The risk was significantly higher in both DM and Non-DM patients whose SBP was greater than or equal to 130 mmHg compared to the risk in Non-DM patients whose SBP was less than 130 mmHg. The risk increased significantly in Non-DM patients with DBP greater than or equal to 80 mmHg. When DBP was even less than 80 mmHg, the risk in DM patients was significantly higher than in Non-DM patients. It was suggested that the target SBP/DBP levels were less than 130/80 mmHg in Japanese hypertensive patients with DM. These findings were in good agreement with the JNC 7 (13) and American Diabetes Association (21) and ESH/ESC (22) guidelines for DM patients, which recommended that the target SBP/DBP be less than 130/80 mmHg.

For patients with hypercholesterolemia and DM, blood pressure should be strictly controlled to help prevent both coronary events and stroke.

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