The Relationship Between the Effect of Pravastatin and Risk Factors for Coronary Heart Disease in Japanese Patients With Hypercholesterolemia

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Background Several epidemiologic studies in Japan have shown the risk factors for coronary heart disease (CHD) in the general population. The present analysis determined the risk factors for CHD in the MEGA Study, a large primary prevention trial with pravastatin in Japanese with hypercholesterolemia.

Methods and Results The relationship between each baseline characteristic and the risk of CHD for the 5-year study period were evaluated using the Cox proportional hazard model. The multivariable predictors of CHD were sex, age, high-density lipoprotein-cholesterol (HDL-C), diabetes mellitus (DM), hypertension (HT), and history of smoking. Serum total and low-density lipoprotein-cholesterol were not independent risk factors for CHD in the current analysis. In addition, the effect of pravastatin was evaluated by subgroups in each risk factor using the interaction in a Cox model. Diet plus pravastatin treatment reduced CHD risk by 14–43% compared with diet alone, regardless of the presence or absence of risk factors.

Conclusions The risk factors for CHD were sex, age, DM, HT, smoking, and low HDL-C in the MEGA Study. The pravastatin treatment was effective for reducing the risk of CHD, regardless of the presence of risk factors. (Circ J 2008; 72: 1576–1582)

Key Words: Coronary heart disease; Hypercholesterolemia; Risk factors; Statin

In Europe and the USA, a large number of epidemiological studies, including the Framingham Heart Study, have been conducted to identify the risk factors for coronary heart disease (CHD). The major risk factors identified by these studies include high serum concentrations of total cholesterol (TC)¹ and low-density lipoprotein-cholesterol (LDL-C)² low serum concentrations of high-density lipoprotein-cholesterol (HDL-C)^{3–5} high serum concentration of triglycerides (TG)^{6,7} male sex⁸ increasing age⁸ smoking habit⁹ hypertension (HT)¹⁰ and diabetes mellitus (DM)¹¹ In addition to these, obesity¹² and family history¹³ of CHD have also been reported as risk factors.

In Japan, major epidemiological studies have been conducted, including the study of the Research Committee on Primary Hyperlipidemia organized by the Ministry of Health and Welfare of Japan, the Hisayama Study,¹⁴ the Okinawa Study,¹⁵ and the NIPPON DATA study.¹⁶ These epidemiological

surveys have also identified increasing age, male sex, DM, smoking habit, HT, and hyperlipidemia as risk factors for CHD, which are similar to the major risk factors identified by the epidemiological studies conducted in Western countries. Among these risk factors, elevated serum cholesterol (hypercholesterolemia) is considered to be an established risk factor for CHD.

Many large-scale clinical studies of cholesterol-lowering therapies have been conducted, and several representative large-scale clinical studies have been published since the middle of the 1990s; these include the Scandinavian Simvastatin Survival Study,¹⁷ the West of Scotland Coronary Prevention Study,¹⁸ and the Air Force/Texas Coronary Atherosclerosis Prevention Study.¹⁹ All of these studies have shown that lowering of elevated serum cholesterol concentrations in high-risk patients can result in a 30% or greater reduction of CHD incidence. These results are considered to strongly lend support to the epidemiological hypothesis that lowering serum cholesterol concentration is beneficial for health and improved outcomes.

Subsequently, data from these clinical studies were used to assess the risk factors for CHD and those associated with stroke in patients with hyperlipidemia using the baseline data in relation to the patient characteristics.^{20,21} The effects of the identified risk factors on the risk of ischemic arteriosclerotic diseases have also been reported. The findings were consistent with those reported from the epidemiological surveys.

In the present study, we assessed the risk factors for CHD using the 5-year follow-up data from the MEGA Study,²² which had shown the efficacy of pravastatin for primary prevention of CHD in Japanese patients with mild-

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to-moderate hyperlipidemia. We also analyzed the efficacy of pravastatin for primary prevention of CHD in relation to the presence of each of the identified risk factors and to the number of risk factor(s) present. We believe that the findings from such an analysis will be beneficial for planning strategies for the treatment of hyperlipidemia in low-risk patients having characteristics similar to the patients in the MEGA Study;²² and that the benefit is not limited to Japanese patients.

Methods

The study design, characteristics of patients, and the major results of the MEGA Study have been reported previously.²² In summary, 7,832 patients aged 40 to 70 years (2,476 men and 5,356 post-menopausal women) with mild-to-moderate hyperlipidemia (serum TC 220 to 270 mg/dl) and no history of CHD or stroke were randomly assigned to the diet therapy group or the diet plus pravastatin treatment group (10 to 20 mg/day, approved dose in Japan), and were followed for 5.3 years on average (41,195 person-years follow-up). The results showed a 33% reduction in the primary endpoint of incidence of CHD in the diet plus pravastatin group, and also showed the long-term safety of pravastatin. The composite primary endpoint in this prospective, randomized, open-labeled, blinded endpoints design study was the first occurrence of CHD (fatal and non-fatal myocardial infarction, angina, cardiac death or sudden death, and revascularization procedure). The secondary endpoints included stroke, CHD plus cerebral infarction, all cardiovascular disease, and total mortality. Throughout the study period, the serum concentration of TC, HDL-C, LDL-C, TG, and lipoprotein(a) [Lp(a)] concentrations were centrally measured at the same laboratory using methods standardized by the US Centers for Disease Control and Prevention (Atlanta, GA, USA). The serum LDL-C concentration was estimated by the Friedewald equation.²³ The baseline cholesterol was the average of measurements taken on 2 or 3 occasions over 12 weeks for entry to the study, using a standardized procedure.

Analysis of Risk Factors

The risk factors for CHD were assessed using the full analysis set 60-month follow-up data from the MEGA Study. A univariable analysis was performed to determine the relevant risk factors (baseline characteristics) and the hazard ratio (HR), 95% confidence interval (CI), and *p*-value were calculated using the Cox proportional hazard model. The evaluated baseline characteristics were sex, age, serum TC, HDL-C, LDL-C, non-HDL-C, TG, Lp(a), presence/absence of DM, fasting blood sugar, presence/absence of HT, past history/no past history of treatment of hyperlipidemia, body mass index (BMI), history/no history of smoking, and history/no history of drinking alcohol. The serum lipid concentration (TC, HDL-C, LDL-C) were the average value of 2 or 3 measurements taken during the 12 weeks before treatment. DM and HT were identified based on clinical diagnosis.

The factors found to be significant (*p*<0.01) were incorporated into the multivariable analysis. Both treatment groups were combined for the analysis. The results of a preparatory analysis of the distribution of the background factors showed that most of those factors exhibited a sex-biased distribution, and thus the present analysis was conducted considering sex as a factor. The HR and the 95% CI were

calculated for the risk factors identified. Elimination of variables using the step-down procedure was performed using a cut-off of *p*<0.20. The serum lipid concentrations were analyzed in 2 combinations (TC, HDL-C and TG or LDL-C, HDL-C and TG). Further, interaction between the risk factors was assessed in the analysis, with all combinations of risk factors assessed, including quadratic interaction.

The relationship between the presence of multiple risk factors and incidence of CHD was assessed using the classification proposed in the Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults:²⁴ age (men >45 years, women >55 years), HT, DM or fasting plasma glucose >110 mg/dl, smoking habit, and low HDL-C (<40 mg/dl). Because the MEGA Study did not take into account a family history of coronary artery disease, we used the number of factor(s) excluding the family history of coronary artery disease. For patients with DM, the lower limit of the number of risk factors was set at 3, in accordance with the recommendation in the Guideline.

Evaluation of the Effect of Pravastatin

The effect of pravastatin on reducing the risk of CHD was evaluated taking into account the presence or absence of the identified risk factors, as well as the number of risk factor(s) present. HRs and 95% CIs were estimated by Cox proportional hazards model. The variation effects of pravastatin among subgroups in each risk factor were evaluated using the interaction in a Cox model.

Results

Risk Factors for CHD

On univariable analysis, DM, HT, serum concentrations of HDL-C, and smoking habit in men, and in women increasing age, low serum concentrations of HDL-C, DM, and HT were significant risk factors for CHD on univariable analysis (Table 1).

On multivariable analysis, the risk factors identified using the step-down method (*p*<0.20) were in men increasing age (*p*=0.1243), lower serum HDL-C (*p*=0.0315), DM (*p*<0.0001), HT (*p*=0.0038), and smoking habit (*p*=0.0448), and in women were increasing age (*p*=0.0107), lower serum HDL-C (*p*=0.0589), DM (*p*<0.0001), HT (*p*=0.0093), and high BMI (*p*=0.1007). The common risk factors identified in both men and women were increasing age, low serum HDL-C, DM, and HT. Notably, higher serum TC and LDL-C were not identified as risk factors, even though they have conventionally been believed to be associated with a high risk of CHD. The effect of smoking could not be determined for women because of the limited number of women who smoked. However, smoking was identified as a strong risk factor in men. In addition, when interaction terms were included in the analysis, a strong interaction was observed between DM and HT (*p*=0.01). The results of an analysis taking these findings into account showed that male sex, increasing age, lower serum HDL-C, DM, HT, and smoking habit were the major risk factors for CHD (Table 2).

Effect of Multiple Risk Factors for CHD

After stratification into 5 groups by the number of risk factors as identified by the Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults;²⁴ the HRs were 2.50 for 2 risk factors, 5.99 for 3 risk factors, and 12.39 for ≥4 risk factors compared with patients with 1 risk

Table 1 Risk Factors for CHD on Univariable Analysis

	All (142/7,832)			Men (80/2,476)			Women (62/5,356)		
	Events/ patients no.	HR	Overall p value	Events/ patients no.	HR	Overall p value	Events/ patients no.	HR	Overall p value
<i>Gender</i>									
Women	62/5,356	1.00		—			—		
Men	80/2,476	2.85	<0.01	—			—		
		(2.05–3.98)							
<i>Age (year)</i>									
<55	33/2,374	1.00		28/1,183	1.00		5/1,191	1.00	
55–<60	23/1,767	0.92		12/407	1.22		11/1,360	1.91	
		(0.54–1.57)			(0.62–2.41)			(0.66–5.50)	
60–<65	37/1,877	1.39	<0.01	19/465	1.68	0.06	18/1,412	3.02	<0.01
		(0.87–2.23)			(0.94–3.01)			(1.12–8.14)	
≥65	49/1,814	1.94		21/421	2.10		28/1,393	4.83	
		(1.25–3.01)			(1.19–3.79)			(1.86–12.49)	
<i>DM</i>									
(–)	74/6,200	1.00	<0.01	40/1,796	1.00	<0.01	34/4,404	1.00	<0.01
(+)	68/1,632	3.52		40/680	2.66		28/952	3.83	
		(2.53–4.89)			(1.72–4.12)			(2.32–4.89)	
<i>HT</i>									
(–)	56/4,555	1.00	<0.01	34/1,480	1.00	<0.01	22/3,075	1.00	<0.01
(+)	86/3,277	2.10		46/996	2.02		40/2,281	2.39	
		(1.50–2.94)			(1.30–3.15)			(1.42–4.02)	
<i>History of hyperlipidemia treatment</i>									
(–)	117/6,625	1.00	0.540	68/2,147	1.00	0.74	49/4,478	1.00	0.54
(+)	25/1,207	1.14		12/329	1.11		13/878	1.33	
		(0.74–1.76)			(0.60–2.05)			(0.72–2.45)	
<i>Body mass index (kg/m²)</i>									
<24	73/4,265	1.00	0.46	36/1,209	1.00	0.48	37/3,056	1.00	0.66
≥24	69/3,548	1.13		44/1,260	1.17		25/2,288	0.89	
		(0.81–1.57)			(0.76–1.82)			(0.54–1.48)	
<i>Smoking</i>									
(–)	101/6,634	1.00	<0.01	41/1,548	1.00	0.03	60/5,086	1.00	0.55
(+)	41/1,184	2.34		39/921	1.63		2/263	0.65	
		(1.63–3.36)			(1.05–2.53)			(0.16–2.67)	
<i>Drinking</i>									
(–)	85/5,456	1.00	<0.01	27/773	1.00	0.66	58/4,683	1.00	0.17
(+)	57/2,363	1.58		53/1,697	0.90		4/666	0.49	
		(1.13–2.21)			(0.56–1.42)			(0.18–2.21)	
<i>Total cholesterol (mg/dl)</i>									
<240	63/3,466	1.00		37/1,171	1.00		26/2,295	1.00	
240–<260	64/3,587	0.99		35/1,106	1.01		29/2,481	1.03	
		(0.70–1.39)	0.97		(0.61–1.61)	0.82		(0.61–1.75)	0.99
≥260	15/779	1.05		8/199	1.27		7/580	1.05	
		(0.60–1.84)			(0.59–2.72)			(0.46–2.42)	
<i>LDL-C (mg/dl)</i>									
<140	17/1,272	1.00		8/468	1.00		9/804	1.00	
140–<160	54/3,113	1.30		33/962	2.01		21/2,151	0.88	
		(0.75–2.24)	0.32		(0.93–4.34)	0.16		(0.40–1.91)	0.51
≥160	67/3,389	1.49		35/1,008	2.06		32/2,381	1.21	
		(0.88–2.54)			(0.96–4.45)			(0.58–2.53)	
<i>HDL-C (mg/dl)</i>									
≥60	20/679	1.00		10/645	1.00		15/2,371	1.00	
40–<60	97/4,137	2.86	<0.01	55/1,470	2.44	0.02	42/2,667	2.51	<0.01
		(1.84–4.44)			(1.24–4.78)			(1.39–4.53)	
<40	25/301	3.73		15/361	2.77		5/318	2.61	
		(2.07–6.71)			(1.25–6.18)			(0.95–7.19)	
<i>Triglycerides (mg/dl)</i>									
<120	45/3,475	1.00		18/738	1.00		27/2,737	1.00	
120–<150	27/1,489	1.39		15/458	1.34		12/1,031	1.17	
		(0.86–2.24)	<0.01		(0.67–2.65)	0.35		(0.59–2.30)	0.38
≥150	70/2,868	1.90		47/1,280	1.49		23/1,588	1.48	
		(1.30–2.76)			(0.86–2.56)			(0.85–2.58)	
<i>Lp(a) (mg/dl)</i>									
<15	61/3,407	1.00	<0.81	37/1,242	1.00	0.41	24/2,165	1.00	0.71
≥15	80/4,304	1.04		42/1,187	1.20		38/3,117	1.10	
		(0.75–1.45)			(0.77–1.87)			(0.66–1.84)	

Patients without baseline data were excluded in each category. DM and HT were reported by physicians. Smoking included only current smoker.

CHD, coronary heart disease; HR, hazard ratio; DM, diabetes mellitus; HT, hypertension; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; Lp(a), lipoprotein (a).

Table 2 Risk Factors for CHD on Multivariate Analysis

	<i>All</i>			<i>Men</i>			<i>Women</i>		
	<i>HR</i>	<i>95%CI</i>	<i>p value</i>	<i>HR</i>	<i>95%CI</i>	<i>p value</i>	<i>HR</i>	<i>95%CI</i>	<i>p value</i>
<i>Group</i>									
<i>Diet</i>	1.00	—	—	1.00	—	—	1.00	—	—
<i>Diet + pravastatin</i>	0.70	0.50–0.98	0.04	0.66	0.42–1.04	0.07	0.74	0.45–1.23	0.24
<i>Gender</i>									
<i>Women</i>	1.00	—	—	—	—	—	—	—	—
<i>Men</i>	2.28	1.57–3.32	<0.0001	—	—	—	—	—	—
<i>HDL-C (mg/dl)</i>									
≥60	1.00	—	—	1.00	—	—	1.00	—	—
40–<60	2.26	1.45–3.25	<0.01	2.40	1.22–4.72	0.01	2.08	1.15–3.76	0.02
<40	2.33	1.28–4.25	<0.001	2.58	1.14–5.80	0.02	1.82	0.66–5.04	0.25
<i>HT/DM</i>									
(–)	1.00	—	—	1.00	—	—	1.00	—	—
<i>HT</i>	2.87	1.74–4.75	<0.0001	2.57	1.33–4.97	<0.01	3.58	1.62–7.94	<0.01
<i>DM</i>	4.63	2.70–7.95	<0.0001	3.45	1.73–6.87	<0.001	7.56	3.17–18.04	<0.0001
<i>HT + DM</i>	6.21	3.61–10.67	<0.0001	5.15	2.57–10.30	<0.0001	8.44	3.51–20.31	<0.0001
<i>Smoking</i>									
(–)	1.00	—	—	1.00	—	—	1.00	—	—
(+)	1.46	0.97–2.19	0.07	1.61	1.03–2.51	0.04	0.70	0.17–2.89	0.63
<i>Age (year)</i>									
<55	1.00	—	—	1.00	—	—	1.00	—	—
55–<60	1.16	0.68–1.99	0.59	1.07	0.54–2.11	0.84	1.82	0.63–5.26	0.27
60–<65	1.61	1.00–2.61	0.05	1.43	0.79–2.59	0.23	2.61	0.96–7.04	0.06
≥65	2.33	1.48–3.68	<0.001	1.90	1.07–3.38	0.03	4.00	1.54–10.42	<0.01

The classification of each factor is as in Table 1. The risk factors were determined by multivariable Cox proportional hazard model using a backward stepping algorithm ($p < 0.20$).

CI, confidence interval. Other abbreviations see in Table 1.

Table 3 Effect of Multiple Risk Factors for CHD

	<i>Number of risks</i>	<i>Events/patients</i>	<i>HR</i>	<i>95%CI</i>	<i>p value</i>
<i>5 risk categories</i>					
<i>All</i>	0	0/637	—	—	—
	1	14/2,509	1.00	—	—
	2	29/2,034	2.50	1.32–4.74	<0.01
	3	78/2,333	5.99	3.99–10.58	<0.0001
	≥4	21/319	12.39	6.30–30.60	<0.0001
<i>Men</i>	0	0/86	—	—	—
	1	5/536	1.00	—	—
	2	13/655	2.09	0.74–5.86	0.16
	3	42/960	4.71	1.86–11.90	<0.01
	≥4	20/239	9.29	3.49–24.75	<0.0001
<i>Women</i>	0	0/551	—	—	—
	1	9/1,973	1.00	—	—
	2	16/1,379	2.48	1.10–5.62	0.03
	3	36/1,373	5.70	2.75–11.83	<0.0001
	≥4	1/80	2.89	0.37–22.82	0.31
<i>3 risk categories</i>					
<i>All</i>	0	0/637	—	—	—
	1–2	43/4,543	1.00	—	—
	≥3	99/26,523	4.00	2.80–5.72	<0.0001
<i>Men</i>	0	0/86	—	—	—
	1–2	18/1,191	1.00	—	—
	≥3	62/1,199	3.49	2.07–5.90	<0.0001
<i>Women</i>	0	0/551	—	—	—
	1–2	25/3,352	1.00	—	—
	≥3	37/1,453	3.43	2.07–6.70	<0.0001

Women (≥55 years), HT, DM or fasting plasma glucose >110 mg/dl, smoking habit, and low HDL-C (<40 mg/dl). For patients with DM, the lower limit of the number of risk factors was set at 3. Abbreviations see in Tables 1, 2.

factor (Table 3). Further analysis showed a 4.00-times higher risk in patients with ≥3 risk factors compared with patients with 1 or 2 risk factors, when the number of categories was reduced to 3. No difference in risk was observed between men and women. However, because of the limited

number of women with ≥4 risk factors, the interpretation of those results is limited.

Effect of Pravastatin

Mean TC was reduced by 2.1% (from 6.27 mmol/L to

Fig 1. The effect of pravastatin on coronary heart disease for each risk factor. CI, confidence interval; DM, diabetes mellitus; HDL, high-density lipoprotein; HR, hazard ratio; HT, hypertension.

6.13 mmol/L) and 11.5% (from 6.27 mmol/L to 5.55 mmol/L) and mean LDL-C by 3.2% (from 4.05 mmol/L to 3.90 mmol/L) and 18.0% (from 4.05 mmol/L to 3.31 mmol/L) in the diet and the diet plus pravastatin groups, respectively. The efficacy of diet plus pravastatin treatment to reduce CHD was assessed in relation to each identified risk factor, that is, male sex, increasing age, lower serum HDL-C, DM, HT, and smoking habit. Diet plus pravastatin treatment reduced CHD risk by 14 to 30%, regardless of the type of risk factor. No interaction was found between the presence or absence of each risk factor (Fig 1).

Discussion

This risk factor analysis of the MEGA Study assessed sex, age, presence or absence of DM, presence or absence of HT, history or no history of smoking, history or no history of drinking alcohol, serum concentrations of TC, LDL-C, HDL-C, and TG, and history or no history of treatment for hyperlipidemia. The risk factors for CHD were identified as male sex, increasing age, low serum HDL-C, DM, HT, and smoking habit.

Univariable analysis identified drinking alcohol, TG, and HDL-C as significant risk factors for CHD. However, on multivariable analysis, only HDL-C was a significant risk factor for CHD; drinking was not a risk factor after adjusting for sex. The tight correlation between HDL-C and TG might contribute to HDL-C being the stronger and significant risk factor on multivariable analysis.

The risk factors that were identified in the present analysis were similar to those from epidemiological surveys and large-scale clinical studies conducted previously in Japan as well as in other countries^{14,16-18}. Assessing these risk factors in further detail, some differences were observed between

men and women for the effect of the CHD risk factors. The incidence of CHD was higher in men and women over 55 years old compared with those who were younger. However, this finding was more pronounced in women than in men, in line with the results from a previously published study²⁵. This is likely because of the post-menopause loss of the protective effect of estrogen, an effect that contributes to a lower incidence of CHD. An epidemiological study showed that the incidence of CHD in women begins to rise sharply beginning at ages 55 to 60 years, ie, at the onset of menopause, and reported that the pattern of the age-related increase of CHD in women tends to lag about 10 years behind that in men²⁶⁻²⁸. Additionally, the effect of DM was stronger for women than men, although it was a strong risk factor for CHD for both men and women. Similar results were reported from risk factor analysis in an observational study (J-LIT) conducted in Japan using simvastatin²⁹. Some cohort studies have suggested that the effect of DM on the risk of ischemic heart disease is greater in women than in men^{30,31}. Given that women have a poorer prognosis than men once myocardial infarction has occurred, despite the lower incidence of ischemic heart disease in women³², the control of DM is especially important for primary prevention of CHD in elderly women. An exploratory analysis about the effect of pravastatin in women in the MEGA Study was recently published in *Circulation*³³. The incidence of cardiovascular events was 26% to 37% lower in the diet plus pravastatin treatment group than in the diet alone group. These differences did not reach statistical significance, yet the overall risk reductions were similar to those in men. In women, the risk of events such as CHD rose with age and tended to rise particularly markedly. Notably, women ≥60 years of age treated with diet plus pravastatin had markedly higher risk reductions for cardiovascular

events (45% to 64%) than did women treated with diet alone. These results in women in the MEGA Study confirm previously reported results from other studies, and highlight the importance of risk factor management for CHD in women, especially woman ≥ 60 years of age.

Interestingly, elevated serum concentrations of TC and LDL-C, which are generally recognized as risk factors for CHD, were not identified as risk factors in the present analysis. There might be several reasons for this difference. The present analysis was including the treatment group, then additional analysis performed in the diet-only group to clarify the relationship between TC, LDL-C, and CHD risk. The risk factors identified in this additional analysis were similar to those in the total population, except for smoking, and no association was observed between TC concentration, LDL-C, and CHD. However, comparing the patients with an LDL-C concentration above or below 160 mg/dl in the diet-only treatment group, LDL-C seemed to be associated with an increased incidence of CHD in men (HR 1.39, $p=0.265$) and women (HR 1.94, $p=0.052$). Therefore, a further study with a sufficiently-sized population is needed to determine the true relationship between LDL-C, TC, and CHD risk. Moreover, we performed an additional analysis of risk factors including on-treatment (mean level during the treatment period) TC or low-density lipoprotein (LDL). The multivariable analysis identified on-treatment TC and LDL as risk factors, satisfying a cut-off of $p<0.20$ (on-treatment TC, $p=0.074$; on-treatment LDL, $p=0.068$), in addition to the baseline risk factors. Then, the HRs of baseline risk factors are almost equivalent to the results without on-treatment TC and LDL. Moreover, the preventive effect of pravastatin treatment remained after adjusting for on-treatment TC or LDL (pravastatin treatment: HR=0.83 (95%CI, 0.57, 1.20) with on-treatment TC; HR=0.78 (95%CI, 0.52, 1.19) with on-treatment LDL). This indicates that pravastatin treatment has a preventive effect separate from its lipid lowering ability. It is very difficult to evaluate the pleiotropic effects of pravastatin quantitatively and to eliminate it. Therefore, the present analysis used the baseline lipid values.

In addition, in the MEGA Study, the entry criterion for serum TC was 220 to 270 mg/dl, which might be too narrow a range for a reasonable comparison. Risk factor analysis at baseline in the West of Scotland Coronary Prevention Study (WOSCOPS) of the effects of pravastatin on primary prevention conducted in Scotland,¹⁸ also showed that serum concentrations of TC and LDL-C were not risk factors. In WOSCOPS, the reason was attributed to the strict inclusion criterion for serum TC concentration.³⁴ The entry criterion was even lower in the MEGA Study²² than in the WOSCOPS.¹⁸ Further, there might have been some patients with a high concentration of LDL-C classified as having a low concentration of LDL-C, as concentrations were determined using the Friedewald equation, which becomes less reliable in persons with high TG concentrations.

Because of the narrow range of the TC concentrations in the MEGA Study and the inclusion of the treatment group in the analysis, it is possible that a different result might be obtained in a larger population than that included in the MEGA Study.

In the present analysis, the strongest risk factors for CHD were diabetes, HT, and diabetes plus HT. A significant interaction was observed between DM and HT, and the presence of both increased the risk of CHD additively. Therefore, it appears that CHD risk in the presence of multiple risk factors can be reasonably estimated by multiplying or

adding the HRs for the individual factors. No interactions were shown among the other risk factors.

As a method to estimate the effects of multiple risk factors, we stratified the population in the present study according to the risk classification in the Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults,²⁴ established based on the results of epidemiological studies, and compared the HRs for each stratification. However, because the classifications in the Guideline are somewhat broad, there might be some question about the appropriateness of using a classification that assigns a similar degree of risk to each risk factor, except for DM, which is assigned a higher degree of risk, based on the data from our present analysis.

Conclusion

In conclusion, in the present analysis, we assessed the efficacy of pravastatin for the primary prevention of CHD in relation to the presence of the identified risk factors for CHD, that is, male sex, increasing age, low serum HDL-C, DM, HT, and smoking habit. Pravastatin is equally effective regardless of the presence of these factors or the presence of multiple risk factors. Further, no significant difference in efficacy between the men and women was found (data not shown), confirming the benefit of pravastatin treatment in men and women.

Elevated TC and LDL-C, generally considered as risk factors for CHD, were not identified as risk factors in the present analysis. Also, as reported previously from the main results of the MEGA Study, no interaction was observed between the effects of pravastatin and LDL-C (>155 mg/dl or <155 mg/dl) on the reduction of CHD incidence.²² In WOSCOPS, too, no significant difference in the effect of pravastatin in decreasing the relative risk of CHD was shown between the 2 groups stratified by LDL-C concentration above or below 5 mmol/L (193 mg/dl).³⁴ Taken together, the results from the present analysis and others show that pravastatin is consistently effective in reducing the risk of CHD, regardless of the serum LDL-C concentration.

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