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Gender Difference in Coronary Events in Relation to Risk Factors in Japanese Hypercholesterolemic Patients Treated With Low-Dose Simvastatin

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Background Gender differences between the risk factors for coronary heart disease and coronary events were examined in the Japan Lipid Intervention Trial, a 6-year observational study.

Methods and Results Men (12,575) and women (27,013) were analyzed for risk of coronary events (acute myocardial infarction and sudden cardiac death). Simvastatin reduced serum low-density lipoprotein cholesterol (LDL-C) by 27% in both genders, and increased serum high-density lipoprotein cholesterol (HDL-C) in men (5%) and women (4%). The incidence of coronary events was lower in women (0.64/1,000 patient-years) than in men (1.57/1,000 patient-years). The risk of coronary events increased by 18% in men and 21% in women with each 10 mg/dl elevation of LDL-C, and decreased by 39% in men and 33% in women with each 10 mg/dl elevation of HDL-C. The risk increased proportionally with aging in women, but not in men. Diabetes mellitus (DM) was more strongly related to the risk of coronary events for women (relative risk 3.07) than for men (relative risk 1.58).

Conclusions The incidence of coronary events is lower in women. Serum LDL-C is related to an increased risk of coronary events to the same extent in both genders. DM seems to be a more important risk factor in women, trading off the lower risk of coronary events among them. (*Circ J* 2006; **70:** 810–814)

Key Words: Coronary events; Hyperlipidemia; Risk factors; Serum cholesterol; Sex differences

Coronary heart disease (CHD), including myocardial infarction and cardiac sudden death, is one of the leading causes of death in Japan[1] The risk of developing CHD is known to be markedly different between men and women:[2,3] CHD incidence is 2 to 5 times higher among middle-aged men than women. In the Japan Lipid Intervention Trial (J-LIT)[4–7] we previously reported that serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) concentrations were positively and serum high-density lipoprotein cholesterol (HDL-C) concentration was inversely related to CHD or cerebrovascular disease risk in patients under treatment for hypercholesterolemia. The role of coronary risk factors in the development of CHD has been studied extensively in men[8–10] but relatively few studies have investigated women[2,11]

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This study aimed to assess gender differences in the association of risk factors with CHD in the J-LIT data. The J-LIT is a nationwide cohort study of 52,421 hypercholesterolemic patients treated with open-labeled low-dose simvastatin (5–10 mg/day)[4,5] The J-LIT included a large number of female patients, and we were able to investigate the gender difference in the role of risk factors in the occurrence of coronary events.

Methods

Study Design

The design of the J-LIT study has been previously described[12] Briefly, study patients with serum TC concentration ≥220 mg/dl, men aged 35–70 years and postmenopausal women aged 70 years or less, were treated with 5–10 mg/day of simvastatin. Body weight, serum lipid concentrations (TC, LDL-C, HDL-C, and triglyceride (TG)) were measured at baseline, and patients were interviewed as regards family history of CHD, number of cigarettes smoked, and the amount of alcohol ingestion. Serum lipid concentrations and CHD-related events (acute myocardial infarction and cardiac sudden death) were monitored every 6 months for 6 years in all patients, including those who discontinued simvastatin. Serum lipid concentrations were determined in each study institution, and the serum LDL-C concentration was calculated using the Friedewald formula for patients with TG concentration ≤400 mg/dl[13] Study physicians recommended dietary and exercise-therapy for hyperlipidemia to all patients. Additional lipid-lowering

agents were allowed only when an adequate response in serum TC concentration was not gained by simvastatin monotherapy. Each patient was informed of the purpose and method of the study, drug efficacy and the need for long-term treatment and they gave verbal, not written, informed consent.

Subjects

Patients who had been previously treated with a lipid-lowering agent were screened for eligibility after a washout period of at least 4 weeks. For patients previously treated with probucol, the washout period was at least 12 weeks. The exclusion criteria were the occurrence of acute myocardial infarction or stroke within the past month, concurrent uncontrolled diabetes mellitus (DM), serious hepatic or renal disease, secondary hypercholesterolemia, cancer or any other illness with potentially poor survival.

Of the 52,421 patients enrolled, 5,127 were excluded because of a history of CHD, 4,934 for lack of follow-up data, and 2,772 for missing data of the covariates. Therefore, data from 39,588 patients (12,575 men, 27,013 women) were used in the present study.

Endpoints

The primary endpoints were major coronary events, defined as nonfatal and fatal myocardial infarction and sudden cardiac death. Incidence of myocardial infarction or death was counted once for each patient during the treatment, and the follow-up data thereafter were excluded from the analysis. The events were reviewed and determined by the Endpoint Classification Committee.

Statistical Analysis

The mean lipid concentrations were calculated using data available at the follow-up points in time during the treatment period. The data of lipid concentrations after the onset of events were excluded. Data during the treatment period after discontinuation of simvastatin were also included for analysis. Mean values for serum lipid concentrations and age were tested with unpaired t-test, and the prevalence of baseline characteristics were tested with the chi-square test for comparison between men and women. Patients in each sex were categorized into 5–6 groups according to the mean lipid concentrations of treatment period for TC, TG, LDL-C and HDL-C with intervals of 20, 50, 20, 10 mg/dl, respectively, and for the LDL-C/HDL-C ratio with an interval of 0.5. The reference category for the relative risk was set on the group with the lowest lipid concentrations and the lowest value of LDL-C/HDL-C ratio. Relative risks and the 95% confidence intervals (CI) were calculated using the Cox proportional hazards model with adjustment for baseline characteristics such as sex, age, hypertension, DM, body mass index (BMI), ECG abnormality, family history of CHD, alcohol ingestion and cigarette smoking. Heterogeneity between men and women was evaluated by the likelihood ratio test. Two-sided p-value <0.05 was considered statistically significant. All the statistical calculations were performed using SAS software (version 8.02, SAS Institute, Inc, Cary, NC, USA).

Results

Serum Lipids and Other Risk Factors

There were no significant difference as regards the prevalence of obesity (BMI ≥25.0 kg/m^2), hypertension, ECG abnormality, and family history of CHD between men and women (Table 1). In men, the prevalence of DM was higher ($p<0.001$), and cigarette smoking and alcohol ingestion were much more frequent ($p<0.001$).

Table 1 Baseline Characteristics of the Subjects

	Men (n=12,575)	*Women (n=27,013)*
Age (years)	*54.0 (9.1)*	*59.5 (6.5)*
Obesity (%)[a)]	*36.7*	*32.2*
Hypertension (%)[b)]	*45.4*	*46.3*
Diabetes mellitus (%)[c)]	*20.0*	*13.9*
ECG abnormality (%)[d)]	*13.4*	*12.9*
Family history of CHD (%)[e)]	*5.1*	*4.8*
Cigarette smoking (%)[e)]	*43.8*	*4.1*
Alcohol use (%)[e)]	*73.4*	*8.7*
Lipid profiles		
Baseline (mg/dl)		
TC	*268 (41)*	*271 (31)*
LDL-C	*178 (34)*	*184 (33)*
TG	*250 (241)*	*169 (111)*
HDL-C	*49 (15)*	*55 (15)*
During the treatment (mg/dl)		
TC	*218 (31)*	*221 (29)*
LDL-C	*130 (31)*	*135 (28)*
TG	*198 (133)*	*148 (77)*
HDL-C	*51 (13)*	*57 (14)*

Figs are mean ± SD unless otherwise specified.
CHD, coronary heart disease; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol.
[a)] Body mass index ≥25 kg/m^2. [b)] Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg or medication for hypertension. [c)] Fasting plasma glucose ≥140 mg/dl or medication. [d)] Study physician's diagnosis. [e)] Self-reported information.

Lipid profiles at baseline and during the treatment period are shown for men and women in Table 1. Men had higher concentrations of serum TG and lower concentrations of serum HDL-C at baseline and during the treatment in comparison with women. Mean percent changes in the TC, LDL-C, TG, and HDL-C concentrations from baseline to during the treatment in men were –18.8% ($p<0.001$), –27.2% ($p<0.001$), –20.9% ($p<0.001$), and +4.7% ($p<0.001$), respectively, and the corresponding values in women were –18.2% ($p<0.001$), –26.6% ($p<0.001$), –12.8% ($p<0.001$) and +4.4% ($p<0.001$), respectively.

Incidence of Coronary Events

The incidence of coronary events was greater (105/12,575) in men than in women (93/27,013) during the treatment period. Incidence rates of coronary events per 1,000 patient-years were 1.57 in men and 0.64 in women. The age-adjusted relative risk of coronary events for men vs women was 2.81 (95% CI 2.10–3.76, $p<0.001$).

Serum Lipid Concentrations During the Treatment Period and Risk of Coronary Events

The risk of coronary events in relation to serum lipid concentrations is shown in Table 2. Increased risk for coronary events was evident at TC ≥240 mg/dl and LDL-C ≥160 mg/dl in both men and women. An increased risk of CHD associated with elevated concentration of TG (≥250 mg/dl) was noted in women but not in men. In men, the relationship between TG and CHD risk was not measurable. A lower risk of coronary events associated with elevation in HDL-C was seen in both sexes, but the protec-

Table 2 Relative Risk of Coronary Events According to Serum Lipid Concentrations During Treatment[a)]

	Men					Women				
	N	Event	RR	95%CI	p value	N	Event	RR	95%CI	p value
TC (mg/dl)										
<200	3,442	24	1.00	(Referent)		5,833	22	1.00	(Referent)	
200–219	3,643	23	0.99	(0.56–1.77)	0.984	8,194	14	0.52	(0.27–1.02)	0.057
220–239	3,029	25	1.46	(0.83–2.56)	0.192	7,070	18	0.88	(0.47–1.64)	0.687
240–259	1,431	15	2.01	(1.05–3.88)	0.036	3,668	22	2.19	(1.21–3.98)	0.010
260–	1,030	18	3.48	(1.86–6.52)	<0.001	2,248	17	2.82	(1.48–5.36)	0.002
LDL-C (mg/dl)										
<120	4,680	27	1.00	(Referent)		8,050	22	1.00	(Referent)	
120–139	3,542	23	1.24	(0.71–2.16)	0.456	8,418	17	0.83	(0.44–1.57)	0.566
140–159	2,406	21	1.84	(1.03–3.26)	0.038	6,185	19	1.42	(0.77–2.64)	0.263
160–179	1,057	12	2.60	(1.31–5.17)	0.006	2,673	17	3.29	(1.74–6.23)	<0.001
180–	648	17	6.58	(3.53–12.25)	<0.001	1,564	17	5.78	(3.03–11.00)	<0.001
TG (mg/dl)										
<100	1,521	11	1.00	(Referent)		6,337	18	1.00	(Referent)	
100–149	3,663	22	0.84	(0.41–1.74)	0.634	10,444	32	0.98	(0.55–1.76)	0.946
150–199	3,127	33	1.51	(0.76–3.02)	0.243	5,861	17	0.87	(0.44–1.71)	0.684
200–249	1,768	18	1.46	(0.68–3.15)	0.330	2,429	9	1.12	(0.50–2.53)	0.783
250–	2,494	21	1.24	(0.58–2.65)	0.572	1,921	17	2.62	(1.32–5.21)	0.006
HDL-C (mg/dl)										
<40	2,198	36	1.00	(Referent)		1,758	10	1.00	(Referent)	
40–44	2,133	23	0.64	(0.38–1.09)	0.099	2,794	17	1.12	(0.51–2.45)	0.776
45–49	2,207	17	0.44	(0.25–0.80)	0.006	4,101	24	1.09	(0.52–2.28)	0.819
50–54	1,956	13	0.39	(0.21–0.74)	0.004	4,440	13	0.57	(0.25–1.30)	0.179
55–59	1,402	8	0.33	(0.15–0.72)	0.005	4,053	13	0.66	(0.29–1.51)	0.324
60–	2,679	8	0.17	(0.08–0.36)	<0.001	9,867	16	0.33	(0.15–0.73)	0.006
LDL-C/HDL-C										
<2.0	2,851	11	1.00	(Referent)		7,426	11	1.00	(Referent)	
2.0–2.4	2,719	11	1.10	(0.48–2.55)	0.817	6,909	19	1.95	(0.92–4.10)	0.080
2.5–2.9	2,598	17	1.91	(0.89–4.10)	0.095	5,884	14	1.68	(0.76–3.72)	0.199
3.0–3.4	1,889	20	3.21	(1.53–6.74)	0.002	3,545	21	4.57	(2.19–9.54)	<0.001
3.5–4.0	1,082	13	3.87	(1.72–8.72)	0.001	1,728	12	5.04	(2.21–11.49)	<0.001
4.0–	1,194	28	8.06	(3.95–16.44)	<0.001	1,398	15	8.56	(3.88–18.88)	<0.001

RR, relative risk; CI, confidence interval. Other abbreviations see in Table 1.

[a)] Coronary events included acute myocardial infarction and sudden cardiac death. Adjustment for age, hypertension, diabetes mellitus, body mass index, ECG abnormality, family history of CHD, cigarette smoking, and alcohol use.

Table 3 Relative Risk of Coronary Events and Baseline Characteristics[a)]

	Men					Women					Heterogeneity p value[b)]
	N	Event	RR	95%CI	p value	N	Event	RR	95%CI	p value	
Age (years)											
<55	6,281	49	1.00	(Referent)		6,137	8	1.00	(Referent)		0.008
55–59	2,182	14	0.74	(0.41–1.34)	0.320	6,488	15	1.82	(0.77–4.29)	0.174	
60–64	2,164	17	0.87	(0.50–1.53)	0.627	7,112	29	3.02	(1.38–6.62)	0.006	
≥65	1,948	25	1.42	(0.86–2.34)	0.168	7,276	41	4.11	(1.92–8.82)	<0.001	
Obesity[c)]	4,621	40	0.99	(0.66–1.48)	0.956	8,700	32	0.91	(0.59–1.40)	0.663	0.676
Hypertension[d)]	5,705	68	2.15	(1.42–3.26)	<0.001	12,511	62	2.05	(1.32–3.18)	0.001	0.864
Diabetes mellitus[e)]	2,513	29	1.58	(1.03–2.43)	0.037	3,747	31	3.07	(1.99–4.74)	<0.001	0.019
ECG abnormality[f)]	1,681	26	1.86	(1.18–2.91)	0.007	3,473	23	1.67	(1.04–2.70)	0.035	0.972
Family history of CHD[g)]	637	10	2.00	(1.04–3.84)	0.038	1,289	13	3.34	(1.85–6.04)	<0.001	0.317
Cigarette smoking[g)]	5,506	52	1.46	(0.98–2.17)	0.063	1,105	9	2.94	(1.43–6.02)	0.003	0.148
Alcohol use[g)]	9,224	70	0.63	(0.41–0.96)	0.031	2,337	6	0.61	(0.26–1.45)	0.266	0.933

Abbreviations see in Tables 1,2.

[a)] Coronary events included acute myocardial infarction and sudden cardiac death. Adjustment for age, hypertension, diabetes mellitus, body mass index, ECG abnormality, family history of CHD, cigarette smoking, and alcohol use. [b)] Heterogeneity between men and women, based on the likelihood ratio test. [c)] Body mass index ≥25 kg/m^2. [d)] Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg or medication for hypertension. [e)] Fasting plasma glucose ≥140 mg/dl or medication. [f)] Study physician's diagnosis. [g)] Self-reported information.

tive association was more evident in men. The relative risk for coronary events was substantially increased in patients with LDL-C/HDL-C ≥3.0 in both men and women.

The increase in the risk of coronary events for each 10 mg/dl elevation of LDL-C concentration during the treatment period was 18% (95% CI 12–24%) in men and 21% (95% CI 15–27%) in women, and the decrease in CHD risk associated with each 10 mg/dl elevation of HDL-C concentration was 39% in men and 33% in women. The relationships of coronary events with baseline LDL-C and HDL-C concentrations were also examined, but were much weaker than those observed during the treatment period. With each 10 mg/dl elevation of LDL-C concentration at baseline, the increase in the relative risk was 7% for men

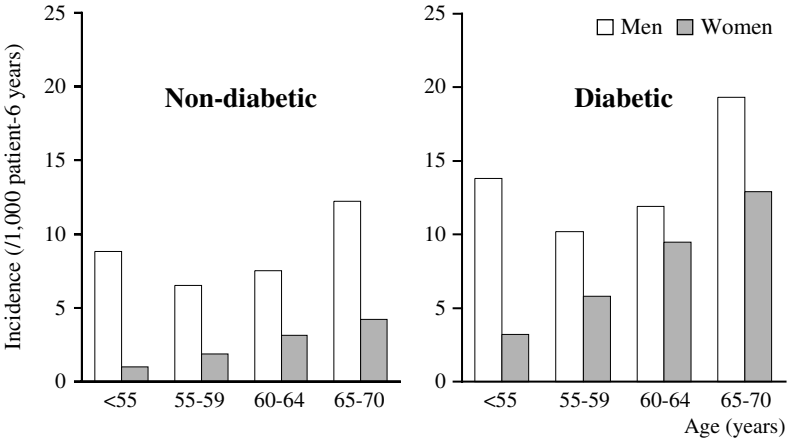

Fig 1. Estimated rates of coronary events according to age in men and women with and without diabetes mellitus (DM). Incidence rates were calculated from coronary heart disease (CHD) relative risks and the proportion of patients in each age category, for men and women separately, using Cox proportional hazards model, in which adjustment was made for age, hypertension, DM, body mass index, ECG abnormality, family history of CHD, cigarette smoking, and alcohol use.

and 9% for women and the decrease in risk with each 10 mg/dl elevation of HDL-C at baseline was 20% in both men and women.

Patient Baseline Characteristics and Risk of Coronary Events

The effect of age on the risk of coronary events was seen in women, but not in men (Table 3). Hypertension, DM, ECG abnormalities and a family history of CHD were also risk factors for coronary events in both men and women, but increased risks associated with DM and a family history of CHD were more marked for women than for men; the relative risk with DM was 1.58 in men and 3.07 in women, and the corresponding values for a family history of CHD were 2.00 in men and 3.34 in women. Obesity was unrelated to coronary events in either men or women. Although alcohol ingestion was protective in both men and women to the same extent, cigarette smoking was more strongly related to an increased risk of coronary events in women.

Discussion

This report addresses the gender differences in the relationship of serum lipid concentrations and other risk factors to CHD risk in Japanese patients under long-term treatment for hypercholesterolemia. Although serum TC and LDL-C concentrations were very similarly related to CHD risk in men and women, there was a difference between men and women in the relationship to serum TG and HDL-C concentrations. An inverse relationship of HDL-C to CHD risk was seen in men and women, but the HDL-C concentration showing a decreased risk of CHD differed by sex. The risk was significantly decreased at HDL-C ≥45 mg/dl in men and at HDL-C ≥60 mg/dl in women. The findings agree with observations published in the United States and Europe[2,3] and further indicate that the criterion of "low HDL-C" must be differential for men and women. An increased risk was observed only in women with an extremely high concentration of TG (≥250 mg/dl). Interpretation of this finding is difficult, and we do not have a clear idea about the implication of the present finding on serum TG.

In the present study, men did not show a clear increase in the risk of coronary events with increasing age, whereas there was a progressive increase in the risk with advancing age in women. The latter finding could be a reflection of the increase in serum TC and LDL-C concentrations with increasing age after menopause. The lack of an increasing trend in the association between age and coronary events in men is an unexpected finding, and may have been due to unknown characteristics of the male participants in the present study.

Whereas DM was related to increased CHD risk in both men and women, the increased risk was much greater in women, as indicated by a statistically significant interaction (p=0.019). These results did not change when further adjusted for TC or LDL-C. However, the risk difference between men and women for DM was not unique to the J-LIT patients. In a meta-analysis of 10 prospective studies, Lee et al showed that the effect of DM on the CHD risk was greater in women than in men![14] They showed that the relative risk of coronary death for DM patients vs non-DM patients was 2.58 (95% CI 2.05–3.26) in women and 1.85 (95% CI 1.47–2.33) in men (interaction p=0.045)![14] It was further noted in a later study that DM diminished the female advantage for lower CHD incidence![15] That DM is a stronger CHD risk factor in women may be related to the lower concentrations of HDL-C. Walden suggested that lower HDL-C concentrations in diabetic women as compared with men might be relevant to a stronger association between DM and CHD in women![16] In the present study, mean HDL-C concentrations in female diabetic patients were lower than those of non-diabetic patients (55.5 vs 57.5 mg/dl, p<0.001), but there was no difference in the HDL-C concentrations between the 2 groups in men (50.8 vs 51.3 mg/dl, p=0.09). The relative risk for DM was unchanged with adjustment for HDL-C. When the predicted rates of CHD incidence according to age were examined in men and women with and without DM (Fig 1), the increase in CHD incidence with aging was augmented in the presence of DM. Notably, DM diminished the women's advantage of having a lower CHD incidence in older patients.

Both cigarette smoking and family history of CHD were related to a greater increase in the risk of coronary events in women than in men. These differential increases in men and women may have been caused by random variation, as indicated by the lack of statistical significance for the interaction. As regards the effect of cigarette smoking, some studies suggest that smoking is a stronger risk factor in women than in men[2,17] but others have failed to find such a finding![18]

Finally, the present study results indicated that hypertension was an important risk factor in men and women equally, and that alcohol ingestion was protective in both sexes. These findings are in agreement with observations reported elsewhere![19–21]

In conclusion, the incidence of coronary events was 60% lower in women than in men among the J-LIT participants. Although the relationship of serum TC and LDL-C concentrations to coronary events was similar in men and women, the HDL-C concentration associated with a decreased risk of coronary events was slightly higher in women. DM was a stronger risk factor in women, and traded off the women's advantage of having a lower risk of coronary events, especially in aged patients.

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