Journal of Atherosclerosis and Thrombosis Vol. 9, No. 5

Original Articles

Effect of Pravastatin–Induced LDL-Cholesterol Reduction on Coronary Heart Disease and Cerebrovascular Disease in Japanese: Hokuriku Lipid Coronary Heart Disease Study-Pravastatin Atherosclerosis Trial (Holicos-PAT)

Junji Koizumi[1], Masami Shimizu[1], Susumu Miyamoto[2], Hideki Origasa[3], Hiroshi Mabuchi[1], for The Hokuriku Lipid CHD Study Group

[1] *School of Medicine, Kanazawa University, Kanazawa, Japan.*
[2] *Himi City Hospital, Himi, Japan.*
[3] *Toyama Medical and Pharmaceutical University, Toyama, Japan.*

The purpose of Holicos-PAT was to investigate the efficacy of serum lipid lowering by pravastatin against coronary heart disease (CHD) and cerebrovascular disease (CVD) in the Japanese population. Hypercholesterolemic men and women (n = 2,232), aged 40-70 years, were followed up for 5 years, while they were receiving pravastatin (group P, n = 1,422) or only diet therapy (group C, n = 810). The primary endpoint was CHD (a composite of onset or worsening of angina pectoris, performing CABG or PTCA, non-fatal myocardial infarction, death from CHD including heart death or sudden death). The secondary endpoints were comprised of CVD, total mortality, variation of serum lipid and apoprotein levels, and a relationship between the LDL-C level and occurrence of CHD. For several reasons (proving to meet the exclusion criteria after registration, etc.), 1,290 cases of group P and 749 cases of group C were used as subjects for the primary analysis. The mean follow-up period was 4.5 years in group P and 4.2 years in group C for events of CHD. The mean LDL-C level (SD) in group P was 176 (29) mg/dl and decreased to 134 (29) mg/dl one year later. This effect continued during the follow-up period. CHD events occurred in 9.2/1000 patient-years for men and 2.4/1000 patient-years for women without a history of CHD. CHD events occurred in 55.3/1000 patient-years for men and 23.6/1000 patient-years for women with a history of CHD, which was 6 times higher in men and 10 times higher in women than in those without a history of CHD, respectively. The adjusted relative risk ratio of group P to group C for CHD events was 0.74 (95%CI: 0.47-1.19). In the patients with a history of CHD, the ratio was 0.55 (95%CI: 0.30-1.00). The effect was apparent in the patients with a history of CHD. The incidence of myocardial infarction in Japanese patients with hypercholesterolemia living in the Hokuriku district was apparently lower, than the worldwide incidence, indicative that pravastatin may have a tendency to inhibit the occurrence of events of arteriosclerotic disease. *J Atheroscler Thromb, 2002; 9: 251-259.*

Key words: Pravastatin, Coronary heart disease, Cerebrovascular disease, Prospective study

Introduction

Epidemic studies have proved that hypercholesterolemia is a risk factor for CHD (1-3). In Japan, this was supported by the Research Group of the Ministry of Welfare, investigating primary hypercholesterolemia of specific diseases (4).

Address for correspondence: Junji Koizumi, MD, The Department of General Medicine, Kanazawa University Hospital, 13-1 Takara-machi, Kanazawa 920-8641, Japan.
E-mail: koizuj@med.m.kanazawa-u.ac.jp
Received February 13, 2002.
Accepted for publication June 12, 2002.

In Western countries, the usefulness of lipid reduction therapy for CHD was demonstrated in large-scale clinical studies using the statins, WOS, AFCAPS/TexCAPS, 4S, CARE, and LIPID (5-9). There have been some reports of its usefulness for CVD (cerebral infarction and hemorrhage) (7, 9, 10). However, the usefulness of treatment with statins has not been confirmed in elderly populations with a low incidence of CHD. The mean life expectancy in Japan, determined in 2000, is 77.64 years for men and 84.62 years for women, and it is estimated that 84.1% of men and 92.2% of women survive until the age of 65. The results of prospective clinical trials on CHD have been reported in Japan by CARS (11) and J-MIC (S) (12), in which coronary arteriosclerosis was prevented from progressing, KLIS (13), in which male patients were used as subjects, and PATE (14), in which aged patients were used as subjects. However, not enough data is available on the incidence and mortality of CHD or CVD in a range of hypercholesterolemic patients in Japan, including relatively young subjects and women. Moreover, there have been only a few reports describing the usefulness of serum cholesterol-lowering therapy for the above populations. Thus the results of clinical trials in the Japanese, who have a low rate of mortality for CHD (15,16) and different life style and hereditary predisposition from the West, are thought to provide valuable infromation on lipid-lowering therapy in low-risk populations.

As for Holicos-PAT, we followed up men and women who had hypercholesterolemia with or without pravastatin treatment, so as to investigate the incidence of CHD events, CVD events, and total mortality. Hypercholesterolemia was defined as a serum cholesterol level of 220 mg/dl (5.69 mmol/l) or higher. Moreover, the treatment effect was compared between those receiving pravastatin and a diet therapy group controlling for risk factors. Furthermore, the relationship between LDL-C reduction and occurrence of CHD was investigated.

Methods

Study design

Hypercholesterolemic men and women, aged 40-70 years, were followed up for 5 years, while receiving pravastatin (group P) or diet only therapy (group C). The administration of pravastatin was not randomized. Treatment was determined by the doctor based on daily medical examinations. If an antilipidemic agent had already been used, the study was initiated with a TC level of 220 mg/dl or higher after the drug had been withdrawn for at least 4 weeks. When sufficient diet therapy had already been achieved, patients with a TC level of 200 mg/dl or higher were used as subjects.

Patients with familial hypercholesterolemia (FH), secondary hypercholesterolemia (hypothyroidism, nephrotic syndrome, type 1 diabetes, severe diabetes using insulin, and others), or complications such as severe liver disease or nephropathy, and patients whom physicians deemed inappropriate, were excluded from the study.

This study was planned according to the Helsinki declaration.

Study organization

The study organization was constructed by an Excutive Committee, an Event Evaluation Committee, and a Statistician as described in Appendix 1.

Administration of drugs and monitoring

During the follow-up period, both group P and group C were examined for diet and non-smoking. The administration in group P started with 10 mg/day and increased to 20 mg/day when the doctor decided that the effect was insufficient. In group C, when the doctor judged that the therapeutic effect was inadequate, the prescription of antilipidemic agents was allowed if needed. In this case, antilipidemic agents other than statin or fibrate were prescribed to the patient. As for treatment for hypercholesterolemia during the follow-up period, the treatment conducted at the time of registration was continued as a rule.

The patient's background included gender, age, BMI level, complication, presence or absence of history of ischemic heart disease and family history of hypercholesterolemia or CHD. During the follow-up period, we examined serum lipid levels, CHD, CVD, adverse events (including death) and medication. The serum lipid levels were measured at each institution under medical supervision everyday, and the LDL-C level was calculated using the Friedewald formula. When CHD or CVD occurred, a precise record was prepared, and the event was evaluated by the Event Evaluation Committee.

Ethical and safety monitoring was performed under the surveillance of the Executive Committee.

Definition of evaluation items and evaluation methods

The primary endpoint was CHD and the secondary endpoints were CVD, total mortality, serum lipid level, apoprotein level, and the relationship between the LDL-C level and occurrence of CHD. When similar events occurred multiple times, time to the first event was adopted. An event of CHD was defined as the onset or worsening of angina pectoris, performing CABG or PTCA, non-fatal myocardial infarction, and death from CHD including heart death and sudden death. An event of CVD was defined as the onset or recurrence of cerebral infarction, the onset of cerebral hemorrhage, or death (cerebral infarction or hemorrhage). Causes of death were classified into myocardial infarction, heart failure, sudden death, cerebral infarction, cerebral hemorrhage, cancer, trauma and suicide, and other diseases.

As for event cases, the treatment group was masked

and two members of the Event Evaluation Committee evaluated the same case independently. When the results were not identical, the case was reviewed at the Event Evaluation Committee and the result was regarded as the final evaluation. When the committee considered that the case needed to be investigated again, a decision was based on the re-investigation, and the result was regarded as the final evaluation.

Statistical analysis

Because the selection of a treatment method was voluntary, the statistical analyses were conducted as in an observational study.

In comparisons of patient background between the two groups, the χ^2 test was used for gender, history of angina pectoris, myocardial infarction and cerebral infarction, complications of hypertension and diabetes, smoking, and family history of CHD, and Fisher's exact test for history of cerebral infarction. Wilcoxon test was used for mean age, SBP, DBP, BMI, and serum lipid level (TC, LDL-C, HDL-C, TG). If TG > 400 mg/dl, the case was regarded as lacking a measured level (17). These factors are based on doctor's report. The comparison of background factors between the groups was aimed at confirming the degree of imbalance and only P-values are shown. As for the incidence of events, the number of occurrences per 1,000 patient-years was calculated after age adjustment. For lipid variation, a comparison of the measured levels at each evaluation time between the two groups was conducted by Wilcoxon test with the Bonferroni method. The primary endpoint was CHD and a comparison between group P and group C was conducted for each evaluation item. The relative risk (risk ratio) and 95% confidence interval on administration of pravastatin were obtained using the Cox proportional hazard model. Adjustment factors were history of CHD, gender, age, TC level, HDL-C level, TG level, diabetes, and smoking. Similar analyses were also conducted for events of cerebrovascular disease and total mortality. All P-values shown as test results were two-sided and the significance level was 5%.

For the analyses, the statistical package SAS version 6.12 (SAS Institute, Inc., Carry, Northcarolina) was used.

Results

A total of 2,232 cases (1,422 cases in group P, 810 cases in group C) had been registered during the period from October 1989 to November 1993, and followed up by 132 physicians at 70 facilities until the end of the study. Among those cases, 132 from group P (12 cases meeting the exclusion criteria, one case rejected immediately after registration, 98 cases lacking measured lipid levels at registration, 21 cases not coming after registration) and 61 cases from group C (10 cases meeting the exclusion criteria, 4 cases rejected immediately after registration, 22 cases lacking measured lipid levels at registration, 24 cases not coming after registration, and one case of unknown date of event occurrence) were excluded (a total of 193 cases). Consequently, 2,039 cases were used for analyses.

Patient background

Table 1 shows the background of patients in both groups. The ratio of men was significantly lower in group P than group C ($p = 0.001$). The mean age was significantly higher in group P ($p < 0.001$). The history of diabetes was signifi-

Table 1. Summary of baseline of characteristics of patients

Variable	Pravastatin (n = 1,290)	Only diet therapy (n = 749)	P value
Gender (men%/women%)	33.4/66.6	43.7/56.3	0.001 †*
Age (year)	57.8 ± 8.9	55.1 ± 9.4	< 0.001 §*
Angina pectoris (%)	14.3	13.5	0.591 †
Myocardial infraction (%)	4.8	3.7	0.258 †
Cerebral infraction (%)	3.0	2.3	0.316 †
Cerebral hemorrhage (%)	0.2	0.1	1.000 ‡
Hypertension (%)	38.3	35.8	0.258 †
Diabetes mellitus (%)	13.0	18.6	0.001 †*
Current smoking (%)	22.6	29.2	0.001 †*
Family history of CHD (%)	7.5	7.2	0.797 †
Systolic blood pressure (mmHg)	134.5 ± 19.7	132.0 ± 21.9	0.001 §*
Diastolic blood pressure (mmHg)	80.3 ± 11.6	78.8 ± 12.6	0.009 §*
Body mass index (kg/m^2)	23.7 ± 2.9	23.5 ± 2.8	0.107 §

*$p < 0.05$

† Based on the chi-square test (for dichotomous variables)

‡ Based on Fisher's exact test

§ Based on the Wilcoxon test

cantly lower in group P ($p = 0.001$). Smoking was significantly lower in group P. SBP and DBP were significantly higher in group P ($p = 0.001$, $p = 0.009$, respectively). No difference in BMI levels was seen between the two groups. Group P showed significantly higher levels of TC, LDL-C, and TG ($p < 0.001$). No difference in HDL-C levels was seen between the groups. No differences between the groups were found in history of angina pectoris, myocardial infarction, and cerebral hemorrhage, complication of hypertension, and family history of CHD.

Follow-up

The cumulative discontinuation rate due to absence at 60 months was 28.0% in group P and 36.3% in group C, being higher in the latter group. As for confirmed final outcome including missing cases, 23 out of 2,039 cases could not be confirmed for death or survival. The mean follow-up period was 4.5 years in group P and 4.2 years in group C for events of CHD, and 4.7 years in group P and 4.4 years in group C for total mortality. Pravastatin was discontinued or changed to some other antilipidemic agent in 38.9% of patients in group P, and a antilipidemic agent was given to 18.2% of patients in group C. The mean dose of pravastatin was 10.1 mg/day in group P.

Treatment effects on lipids

Fig. 1 shows the variations of TC, LDL-C, TG, and HDL-C levels for five years after initiation of the study. LDL-C levels in group P decreased from 176.3 mg/dl initially to 133.8 mg/dl (– 24.1%) one year later, and this effect continued throughout the study period. LDL-C levels in group C decreased from 156.8 mg/dl to 149.1 mg/dl (– 4.9%) one year later and similar variation was seen during the study period. As for the difference between groups, group P showed a significantly higher level at the start of the study ($p < 0.05$) and a significantly lower level during the study period after one year ($p < 0.05$). The TC level shifted similarly to the LDL-C level. The HDL-C level in group P did not change, being 51.4 mg/dl at the start and 53.6 mg/dl (+ 4.3%) one year later, and similar variation was seen during the study period. Group C also showed no change in the HDL-C level from 51.9 mg/dl to 52.1 mg/dl (+ 3.9%) one year later, and similar variation was seen during the study period. No significant difference was found between the groups. The TG level in group P decreased from 165.3 mg/dl initially to 148.9 mg/dl (– 9.9%) one year later, and this effect continued throughout the study period. The TG level in group C increased from 139.3 mg/dl to be 143.1 mg/dl (+ 2.7%) one year later, and similar variation was seen during the study period. As for the difference between the groups, group P showed a significantly higher level initially ($p < 0.05$), and no significant difference between the groups was seen during the study period after one year. ApoA-I in group P increased from 130.7 mg/dl ($n = 864$) at the start to 137.3 mg/dl (+ 5.3%, $n = 527$) one year later and then to 145.2 mg/dl (+ 11.1%, $n = 286$) five years later. ApoA-I in group C increased from 129.5 mg/dl ($n = 523$) to be 133.1 mg/dl (+ 2.8%, $n = 274$) one year layer and then 139.8 mg/dl (+ 8.0%, $n = 135$) five years later. No significant difference was seen between the two groups. ApoB in group P decreased from 124.7 mg/dl ($n = 866$) to be 106.3 mg/dl

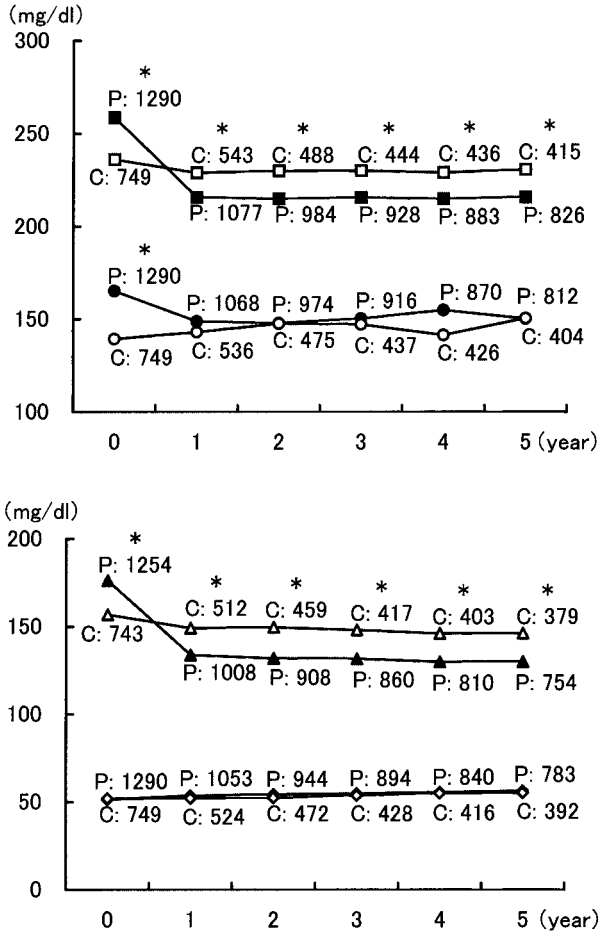

Fig. 1. Effects of pravastatin treatment on serum lipid levels
Numbers of patients are shown over or under the curve.
P = pravastatin; C = only diet therapy
total cholesterol (Group P) =closed square; total cholesterol (Group C) =open square; Triglyceride (Group P) = closed circle; Triglyceride (Group C) = open circle; LDL-cholesterol (Group P) = closed triangle; LDL-cholesterol (Group C) = open triangle; HDL-cholesterol (Group P) = closed diamond; HDL-cholesterol (Group C) = open diamond. LDL-C levels in group P decreased from 176.3 mg/dl at the start to 133.8 mg/dl (– 24.1%) one year later, and this effect continued throughout the study period. LDL-C levels in group C decreased from 156.8 mg/dl to 149.1 mg/dl (– 4.9%) one year later. Group P showed a significantly higher level at the start of the study and a lower level during the study period after one year than group C.
*$p < 0.05$ (Wilcoxon test with Bonferroni's method)

(– 14.8%, n = 528) one year later, and similar variation was seen during the study period. Group C showed no change of ApoB, being 112.1 mg/dl (n = 523) at the start and 112.2 mg/dl (+ 0.1%, n = 274) one year later, and similar variation was seen during the study period. No significant difference was found between the two groups.

Treatment effects on evaluation items

CHD events occurred in 9.2/1,000 patient-years for men and 2.4/1,000 patient-years for women without a history of CHD. CHD events occurred in 55.3/1,000 patient-years for men and 23.6/1,000 patient-years for women with a history of CHD, which was six times higher in men and 10 times higher in women than for those without a history of CHD, respectively. Myocardial infarction occurred in 4.5/1,000 patient-years for men and 0.2/1,000 patient-years for women without a history of CHD, and 8.4/1,000 patient-years for men and 5.7/1,000 patient-years for women with a history of CHD. Table 2 shows the relative risk for the primary and secondary endpoints and the 95% confidence interval (95%CI). Patient numbers for onset or worsening of angina pectoris, performing CABG or PTCA, non-fatal myocardial infarction, and death of CHD including heart failure and sudden death were 31, 13, 13, and 1 in group P and 16, 16, 3, and 2 in group C, respectively. The adjusted relative risk in group P for CHD events was calculated to be 0.74 (95%CI: 0.47-1.19).

CVD events occurred in 2.4/1,000 patient-years for men and 2.2/1,000 patient-years for women without a history of CHD, and 9.4/1,000 patient-years for men and 3.5/1,000 patient-years for women with a history of CHD. Patient numbers for onset or recurrence of cerebral infarction, onset of cerebral hemorrhage, and death (cerebral infarction or hemorrhage) were 11, 2, 3, and 1 in group P, and 6, 2, 3, and 0 in group C, respectively. The adjusted relative risk in group P for CVD events was calculated to be 0.71 (95%CI: 0.31-1.63). In the cases with a history of CHD, the adjusted risk of group P for CVD events relative to group C was 0.59 (95%CI: 0.35-1.64).

The ratio of CHD events to causes of all deaths was 8%, while cancers accounted for 45% of all deaths. There was myocardial infarction (0.16%), heart failure (0.16%), cerebral hemorrhage (0.16%), cancer (1.01%), trauma or suicide (0.16%), and other diseases (0.39%) in group P. There was myocardial infarction (0.13%), sudden death (0.13%), cerebral infarction (0.13%), cancer (0.53%), trauma or suicide (0.27%), and other diseases (0.40%) in group C. After adjustments, the relative risk in group P for total mortality was calculated to be 0.76 (95%CI: 0.35-1.64).

One man without a history of CHD and 2 men with a history of CHD developed both CHD and CVD. A man and a woman without a history of CHD and 4 men and 2 women with a history of CHD developed CHD and died. Four women without a history of CHD and one man with a history of CHD developed CVD and died.

Compared with the cases without a history of CHD, the cases with it showed an apparent treatment effect of pravastatin on CHD events, CVD events and total mortality.

Study according to the achieved LDL-C levels

As a secondary analysis, the achieved LDL-C level and occurrence of CHD events were investigated. Among 2,039 cases as subjects for analyses, 17 cases without measured LDL-C levels at registration and during the course or in which the LDL-C level could not be calculated due to TG > 400 mg/dl were excluded. To confirm the treatment effect, 26 cases in which CHD events occurred within 180 days after initiation of the study were also excluded. Consequently, 1,996 cases were used for analyses. When only measured LDL-C levels during follow-up were lacking, the baseline levels were adopted. To test significance, the Cox proportional hazard model was used. Adjustment factors included gender, age, family history of CHD, anginal pain, smoking, diabetes, HDL-C level, TG level, and LDL-C level. Table 3 shows the results of a comparison in which the occurrence of CHD events was compared between the group in which the mean LDL-C level during the follow-up period reached the treatment goal and the group in which it did not. The LDL-C treatment goal of 140 mg/dl in the guideline of hypercholesterolemic treatment was made a cut-off as a reference.

In all cases of group P and group C, the adjusted relative risk in the group achieving the goal was 0.63 (95%CI: 0.39-1.02). The occurrence of CHD events

Table 2. Numbers of Events and Age-adjusted Rate for the pravastatin group versus the diet therapy group

Event	Pravastatin (n = 1,290)		Only diet therapy (n = 749)		Adjusted RR (95% CI)‡
	Number of events	Age-adjusted rate†	Number of events	Age-adjusted rate†	
CHD events§	58	9.5	37	12.3	0.74 (0.47-1.19)
CVD events§	17	2.7	11	3.6	0.71 (0.31-1.63)
Total mortality§	26	4.1	12	4.1	0.76 (0.35-1.64)

† Rate per 1,000 patient-years. Calculated by the direct method using the patient-years by 10-year age class in the whole subjects standard. ‡ Based on Cox hazards model controlling for gender, age, serum total cholesterol, serum HDL cholesterol, serum triglyceride, history of CHD, diabetes mellitus and smoking. § The earlier event was counted in the case of concurrent occurrences.

Table 3. Numbers of events and adjusted relative risks for the average LDL-C levels during the follow-up over 140 mg/dl versus those less than 140 mg/dl.

Group	LDL-C (mg/dl)	Number of events	Age-adjusted rate†	Adjusted RR (95% CI)‡
ALL (n = 1996)	< 140	32	6.7	0.63 (0.39-1.02)
	≥ 140	36	8.4	
No history of CHD (n = 1647)	< 140	14	3.7	0.77 (0.37-1.60)
	≥ 140	17	4.3	
History of CHD (n = 349)	< 140	18	18.5	0.53 (0.28-1.01)
	≥ 140	19	35.0	

† Rate per 1,000 patient-years. Calculated by the direct method using the patient-years by 10-year age class in the whole subjects standard. ‡ Based on Cox hazards model controlling for gender, age, serum LDL cholesterol, serum HDL cholesterol, serum triglyceride, family history of CHD, anginal pain, diabetes mellitus and smoking.

tended to decrease. In cases having a history of CHD, the adjusted relative risk in the group achieving the goal was 0.53 (95%CI: 0.28-1.01) and a similar tendency was seen.

Safety

Cancer-related mortality was 2.0/1,000 patient-years in group P and 1.4/1,000 patient-years in group C. Adverse events reported by physicians included increased CPK in the musculoskeletal system, and hepatic dysfunction and increased GOT and GPT in the hepatobiliary system. No serious adverse events were observed in association with long-term treatment with pravastatin.

Discussion

The present study can be characterized as (1) a follow-up study in hypercholesterolemic patients with a low incidence of CHD, including women; (2) using low doses of pravastatin, compared with those in studies in Western countries; and (3) the presence of a control group, despite non-randomization.

The incidence of myocardial infarction was compared between the Holicos-PAT and AFCAPS/TexCAPS. In the AFCAPS/TexCAPS conducted in the USA, which showed the lowest incidence of events among previous major trials, the incidence of myocardial infarction was reported to be 5.6/1,000 patient-years in the placebo group (6). After adjustment for gender on primary prevention, the incidence of events in the present study was about 1/3 that of the above study. The incidence of CHD events in other domestic studies was so low that the annual incidence of myocardial infarction with a serum cholesterol level of 218 mg/dl or higher in Okinawa was 4.6/1,000 person-years for men and 2.2/1,000 person-years for women (18). In the KLIS, in which only male patients were used as subjects, CHD events, including myocardial infarction, coronary angioplasty and bypass operation, heart death, and sudden death, occurred at 5.95/1,000 patient-years in the conventional drug therapy group (13). In the Holicos-PAT, the incidence of CHD events in group C was 5.63/1,000 patient-years. In the J-LIT (19) performed in Japan on patients treated with simvastatin, the incidence of myocardial infarction on primary prevention was 0.86/1,000 patient-years (percentage of men: 32.2%). In the Holicos-PAT, the incidence of myocardial infarction in group P was 1.58/1,000 patient-years (percentage of men: 33.4%). In the Holicos-PAT, the incidence of CHD events was 3.8 times higher in men than in women without a history of CHD and 2.3 times higher than in women with a history of CHD. The incidence of CHD events for those without a history of CHD was 3.8 times higher in men and 1.1 times higher in women. In Japan, the ratio of heart failure to all causes of death is generally comparable to that of CVD-related deaths, and hypercholesterolemic patients are thought to be prone to develop CHD, compared with CVD.

Pravastatin has been used in Japan at a dose of 10 mg/day, up to 20 mg/day. The worldwide dose is double this, and the results of large-scale clinical trials in Western countries have been obtained with doses exceeding those applicable in Japan. The reduction of LDL-C from the pretreatment level was 24% in the present study, demonstrating a reduction of the same degree as that observed in the WOSCOPS and CARE.

This study was not a randomized-controlled trial. The analyses in the non-randomized clinical trial were limited to interpret the results. The effectiveness of the treatment with pravastatin was statistically analyzed by dividing the patients into those treated with pravastatin and those only on diet therapy. TC and LDL-C levels were significantly lower in group P than in group C, and differences in TC and LDL-C levels between the 2 groups were 12.8 and 15.1 mg/dl five years later, respectively. Thus, no significant difference was found in comparisons of adjusted relative risk in events of CHD or CVD, and total mortality. However, when the high risk group with a LDL-C level of almost 180 mg/dl was treated with pravastatin, the LDL-C level could be reduced to that in patients whose level was controlled to less than 150 mg/dl by diet therapy

in terms of events of CHD or CVD and total mortality. Compared with group C, the risk reduction in group P was 26% for CHD events, 29% for CVD events, and 24% for total mortality. The risk reduction rates were similar to those in Europe and the U.S.A. The tendency was most notable in cases having a history of CHD, where the risk of CHD events decreased by 45%. It is unclear why the risk reduction rates for events were comparatively large despite a small difference in LDL-C levels between the 2 groups in the present study. This finding may indicate that there are direct effects of pravastatin, such as a tendency for thrombosis to decrease (20), correcting the oxidation resistance of lipoproteins (21), etc., other than effects related to cholesterol lowering. In cases in which mean LDL-C levels achieved the treatment goal in the secondary analysis, the risk of CHD events decreased. The treatment effect was particularly notable in cases with a history of CHD.

This result supported the results reported in Japan and Western countries. (5, 8, 9)

In this study, no critical events due to administration of pravastatin for a long period were found. Cancer-related mortality was 2.0/1,000 patient-years in group P and 1.4/1,000 patient-years in group C. As for death due to cancer, when the expected number of the cancer deaths in the Japanese based on age (22) was applied to the cases in this study, the incidence was estimated at 2.9/1,000 patient-years in group P and 2.5/1,000 patient-years in group C. The incidence in both groups did not exceed these values.

Conclusion

The present study demonstrates the outcomes of CHD and CVD in hypercholesterolemic patients, including women, revealing a lower incidence of CHD in Japan, compared with Western countries. Pravastatin could be safely used, and it was suggested that the cholesterol-lowering therapy with pravastatin has inhibitory effects on CHD, CVD, and total mortality. The effect was notable in cases with a history of CHD. In a lower risk group such as the Japanese, just how high risk patients showed be identified and treated remains to be studied.

Appendix 1

The following investigators participated in the Holicos-PAT.

Ishikawa prefecture: Akimichi Asano, Yorito Emoto, Noboru Fujino, Shigeo Hamada, Tetsuji Hashiba, Seiji Hayashi, Toshinori Higashikata, Miki Hiramaru, Yuhki Horita, Takayuki Hoshiba, Takahiko Igawa, Masatoshi Ikeda, Akihiro Inazu, Hidekazu Ino, Hideaki Ito, Norio Iwaki, Shigeru Jinkawa, Bunji Kaku, Nobuo Kamon, Akira Kaneto, Ken-ichi Katsuki, Suguru Kawasaki, Yoshihito Kita, Masaru Kitamura, Ichiro Koizumi, Kunio Kondo, Kensyo Konishi, Akira Matsui, Masami Matsumura, Masahiro Minamoto, Yasushi Miyake, Masaji Miyamoto, Kiyoo Mori, Toshinari Mura, Takuro Muramoto, Yuko Murase, Takeshi Nakao, Atsushi Nohara, Hisanori Oiwake, Eizo Okino, Shinsuke Shibayama, Yasushi Shiire, Toshimi Shimada, Tokei Shin, Ryuichiro Soma, Norihiko Sugihara, Takashi Takahashi, Yoshihiro Takayama, Hiroaki Takimoto, Nariaki Terashima, Yoshiki Tokuhisa, Taketsugu Tsuchiya, Ryosei Ueda, Yoshihisa Uetani, Kunimasa Yagi, Shinji Yagi, Jundo Yamaguchi, Masato Yamaguchi, Tsukasa Yamazaki, Haruya Yanase, Kikuo Yasuda, Toshihiko Yasuda, Yoshiaki Yasuda, Masahiro Yonejima, Kohei Yoshimitsu, Akira Yoshimura, Kimiaki Yoshino, Hiroyuki Yoshio

Toyama prefecture: Yutaka Igarashi, Kazuhiro Iki, Morimitsu Kawai, Katsunori Kyoi, Takao Matsubara, Takayuki Matsumura, Tohru Matsuyama, Katsufumi Misawa, Akira Mitani, Tadayuki Nagai, Shinya Nagasawa, Yutaka Nitta, Minoru Noto, Hirofumi Oda, Kazuyasu Okeie, Michio Seo, Kuniyoshi Shimizu, Mitsuaki Takeda, Shinya Takeda, Yoshihiro Takeuchi, Yasuhiro Todo

Fukui prefecture: Akihiko Akai, Yoshiyuki Arai, Hideo Araki, Toshihiro Haba, Jun-ichi Hirai, Akira Honjo, Toshinori Imamura, Seigo Ito, Kiyoshi Kimizu, Jongi Kim, Hiromasa Kokado, Toshio Konno, Naotake Matsuda, Akitaka Misaki, Sumio Mizuno, Tatsuaki Murakami, Kazuo Ohsato, Takeshi Sakai, Eiichiro Sato, Chieko Shimada, Tetsuo Suematsu, Kuniaki Taga

Kanagawa prefecture: Motohiro Miura

Aichi prefecture: Takehide Shinohara

Executive Committee: Hiroshi Mabuchi (principal investigater), Junji Koizumi, Masami Shimizu, School of Medicine,Kanazawa University; Kouji Kajinami, Kanazawa Medical University; Ryouyu Takeda (adviser), Hokuriku Hospital; Takio Ohka, Honin Kanaya, Yoshihide Uno, Ishikawa prefectural Central Hospital; Kousei Ueda, Komatsu Municipal Hospital; Tadayoshi Takegoshi, Wajima Municipal Hospital; Takanobu Wakasugi, Fukui Prefectural Hospital; Susumu Miyamoto, Himi City Hospital; Masayuki Ohta, Tetsuji Sumitani, Takaoka City Hospital; Tomio Kametani, Koseiren Takaoka Hospital; Akira Watanabe, Shinminato City Hospital; Hajime Fujita, Fujita Clinic; Senshyu Hifumi, Hokuriku Central Hospital

Event Evaluation Committee: Hiroshi Mabuchi, Junji Koizumi, Masami Shimizu, School of Medicine,Kanazawa University; Susumu Miyamoto, Himi City Hospital; Kouji kajinami, Kanazawa Medical University

Statistician: Hideki Origasa, Toyama Medical and Pharmaceutical University

Appendix 2

Endpoints

I. Angina pectoris – chest pain or discomfort with all of the following characteristics:
   (1) Site must include the sternum (any level)
   (2) Must occur during a time of exertion or

stress and must usually last at least 30 sec
(3) Must on most occasions disappear within 10 min of rest or a decreases in the intensity of exertion
(4) Must usually be relieved in 2-5 min by nitroglycerine

The Reappearance or exacerbation of chest pain or discomfort with characteristics fulfilled by (1–4) was considered as a worsening of angina pectoris, when the event was accompanied with a change of therapy.

II. Event of coronary artery bypass surgery or angioplasty

III. Non-fatal myocardial infarction – any one or more of the following categories using the stated definitions:
(1) Diagnostic ECG at the time of the event
(2) Ischemic cardiac pain and diagnostic enzymes
(3) Ischemic cardiac pain and equivocal enzymes and equivocal ECG
(4) A routine ECG is a diagnostic for myocardial infarction while the previous one was not

IV. Death from CHD including heart failure and sudden death – either or both of the following categories:
(1) Heart death – one or both of the following categories:
(i) Deaths occurring subsequently to definite or suspected myocardial infarction
(ii) Deaths occurring in those with known CHD when no cause other than CHD could be ascribed as the cause of death
(2) Sudden and unexpected death (requires all three characteristics)
(i) Deaths occurring within 1hr after the onset of severe symptoms or having last been seen without them
(ii) No known non-atherosclerotic acute or chronic process or event that could have been potentially lethal
(iii) An "unexpected death" occurs only in a person who is not confined to their home, hospital, or other institution because of illness within 24hr of the death

V. Cerebrovascular disease – a diagnosis requires all of the following:
(1) History of recent onset of unequivocal and objective findings of a localizing neurologic deficit documented by a physician
(2) Findings persist longer than 24 hr
(3) The neurologic findings are not referable to an extracranial lesion
(4) Findings of a computed tomographic (CT) or magnetic resonance image (MRI) taken within 3 weeks after onset, or autopsy record to classify the cerebrovascular disease into cerebral hemorrhage or cerebral infarction. Cerebral infarction was defined as a stroke accompanied by CT and/or MRI scan(s) that showed an infarct in the expected area on the basis of the clinical findings or a stroke for which there was evidence of cerebral infarction at autopsy. Cerebral hemorrhage was classified on the basis of evidence obtained on CT or MRI scan or at autopsy, excluding hemorrhagic conversion of infarction.

VI. All cause mortality

Glossary

I. Ischemic cardiac pain – severe substernal pain having a deep or visceral quality and lasting for 30 min or more

II. ECG (classified by Minnesota Code)
(1) Diagnostic – either of the following must be present:
(i) Unequivocal Q or QS pattern (Code 1-1)
(ii) Q or QS pattern (Codes 1-2-1 to 1-2-7), plus any T-wave item (Codes 5-1 to 5-3)
Only the first criterion applies in the presence of ventricular conduction defects
(2) Equivocal – any of the following must be present:
(i) Q or QS pattern (Codes 1-2-1 to 1-2-7)
(ii) ST junction and segment depression (Codes 4-1 to 4-3)
(iii) T-wave items (Codes 5-1 to 5-2)
(iv) Left bundle-branch block (Code 7-1)

III. Enzymes
(1) Diagnostic enzymes – all of the following conditions:
(i) Creatine kinase, GOT, or lactic dehydrogenase values determined coexistent with the event
(ii) The upper limit of normal for the local laboratory is recorded
(iii) The determined value for one or more enzymes is at least twice the upper limit of the local laboratory
(2) Equivocal enzymes – all of the following

conditions:

(i) Creatine kinase, GOT, or lactic dehydrogenase values determined coexistent with the event

(ii) The upper limit of normal for the local laboratory is recorded

(iii) The determined value for one or more enzymes is elevated but does not fulfill criteria for diagnostic enzymes

References

(1) The Pooling Project Research Group: Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the pooling project. J Chron Dis, 31: 201-306, 1978

(2) Stamler J, Wentworth D, Neaton JD, *et al.*: Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous or grded? Findings in 356, 222 primary screeness of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA, 256: 2823-2828, 1986

(3) Pocock SJ, Shaper AG, and Philips AN: Concentrations of high density lipoprotein cholesterol, triglycerides, and total cholesterol in ischaemic heart disease. BMJ, 298: 998-1002, 1989

(4) Research Group of the Ministry of Welfare, concerning primary hyperlipidemia of specific diseases: 1986 and 1987 research reports.

(5) Shepherd J, Cobbe SM, Ford I, *et al.*: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med, 333: 1301-1307, 1995

(6) Downs JR, Clearfield M, Weis S, *et al.*: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels Results of AFCAPS/TexCAPS. JAMA, 279: 1615-1622, 1998

(7) Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet, 344: 1383-1389, 1994

(8) Sacks FM, Pfeffer MA, Moye LA, *et al.*: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med, 335: 1001-1009, 1996

(9) The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med, 339: 1349-1357, 1998

(10) Plehn JF, Davis BR, Sacks FM, *et al.*: Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol and Recurrent Events (CARE) study. Circulation, 99: 216-223, 1999

(11) Tamura A, Mikuriya Y, and Nasu M: Effect of pravastatin (10mg/day) on progression of coronary atherosclerosis in patients with serum total cholesterol levels from 160 to 220mg/dl and angiographically documented coronary artery disease. Coronary Artery Regression Study (CARS) Group. Am J cardiol, 79: 893-896, 1997

(12) Yui Y, Shinoda E, Hattori R, *et al.*: Preventive effect of pravastatin on progression of coronary artery stenosis-Assessment with quantitative coronary arteriography (caliper method). HEART, 33 (1): 15-24, 2001

(13) The Kyushu Lipid Intervention Study Group: Pravastatin Use and Risk of Coronary Events and Cerebral Infarction in Japanese Men with Moderate Hypercholesterolemia: The Kyushu Lipid Intervention Study. J Atheroscler Thromb, 7 (2): 110-121, 2000

(14) Ito H, Ouchi Y, *et al.*: A Comparison of Low Versus Standard Dose Pravastain Therapy for the Prevention of Cardiovascular Events in the Elderly: The Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE). J Atheroscler Thromb, 8 (2): 33-44, 2001

(15) Uemura K and Pisa Z: Trends in cardiovascular disease mortality in industrialized countries since 1950. World Health Stat Quart, 41: 155-178, 1988

(16) Shimamoto T, Komachi Y, Inada H, *et al.*: Trends for coronary heart disease and stroke and their risk factors in Japan. Circulation, 79: 503-515, 1989

(17) Friedewald WT, Levy RI, and Fredrichson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem, 18: 459-502, 1972

(18) Wakugami K, Iseki K, Kimura Y, *et al.*: Relationship Between Serum Cholesterol and the Risk of Acute Myocardial Infarction in Screened Cohort in Okinawa, Japan. Jpn Circ J, 62: 7-14, 1998

(19) Itakura H, et al.: J-LIT. J-LIT study group. The Lipid, 12 (3): 239-247, 2001

(20) Lacoste L, Lam JY, Hung J, *et al.*: Hyperlipidemia and coronary disease. Correction of the increased thrombogenic potential with cholesterol reduction. Circulation, 92: 3172-3177, 1995

(21) Salonen R, nyyssonen K, Porkkala-Sarataho E, et al.: Kuopio Atherosclerosis Prevention Study (KAPS): Effect of pravastatin treatment on lipids, oxidation resistance of lipoproteins, and atherosclerotic progression. Am J Cardiol, 76: 34C-39C, 1995

(22) Cancer research Fund of the Ministry of Welfare "A study on improvement of accuracy of regional cancer registration and its use" (Chief researcher: Akira Oshima) 1998 report.