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Original Articles

Risk Evaluation of Coronary Heart Disease and Cerebrovascular Disease by the Japan Atherosclerosis Society Guidelines 2002 Using the Cohort of the Holicos-PAT Study

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Our purpose in this study was to evaluate the new JAS guidelines as a risk assessment tool in Japanese patients with hypercholesterolemia, using the cohort of the Holicos-PAT study. The Holicos-PAT study was designed as a prospective observational study. 2039 patients were followed with or without pravastatin for 5 years. We assessed coronary heart disease (CHD) and cerebrovascular disease (CVD) risks by the patient categories described in the JAS guidelines. In the Holicos-PAT study, the primary endpoints were CHD, and the secondary endpoints were CVD and total mortality. CHD event includes onset and worsening of angina pectoris, performing CABG or PTCA, non-fatal and fatal myocardial infarction, and death from CHD including heart death and sudden death. CVD events are onset or recurrence of cerebral infarction, onset of cerebral hemorrhage, and death from cerebral infarction or hemorrhage. The event rates were calculated by the person-years method, and the differences in event rates between category groups were analyzed by chi-square test. The event rates of CHD in Category A, B1, B2, B3, B4 and C, were 1.1, 4.0, 2.8, 5.7, 18.2 and 38.8 per 1,000 person-years. The rates of CHD events in the higher risk category groups, Category B4 group ($p = 0.004$ in whole patients) and C group ($p < 0.001$ in whole patients), were significantly higher than that in the combined category groups A + B1 + B2. The event rates of CVD in Category A, B1, B2, B3, B4 and C, were 2.1, 1.8, 1.8, 0.6, 10.8 and 6.4 per 1,000 person-years. The event rates of CHD in men were significantly higher than those in women, in categories B4 ($p < 0.001$) and C ($p < 0.001$). From these results, each category classified by accumulation of risk factors, showed increasing event rates of CHD and CVD. The categories in the JAS guidelines are useful to assess CHD and CVD risk in Japanese patients with hypercholesterolemia. However, the risk evaluation by the JAS guideline categories may underestimate the risk in men and overestimate it in women. *J Atheroscler Thromb, 2005; 12: 48–52.*

Key words: Risk assessment, Coronary heart disease, Cerebrovascular disease, Guidelines

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Introduction

The Japanese Atherosclerosis Society (JAS) published new guidelines for the diagnosis and treatment of atherosclerotic cardiovascular diseases in 2002 (1, 2). Hypercholesterolemia is one of the major risk factors that contributes to the development of coronary atherosclerosis (3). Recent clinical practice guidelines recommend that physicians and patients make decisions regarding coronary heart disease (CHD) prevention on assessment of underlying global CHD risk (3–9).

It has been reported that the incidence of CHD is lower in Japanese, compared with North American and European peoples (10, 11). The Japan Lipid Intervention Trial (J-LIT) was undertaken and reported in 2002 (12, 13). The J-LIT involved 52,421 patients with simvastatin treatment, and the results showed a positive relationship between LDL-C levels and CHD events, and a negative relationship between HDL-C levels and CHD events. The results from the studies in Japan such as the Hisayama study (14), NIPPON DATA (15), KLIS (16) as well as those from J-LIT, were incorporated into the new JAS guidelines, considering the clinical decision making according to the person's absolute risk.

Our purpose in this study is to evaluate the JAS guidelines as a risk assessment tool in Japanese patients with hypercholesterolemia, using the cohort of the Holicos-PAT study (17). The Holicos-PAT study was designed in 1989 in the Hokuriku district, as a prospective observational study. 2039 patients were followed with or without pravastatin for 5 years. The primary endpoints were CHD, and the secondary endpoints were CVD and total mortality. CHD event includes onset and worsening of angina pectoris in the Holicos-PAT, in contrast to the other studies.

Patients and Methods

We assessed CHD and cerebrovascular disease (CVD) risks by the patient categories, in the 2,039 patients of Holicos-PAT study. The main outcome measures were CHD events and CVD events, identified in the Holicos-PAT study. The event rates were calculated by the person-years method. The patient category was described in the JAS guidelines. In brief, Category A is absence of CHD and absence of atherosclerosis risk factors other than hypercholesterolemia, B1, B2, B3 and B4 are absence of CHD but presence of one to four atherosclerosis risk factors other than hypercholesterolemia, and C is presence of CHD.

The results of the Holicos-PAT study are described in full elsewhere (17). The patients with hypercholesterolemia (total cholesterol was greater than 220 mg/dl) were registered, and followed up by 132 physicians at 70 facilities. 2,232 patients were recruited and 193 patients were excluded. 1290 patients received pravastatin and 749 patients were followed without pravastatin (Diet group) for 5 years. Baseline characteristics are shown in Table 1. About 60% were women, and the mean age was 56.8 years. Hypertension was present in 37% and diabetes mellitus in about 15%. 82% had no history of CHD, and 18% had a history of CHD. The primary endpoints were CHD, and the secondary endpoints were CVD and total mortality. Coronary heart event includes onset and worsening of angina pectoris, performing CABG or PTCA, non-fatal and fatal myocardial infarction, and death from CHD including heart death and sudden death. Cerebrovascular events: CVD events are onset or recurrence of cerebral infarction, onset of cerebral hemorrhage, and death from cerebral infarction or hemorrhage.

Statistical Analysis

As for the incidence of events, the number of occurrences per 1,000 patients-years was calculated. Data of the patients with or without pravastatin treatment were combined in the groups of whole patients, men and women, because there were no significant differences in the event rates between them that was described in the previous paper (17). Baseline imbalances were compared between men and women by using either t test or chi-square test according to the type of variables. In comparisons of the event rates with person-year data between two groups, chi-square test assuming a Poisson model was used. The significance level was 5%, and the statistical package SAS version 6.12 (SAS Institute, NC) was used.

Results

The patient background was shown in Table 1. There were the significant differences between men and women, in the variables of age ($p < 0.001$), angina pectoris ($p < 0.001$), myocardial infarction ($p < 0.001$), cerebral infarction ($p = 0.022$), hypertension ($p = 0.002$), diabetes mellitus ($p < 0.001$), current smoking ($p < 0.001$), body mass index ($p < 0.001$) and serum lipids ($p < 0.001$). LDL-C and HDL-C levels in men were significantly lower than those in women ($p < 0.001$), but triglyceride level in men was significantly higher than that in women ($p < 0.001$). The percent pravastatin treatment in men (56.9%) was significantly lower than that in women (67.1%) ($p < 0.001$). The number of patients in each category group was shown in Table 2. The percent secondary prevention, Category C was 18%. Category B4 was only 123 patients.

In the whole patients group, the event rates of CHD in Category A, B1, B2, B3, B4 and C, were 1.1, 4.0, 2.8, 5.7, 18.2 and 38.8 per 1,000 person-years (Table 3). When the event rates of CHD in the Category B4 and C groups

Table 1. Baseline characteristics of the Holicos-PAT study.

Variable	Whole (n = 2,039)	Men (n = 758)	Women (n = 1,281)	Diet (n = 749)
Gender (men%/women%)	37.2 / 62.8	–	–	43.7 / 56.3
Age (year)	56.8 ± 9.2	53.5 ± 9.9	58.7 ± 8.2***	55.1 ± 9.4
Angina pectoris (%)	14.0	17.6	11.9***	13.5
Myocardial infarction (%)	4.4	8.8	1.8***	3.7
Cerebral infarction (%)	2.8	3.8	2.1*	2.3
Cerebral hemorrhage (%)	0.2	0.3	0.2	0.1
Hypertension (%)	37.4	33.0	40.0**	35.8
Diabetes mellitus (%)	15.0	18.6	12.9***	18.6
Current smoking (%)	25.0	57.5	5.8***	29.2
Family history of CHD (%)	7.4	7.9	7.1	7.2
Systolic BP (mmHg)	133.6 ± 20.6	130.0 ± 20.0	135.7 ± 20.6***	132.0 ± 21.9
Diastolic BP (mmHg)	79.8 ± 12.0	80.0 ± 12.8	79.7 ± 11.5	78.8 ± 12.6
Body mass index (Kg/m^2)	23.7 ± 2.9	23.9 ± 2.6	23.5 ± 3.0***	23.5 ± 2.8
Total cholesterol (mg/dl)	250.3 ± 28.6	247.1 ± 28.4	252.2 ± 28.5***	236.1 ± 24.1
LDL choresterol (mg/dl)	169.0 ± 29.5	166.2 ± 30.4	170.7 ± 28.9***	156.8 ± 25.9
HDL choresterol (mg/dl)	51.6 ± 14.7	47.3 ± 13.5	54.2 ± 14.7***	51.8 ± 14.7
Triglycerides (mg/dl)	155.7 ± 97.9	181.2 ± 111.9	140.6 ± 85.1***	139.3 ± 76.9

Statistical differences between men and women are shown by *P* values: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Diet: the patients with diet only therapy.

were compared to that in the combined category groups A + B1 + B2, the rates of CHD events in the higher risk category groups, Category B4 group ($p = 0.004$ in whole patients) and C group ($p < 0.001$ in whole patients), were significantly higher than that in the lower risk category group. The event rates of CHD in men were significantly higher than those in women, in the category B4 ($p < 0.001$) and C ($p < 0.001$).

The event rates of CVD in Category A, B1, B2, B3, B4 and C, were 2.1, 1.8, 1.8, 0.6, 10.8 and 6.4 per 1000 person-years, in the whole patients group (Table 4). When the event rates of CVD in the category B4 and C groups were compared to that in the combined category groups A + B1 + B2, the rates of CVD events in the higher risk category groups: Category B4 group ($p = 0.027$ in whole patients) and C group ($p = 0.142$ in whole patients), were higher than that in the lower risk category group. The event rates of CVD in men showed the same tendency as those in women.

Table 2. Number of the patients in each patient category.

Patient category	Whole	Men	Women	Diet
A	212 (10.4%)	33 (4.4%)	179 (14.0%)	81 (10.8%)
B1	502 (24.6%)	126 (16.6%)	376 (29.4%)	192 (25.6%)
B2	482 (23.6%)	170 (22.4%)	312 (24.4%)	154 (20.6%)
B3	348 (17.1%)	164 (21.6%)	184 (14.4%)	144 (19.2%)
B4	123 (6.0%)	80 (10.6%)	43 (3.4%)	43 (5.7%)
C	372 (18.2%)	185 (24.4%)	187 (14.6%)	135 (18.0%)
Total	2,039 (100%)	758 (100%)	1,281 (100%)	749 (100%)

Discussion

This study examined the risk of CHD and CVD in Japanese patients with hypercholesterolemia, classified by the categories in JAS guidelines, using the cohort of the

Table 3. The event rate of coronary heart disease.

Patient category	Whole	Men	Women	Diet
A	1.1	8.2	0.0	2.8
B1	4.0	3.7	4.1	4.8
B2	2.8	5.3	1.4	3.0
B3	5.7 ^{ns}	9.7 ^{ns}	2.3 ^{ns}	4.8 ^{ns}
B4	18.2¶	25.4§	5.1***	5.4 ^{ns}
C	38.8§	55.4§	23.6***§	50.7§
Total	10.5	19.8	5.3	11.7

Statistical differences between men and women are shown by P values: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Statistical differences of category B3, B4 and C, to the combined category groups A + B1 + B2, are shown by *P* values: $^{†}p < 0.05$, $^{¶}p < 0.01$, $^{§}p < 0.001$, ^{ns} no significance.
Numbers are per 1,000 person-years.

Table 4. The event rate of cerbrovascular disease

Patient category	Whole	Men	Women	Diet
A	2.1	0.0	2.5	0.0
B1	1.8	3.7	1.2	3.6
B2	1.8	0.0	2.8	1.5
B3	0.6 ^{ns}	1.3 ^{ns}	0.0 ^{ns}	1.6 ^{ns}
B4	10.8†	8.3 ^{ns}	15.4¶	10.9†
C	6.4 ^{ns}	9.4†	3.5 ^{ns}	6.9 ^{ns}
Total	3.0	4.2	2.4	3.4

Statistical differences between men and women are shown by P values: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.
Statistical differences of category B3, B4 and C, to the combined category groups A + B1 + B2, are shown by *P* values: $^{\dagger}p < 0.05$, $^{\P}p < 0.01$, $^{\S}p < 0.001$, ^{ns} no significance.
Numbers are per 1,000 person-years.

Holicos-PAT study. The JAS guidelines reported the absolute and relative risk of CHD classified by accumulation of risk factors, calculated according to the data from J-LIT. In J-LIT, the relative rate of CHD is 2 in one risk factor group, 4 in two risk factors group, 8 in three risk factors group, and 15 in four risk factors group (1). The relative risk of CHD from the Holicos-PAT is 4 in one risk factor group, 3 in two risk factors group, 5 in three risk factors group, and 17 in more than four risk factors group. The relative risk was similar between the two trials. The absolute risk was not compared directly, because of the different endpoints. The endpoints in Holicos-PAT include the onset and worsening of angina pectoris, but the J-LIT does not include these. Angina pectoris accounted for 49.5% of the whole CHD events. In the Holicos-PAT study, CHD events occurred in 55.4 per 1,000 patients-year for men and 23.6 per 1,000 patients-year for women with a history of CHD, and myocardial infarction occurred in 8.4 per 1,000 patients-year for men, and 5.7 per 1,000 patients-year for women with a history of CHD (17). CHD events including nonfatal/fatal myocardial infarction and cardiac sudden death in the J-LIT, was 4.45 per 1,000 patients-year in the patients with a history of CHD (12). The interpretation of the results from the Holicos-PAT may be limited, because of the small number of the events.

The incidence of CHD events was 3.5 times higher than that of CVD events in this study. The CVD event rate in the Holicos-PAT (3.0 per 1,000 patients-year in whole patients) was lower than that in the KLIS (5.2 per 1,000 patients-year in the control group). CHD and CVD event rates in the KLIS showed 6.0 and 5.2 per 1,000 patients-year in the control group, respectively, in a 5-year follow-up (16). There were 249 deaths from CHD, and 174 deaths from CVD in Nippon Data (15). The difference may be accounted by the different endpoints: the endpoints in KLIS did not include onset and worsening of angina pectoris. From other points, the events of CVD were defined in Holicos-PAT as the onset and recurrence of cerebral infarction, the onset of cerebral hemorrhage, or death from the clinical findings and CT scanning. The events of CVD may have been underestimated because of lack of autopsy. The number of CHD death gradually increased, in comparison with CVD death, in Japan.

Current guidelines in the world recommend lipid-lowering therapy by specific drugs, if the absolute risk exceeds a certain threshold (18). The threshold is 20% over 10 years according to the joint European Societies guidelines (4, 5) and 15% over 10 years according to the joint British guidelines (6). Most Japanese patients are of low risk for CHD, but 16% of Japanese die of cardiac disease, and 13% of cerebrovascular disease (19). The number of CHD deaths has exceeded that of CVD deaths, since 1990. As a result, substantial number of Japanese die of atherosclerotic diseases. To make a strategy for prevention of the atherosclerotic diseases in Japan, we have to consider the traits in patient preference regarding the lipid-lowering therapy and cost-effectiveness.

Various guidelines use different risk assessment methods. There are a lot of Framingham-based risk calculation tools (20). The Framingham Scores, originally developed in a white, middle-class population, overestimated CHD risk in Japanese-American and Hispanic men and Native American women (10). These results suggest that the Framingham Score should be used after recalibration, which requires data on each cohort's CHD risk factor prevalence and CHD event rates (11).

The event rate of CHD was analyzed in the male and female groups. The event rate of CHD in men was higher than that in women, even though the factor of gender was considered when the patients were categorized. The factor of gender may be more potent than one risk factor for CHD, and the risk may be underestimated in men and overestimated in women. We have to consider the differences between men and women when using the JAS guidelines.

From these results, we thought that the categories in the Japanese guidelines are useful to assess CHD and CVD risk in Japanese patients with hypercholesterolemia.

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References

(1) Japan Atherosclerosis Society: Japan atherosclerosis society (JAS) guidelines for diagnosis and treatment of atherosclerotic cardiovascular disease.

2002
(2) Saito Y: Editorial. J Atheroscler Thromb, 11: 101–103, 2004
(3) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA, 285: 2486–2497, 2001
(4) Pyorala K, De Backer G, Graham I, Poole-Wilson P, and Wood D: Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J, 15: 1300–1331, 1994
(5) Pyorala K and Wood D: Prevention of coronary heart disease in clinical practice. European recommendations revised and reinforced. Eur Heart J, 19: 1413–1415, 1998
(6) Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. Heart, 80 Suppl 2: S1–S29, 1998
(7) Ramsay LE, Haq IU, Jackson PR, Yeo WW, Pickin DM, and Payne JN: Targeting lipid-lowering drug therapy for primary prevention of coronary disease: an updated Sheffield table. Lancet, 348: 387–388, 1996. Erratum in: Lancet, 348: 1251, 1996
(8) Assmann G, Cullen P, and Schulte H: Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation, 105: 310–315, 2002. Erratum in: Circulation, 105: 900, 2002
(9) Durrington PN, Prais H, Bhatnagar D, France M, Crowley V, Khan J, and Morgan J: Indications for cholesterol-lowering medication: comparison of risk-assessment methods. Lancet, 353: 278–281, 1999. Erratum in: Lancet, 354: 166, 1999
(10) Kent DM and Griffith J: The Framingham scores overestimated the risk for coronary heart disease in Japanese, Hispanic, and Native American cohorts. ACP Journal Club, 136: 36, 2002
(11) D'Agostino RB Sr, Grundy S, Sullivan LM, and Wilson P; CHD Risk Prediction Group: Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA, 286: 180–187, 2001
(12) Mabuchi H, Kita T, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, and Itakura H; J-LIT Study Group: Japan Lipid Intervention Trial. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia and coronary heart disease: secondary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT). Circ J, 66: 1096–1100, 2002
(13) Matsuzaki M, Kita T, Mabuchi H, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, and Itakura H; J-LIT Study Group: Japan Lipid Intervention Trial. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia. Circ J, 66: 1987–1095, 2002
(14) Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, and Yoshitake T: Diabetes and cardiovascular disease in a prospective population survey in Japan: The Hisayama Study. Diabetes, Suppl 3: S14–S16, 1996
(15) Sakata K, Hashimoto T, Ueshima H, and Okayama A; NIPPON DATA 80 Research Group: Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980-1994. National Integrated Projects for Prospective Observation of Non-communicable Diseases and its Trend in the Aged. Eur J Epidemiol, 17: 461–468, 2001
(16) 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: 110–121, 2000
(17) Koizumi J, Shimizu M, Miyamoto S, Origasa H, and Mabuchi H: 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). J Atheroscler Thromb, 9: 251–259, 2002
(18) Broedl UC, Geiss HC, and Parhofer KG: Comparison of current guidelines for primary prevention of coronary heart disease: risk assessment and lipid-lowering therapy. J Gen Intern Med, 18: 190–195, 2003
(19) Statistics and Information Department, Minister's Secretariat, Ministry of health, labour and Welfare: Vital statistics of Japan 2003, http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suikei03/index.html
(20) Sheridan S, Pignone M, and Mulrow C: Framingham-based tools to calculate the global risk of coronary heart disease: a systematic review of tools for clinicians. J Gen Intern Med, 18: 1039–1052, 2003