Risk Factors for Coronary Heart Disease in the Japanese — Comparison of the Background of Patients with Acute Coronary Syndrome in the ASPAC Study with Data Obtained from the General Population

Akira Yamamoto¹, Gemma Richie², Haruo Nakamura³, Saichi Hosoda⁴, Masakiyo Nobuyoshi⁵, Masunori Matsuzaki⁶, Chee-Eng Tan⁷, and Anthony Keech² for the ASPAC study members in Japan, and Hiroshi Mabuchi⁸, Hiroshi Horibe⁹, and Hitomi Tenba¹ for the Research Committee on Serum Lipid Survey 1990 Japan

¹ National Cardiovascular Center Research Institute, Suita, Osaka, Japan.

² NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia.

³ Mitsukoshi Welfare Foundation, Shinjuku-ku, Tokyo, Japan.

⁴ Sakakibara Memorial Hospital and Tokyo Women's Medical College, Shibuya-ku, Tokyo, Japan.

⁵ Kokura Memorial Hospital, Kokura, Japan.

⁶ Second Department of Internal Medicine, Yamaguchi University School of Medicine, Ube, Japan.

⁷ Department of Endocrinology, Singapore General Hospital, Singapore.

⁸ Second Department of Internal Medicine, Kanazawa University School of Medicine, Kanazawa, Japan.

⁹ Sugiyama Jogakuen University, Nagoya, Japan.

The relative importance of metabolic risk factors for coronary heart disease (CHD) in the Japanese is assessed by comparing their prevalence in patients with acute coronary syndrome (ACS) enrolled in the Asia-Pacific Collaboration on CHD Risk Factor Intervention (ASPAC) study to that obtained by a serum lipid survey carried out in 1990 and also by comparing them to the ASPAC data from other countries and regions in this area. Hypertension was the most prevalent risk factor among Japanese patients with ACS as in the other countries and regions. The prevalence of obesity with a body mass index (BMI) of 30 or more was several times higher than that in the general population, although the rate was still much lower than in New Zealand and Singapore. In addition to hypercholesterolemia, hypertriglyceridemia and diabetes mellitus were frequently found in Japanese patients with ACS. When the prevalence of metabolic risk factors was compared between people with and without hypertension in the general population, the most remarkable difference was seen in BMI, followed by triglyceride and total cholesterol. These results indicate that hypertriglyceridemia and diabetes mellitus may be more important CHD risk factors in the Japanese population than LDL-cholesterol. *J Atheroscler Thromb*, 2002; 9: 191–199.

Key words: Coronary risk factors, Multiple risk factor syndrome, Diabetes mellitus, Acute coronary syndrome

Introduction

Ever since the Seven Countries Study (1) started, Japan has been known for a low incidence of coronary heart disease (CHD) in spite of its industrialization and modernized life style. The mortality from CHD is still one of the lowest in the world; the age-adjusted death rate shown in the World Health Organization Annual Statistics has

Address for correspondence: Akira Yamamoto, MD, Health Care Facilities for the Aged, Minoh 5-8-2 Kayano, Minoh, Osaka 562-0014, Japan

E-mail: ymmt-a@juno.dti.ne.jp

Received March 8, 2002.

Accepted for publication May 8, 2002.

been decreasing even in the last 20 years (2). The mortality from stroke, mainly due to hypertension, was the highest in the world until about 30 years ago. However, owing to a decrease in the incidence of cerebral haemorrhage, the mortality from stroke is now only a little higher than in the United States, although still 1.5-fold higher than that in France. The age-adjusted death rate from stroke has also been decreasing in the last 20 years, contributing to the highest longevity in the world. Consistent with the mortality data, results obtained in a recent epidemiological study (NIPPON DATA) (3) and also in a post-marketing survey of patients receiving simvastatin for the control of hypercholesterolemia (Japan Lipid Intervention Trial: JLIT) (4) showed a much lower incidence of coronary events than that shown in the data obtained in Europe and America (5,6). Although such a low incidence and low mortality rate of CHD can be partially explained by relatively low levels of low-density lipoprotein (LDL)-cholesterol, the possible involvement of other genetic or environmental factors should be considered. Recent data reported from a 25 year follow-up of the Seven Countries Study clearly showed that the incidence of CHD was remarkably different among countries and regions with different cultures; the rate being highest in Northern Europe and America, while it was much lower in Southern Europe and Mediterranean islands (7). The cholesterol level in Japan was very low at the start of the study, and unfortunately, data were not available for subjects with total serum cholesterol levels above 5.17 mmol/L (200 mg/dl).

In view of such a background, it seems important to evaluate the difference in risk factors for CHD between Japan and Western countries, both in a qualitative and a quantitative manner, for an exact understanding of the nature of CHD in various populations with different hereditary traits and environmental factors. In 1996, a survey on CHD risk factors and their management was carried out in the Asian-Pacific Area (Asia-Pacific Collaboration on CHD Risk Factor Intervention: ASPAC), studying the background of patients treated in hospitals by a unit expertized in the cure of acute coronary syndrome (ACS) in 10 countries and regions (8,9). Our area includes different ethnic groups of Asians and also Caucasian populations. In addition, some of the Asian populations as in Singapore have a very westernized life style, while others like the Japanese maintain a traditional life style in spite of industrialization.

In Japan, measurements of serum lipids have been carried out every 10 years since 1960 (10) and a precise analysis of lipid data according to age, sex, body mass index (BMI) and the effect of smoking was performed in a survey in 1990 (10,11). Records on serum triglyceride and HDL-cholesterol were included in addition to the common major risk factors (cholesterol, blood pressure, glucose intolerance, smoking, and BMI) in the data-base of this survey and also in that of the Japanese patients

enrolled in the ASPAC study. It is therefore possible to assess the relative importance of these major risk factors by comparing the data from these two studies.

HDL-cholesterol is 0.13–0.26 mmol/L (5–10 mg/dl) higher in the Japanese than in the European and American populations (11), and this seems to be related to relatively low triglyceride levels. In early versions of the National Cholesterol Education Program (NCEP) in the United States (12,13), the significance of serum triglyceride as a risk factor for CHD was not evaluated in detail. However, in its latest version (14), triglyceride levels above 150 mg/dl have been mentioned as a component of multiple risk factor syndrome. In this paper, discussion will be focused on the difference in the relative weight of each risk factor in various regions of the world, by comparing the data from Japan with those from other countries and regions in the Asian-Pacific area and also referring to the data from European countries (EURASPIRE study) (15).

Subjects and methods

Design of the ASPAC study

ASPAC is a retrospective survey of case management using hospital-based medical records over a period of six months from a random sample of hospitals that routinely manage ACS. Participating countries were Australia, Indonesia, Japan, Korea, Malaysia, New Zealand, the Philippines, Singapore, Taiwan and Thailand. The study was coordinated centrally at the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, with Anthony Keech as the principal investigator. The center functioned as the data management center for the project and prepared all analyses on the data set for the ASPAC Collaborative Group. Data were obtained from 400 patients from each country. In Japan, data collection was done by trained study nurses at a clinical research laboratory (CMIC, Tokyo) under the supervision of a chief and 4 associate investigators.

Before the collection of data, ethical approval for access to the record was obtained. The NHMRC Clinical Trial Centre made contract with CMIC including an agreement on the confidentiality of the personal information. Ethical approval was given by the director of each hospital or institutional review board according to the administration of each hospital.

Selection of hospitals

The selection of hospitals was based on the population-weighted sampling frame. In Japan, 48 hospitals that routinely manage at least 50 cases of ACS per year at their coronary care unit or specialized sections were registered from various regions with the agreement of the director of the sections or hospitals. Among them, 22 hospitals were randomly selected at the coordinate center in Sydney according to the distribution of the population in 6 re-

Table 1. Hospitals selected for the ASPAC study to represent 6 regions in Japan

Region	Hospital
1. Hokkaido	Hokkaido Prefectural Hospital Kitami
2. Tohoku-Kanto	Towada City General Hospital Saiseikai Maebashi Hospital National Defense Medical College
3. Tokyo Metropolitan Area Chiba-Tokyo-Saitama-Kanagawa	Ohara Cardiovascular Center Saitama Chiba Hokuso Hospital, Nippon Medical School Tokyo Women's Medical College Sakakibara Memorial Hospital Tokyo Hiroo Hospital New Tokyo Hospital Sagamihara Kyodo Hospital
4. Central Japan Tokai-Hokuriku Area	Shizuoka General Hospital Shizuoka City Shizuoka Hospital Nagoya Ekiseikai Hospital
5. Osaka-Kyoto Metropolitan Area Kinki	National Cardiovascular Center Osaka National Hospital Shiga Medical Center for Adults
6. West Japan Chugoku-Kyushu-Shikoku-Okinawa	Yamaguchi University School of Medicine Matsue Red Cross Hospital Kokura Memorial Hospital National Hospital Kyushu Medical Center Saiseikai Kumamoto Hospital

gions from north to south (Table 1), so that the number of hospitals selected in each region was representative of its proportion of the national population. The 6 regions were in accord with those used at the National Survey of Circulatory Disorders carried out in 1980 by the Ministry of Health and Welfare.

Data collection

Within each hospital we identified all male and female patients of any age with a diagnosis of myocardial infarction or unstable angina pectoris. The survey period commenced on June 30th, 1995, and the hospital and follow-up medical records of a total of 480 eligible patients were abstracted for inclusion.

All data were obtained by a retrospective review of accessible medical records as described in previous papers (8,9), comprising personal and demographic data, past cardiac history, prevalent risk factors including hypertension, smoking, obesity, diabetes mellitus and glucose intolerance, physical activity, hypercholesterolemia, and family history of CHD. In addition to these common major risk factors, levels of triglyceride and HDL-cholesterol were recorded almost universally in Japan, though they were not included in the analysis of major risk factors in the ASPAC study.

Risk factors were defined as follows:

Hypertension: A history of hypertension specifically recorded in the medical record or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at least 24 hours after admission with or without blood pressure-lowering medication commenced during the survey period.

Obesity/overweight: Presence of obesity specifically recorded in the medical record or height and weight recorded as giving a BMI ≥ 30 kg/m² (obesity) or 25 to 29.9 kg/m² (overweight) at any time during the survey period.

Hypercholesterolemia: A history of hypercholesterolemia specifically recorded in the medical record or measured total cholesterol ≥ 5.5 mmol/L (213 mg/dl) with or without cholesterol-lowering medication at any time during the survey period. Moderate to severe hypercholesterolemia was defined as a total cholesterol value of ≥ 6.5 mmol/L (251 mg/dl). Measurement of serum lipids including total and HDL-cholesterol and triglyceride was usually done using a blood sample obtained in the fasting state.

Diabetes mellitus: A history of diabetes mellitus specifically recorded in the medical record or recorded blood glucose (RBG) ≥ 15 mmol/L (270 mg/dl) during the first 48 hours after admission, RBG ≥ 11.1 mmol/L (200 mg/dl) at

any time, or the use of anti-diabetic medication at any time during the survey period.

Data from the general population

Data used for the reference were those obtained in 1990 from a survey of serum lipid levels in the general Japanese population (10). A survey of serum lipid levels had been carried out in Japan sponsored by the Japan Atherosclerosis Society every 10 years since 1960. A large number of people (20,279 men and 14,536 women) aged 4 through 99 years were enrolled in this survey, and a precise analysis based on BMI and smoking habits was also carried out (11). Blood samples were obtained in the fasting state. All the data collected from 39 institutes were analyzed in a statistical package without identifying any individual names or personal information. Statistical analysis of the difference in BMI and lipid parameters between normotensive and hypertensive subjects was performed with Student's *t*-test.

Results

Patients' characteristics in the ASPAC study

Of 480 patients, whose records were examined in this study, 78% were men and 22% were women. Higher rates for women were seen in Australia-New Zealand (39%), and the Philippines (36%). Japan had the lowest rate for women, next to Indonesia (19%), although there was a wide range of variation (2-40%) between hospitals. The percentages of myocardial infarction and unstable angina were 78% and 22%, respectively (70% and 30% on average of all the countries and regions). There was a wide range of inter-hospital variation in the presence of CHD in the past history (0-70%). The median age of the patients was 64 years for men and 69 years for women (54-67 years for men and 61-72 years for women in all the countries and regions).

Position of Japan among countries and regions in the ASPAC study regarding risk factor prevalence (Table 2)

Prevalence rates of hypertension in Japanese patients were 70% for men and 79% for women. These values were in the middle to top grade among the 10 countries and regions where records were obtained in the ASPAC study (66.3 ± 9.6 for men and 73.0 ± 7.3 for women on average). Overall, 93% of the Japanese patients diagnosed as having hypertension received drug treatment, with calcium channel blockers as the most common anti-hypertensive drugs being used in 78% of the total number of patients.

Records on serum total cholesterol values in the past history of more than 80% of the patients were obtained in about half of the hospitals. Serum lipid values were measured overall in 99% of the patients on initial admission to hospital (100% in 19 hospitals and 97, 97, and 80% of

Table 2. Comparison of the prevalence of risk factors in patients with coronary events between EUROASPIRE and ASPAC studies

	EUROASPIRE ^{#1}		ASPAC ^{#1}		
	by centre at admission		A-NZ	Singapore	Japan
Obesity					
BMI ≥ 30	25.3 %	18.5	59	39	11
BMI ≥ 25					32
Current smokers	19.4	34.4	20	51	48
Hypertension ^{#2}	53.1	57.8	71	83	72
Hypercholesterolemia					
≥ 5.5 mmol/L (213 mg/dl)	44.0	71.1	79	71	58
≥ 6.5 mmol/L (251 mg/dl)	13.7	—	34	31	18
Diabetes mellitus ^{#3}	18.0	21.8	19	44	34

A-NZ: Australia-New Zealand

^{#1}: Data of the EUROASPIRE study were from Reference 15 and those of the ASPAC study were from Reference 9.

^{#2}: Systolic blood pressure ≥ 140 mmHg and/or Diastolic blood pressure ≥ 90 mmHg

^{#3}: Recorded blood glucose ≥ 11.1 mmol/L (200 mg/dl)

the patients in the other 3 hospitals). Such a high rate of assessment at the initial admission was seen in Korea (95%), but not in the other countries and regions. The rate of assessment by follow-up in 6 months (91%) was unusually high in Japan compared to other countries, where the values ranged between 6 and 30%. When the definition of hypercholesterolemia was given with documented history, measured total cholesterol ≥ 5.5 mmol/L (213 mg/dl) at any time during the survey period, or the use of antilipidemic drugs, the prevalence rates of hypercholesterolemia in Japanese patients were 54% for men and 71% for women, and these values were in the middle grade among the countries and regions (57.3 ± 12.6 for men and 60.6 ± 17.7 for women on average). The rates were highest in Australia-New Zealand, and other relatively high values were seen in Singapore and Malaysia. According to the measurement at the initial hospital admission or at anytime during follow-up, 45% of the patients had hypercholesterolemia with total cholesterol ≥ 5.5 mmol/L (213 mg/dl) and 18% with cholesterol ≥ 6.5 mmol/L (251 mg/dl). The prevalence of patients with total cholesterol ≥ 6.5 mmol/L in Australia-New Zealand was 34% and that in Singapore 31%, while the rates were much lower in Malaysia, Thailand, and Taiwan (11-14%), and in Korea and Philippines (8-9%). The prevalence of patients with HDL-cholesterol < 1 mmol/L (38.7 mg/dl) was 40% (39.9 ± 10.9 among different hospitals) and with triglyceride ≥ 2.3 mmol/L (204 mg/dl) was 25% (25.3 ± 13.9 %).

A measurement of blood glucose was made in 99% of the patients on initial admission to hospital and in 91%

during follow-up for 6 months. The prevalence rate of diabetes mellitus was 31% in men and 44% in women. Among the countries and regions, it ranged 17-31% ($26.4 \pm 7.0\%$ on average) for men and 17-55% ($38.1 \pm 12.3\%$) for women. The lowest rates were obtained in Australia-New Zealand with values of 21 and 17%, respectively, for men and women, and in Korea with values of 17 and 27%. About 38% of the patients received insulin or oral antidiabetic agents at discharge or at survey end, although there was a very wide range of variation between hospitals in Japan ($37.8 \pm 28.1\%$, ranging 0-100%).

A marked variation was observed between countries in the ASPAC study in the prevalence of obesity with BMI ≥ 30 (8-58% in men and 12-62% in women). It was 9% in men and 17% in women in the Japanese patients. The highest values were seen in Australia-New Zealand (58 and 62%, respectively, for men and women) and Japan was at the lowest grade with the Philippines (8 and 18%, respectively, for men and women). The rate of prevalence of overweight with BMI ≥ 25 in Japan (32%) was still much less than the rate of obesity (BMI ≥ 30) in Australia-New Zealand.

Smoking status was recorded in almost all ($\geq 95\%$) the patients in 19 out of 22 hospitals participating in this study. Smoking rates in males were very high in almost all the countries and regions in the Asian Pacific area except Australia-New Zealand. In Japan, smoking rates were 57 and 16%, respectively, for men and women. The smoking rate in women ranged between 11 and 25% in all countries and regions except Indonesia, where the rate in women was nearly 0. The highest rates of smoking were seen in Korea (64% in men and 25% in women), almost triple those in New Zealand (23 and 17%).

Risk factors in patients with ACS in comparison with prevalence in the general population

Prevalence rates of risk factors in patients in the ASPAC study were compared with those in the general population calculated from the data obtained at a survey on a large scale carried out in Japan in 1990 (Table 3). Hypertension was highly prevalent in the aged Japanese. Percentages of subjects with hypertension at the survey and/or a history of hypertension in men and women obtained in the lipid survey carried out in 1990 were nearly 40%, almost comparable to the data obtained in other epidemiological studies, while the prevalence of hypertension in patients in the ASPAC study was much higher.

The average BMI value in both adult men and post-menopausal women was about 23 in the general population and the rates for people with BMI ≥ 25 were 23 and 27%, respectively, for men and women. The prevalence of overweight (BMI ≥ 25) in men enrolled in the ASPAC study (33%) was only 1.4 times as much as in the general population and there was no difference in the prevalence rate

between the ASPAC patients and the general population for females. In contrast, the prevalence of obesity with BMI ≥ 30 was markedly higher than (more than 5 times) that in the general population (1-3%) for both men and women.

The average total cholesterol of Japanese men aged 50-74 years was 5.06 mmol/L (196 mg/dl) and the prevalence of hypercholesterolemia with values ≥ 5.5 mmol/L (213 mg/dl) was 33% in the survey on the general population in 1990. In postmenopausal women, these values were 209mg/dl and 50%, respectively. The prevalence rate of moderate to severe hypercholesterolemia with total cholesterol at or above 6.5 mmol/L (251 mg/dl) in the general population aged 50-74 years was 8 and 16%, respectively, for men and women. As in the case of BMI, the prevalence rates of moderate to severe hypercholesterolemia with total cholesterol ≥ 6.5 mmol/L (251 mg/dl) were markedly higher than (about twice) in the general population, while the differences were not so remarkable in the prevalence rates of mild hypercholesterolemia with total cholesterol at or above 5.5 mmol/L (213 mg/dl).

The serum triglyceride value of 2.3 mmol/L (204 mg/dl), used as a criterion for hypertriglyceridemia in this study,

Table 3. Prevalence of Risk factors in Patients with Acute Coronary Syndrome (ASPAC study) in Comparison to the General Population

Risk Factors	ASPAC study		1990 Survey in General Population	
	Male	Female	50-74y male	50-74y female
Hypertension ^{#1}	70%	79%	38%	36%
Current smokers	57%	16%	49%	5-6%
(Ex smokers)	8%	4%		
BMI ≥ 25	33%	27%	23%	27%
≥ 30	9%	17%	1.2%	2.9%
Ch ^{#2} ≥ 5.5 mmol/L	54% ^{#3}	71% ^{#3}	33%	50%
213 mg/dl				
≥ 6.5 mmol/L	15%	30%	8%	16%
251 mg/dl				
HDL-cholesterol				
< 1 mmol/L	40%		19%	11%
38.7 mg/dl				
Triglyceride				
≥ 2.3 mmol/L	26%	21%	11%	6%
204 mg/dl				
Diabetes mellitus	31%	44%	7.3% ^{#4}	3.7% ^{#4}

Data of the ASPAC study were from Reference 9)

^{#1} Systolic blood pressure ≥ 140 mmHg and /or Diastolic blood pressure ≥ 90 mmHg, or a history of hypertension in the past or present. ^{#2} total cholesterol

^{#3} includes patients with documented history or use of antilipidemic drugs

^{#4} Fasting blood glucose ≥ 0.7 mmol/L (126mg/dl) or history of diabetes mellitus in the past or present

almost corresponded to the 90 percentile values in men aged 50-74 years and about 95 percentile value in postmenopausal women. The prevalence rate of hypertriglyceridemia in the ASPAC patients was therefore nearly 3 times as much as in the general population.

Average HDL-cholesterol levels in the general population were 1.32 mmol/L (51 mg/dl) in men aged 30-79 years and 1.40 mmol/L (54 mg/dl) in postmenopausal women, and the prevalence of low HDL-cholesterol with values less than 1 mmol/L (38 mg/dl) was 19% in men and 11% in women. The prevalence rate of low HDL-cholesterol was 40% in the ASPAC study, being markedly higher than the values obtained from the general population.

The prevalence of diabetes mellitus judged by a fasting blood glucose (FBG) of 126 mg/dl or more or the presence of a history in the lipid survey of 1990 in the general population in Japan was 7.3 and 3.7%, respectively, for men and women. The values for the prevalence of diabetes mellitus in the ASPAC study (31% for men and 44% for women) were much higher than those in the general population.

Comparison of the prevalence of metabolic risk factors between hyper- and normotensive subjects in the general population

Because hypertension is the most common risk factor for CHD as well as stroke in Japan, the prevalence rates of the major metabolic risk factors (BMI, total and HDL-cholesterol, and triglyceride) were compared between the subjects with and without hypertension enrolled in the 1990 lipid survey. Only the data for men are shown in the table (Table 4). The prevalence rate of BMI above 25 was almost twice as much as that in normotensive subjects. The average total cholesterol was also higher in hypertensives. Interestingly, the differences in average of HDL- and LDL-cholesterol between hypertensive and normotensive subjects were not as significant as those of total cholesterol for both younger and older age groups. In contrast, nonHDL-cholesterol (total minus HDL-cholesterol) values showed remarkable differences between normotensive and hypertensive subjects, with t-values much greater than LDL-cholesterol or even larger than total cholesterol in the younger age group. The statistical significance shown by the t-value of the difference in the average of serum triglyceride was comparable to or greater than that of total cholesterol.

Discussion

The ASPAC study (8,9) was carried out with the same objectives and design as the EUROASPIRE study (15) to ascertain the CHD risk factors and find to what extent their management was achieved in each country and region. The reliability of the ASPAC study was proven by the fact that the data obtained in New Zealand were

Table 4. Metabolic Parameters in Hypertensive and Normotensive Subjects in the General Population from the 1990 Survey of Serum Lipid Levels in Japanese

	Hypertensive	Normotensive	Difference:t value*
Male 20-39 y	n = 332	n = 2713	
BMI	24.5 ± 3.5	22.6 ± 2.9	10.99 (P<0.001)
BMI > 25	38.5 %	17.6 %	
Total cholesterol [#]	5.20 ± 1.08 (201.1 ± 41.6)	4.87 ± 0.90 (188.1 ± 34.7)	6.30 (P<0.001)
Triglyceride [#]	1.69 ± 1.30 (150.6 ± 115.4)	1.31 ± 1.03 (117.0 ± 92.0)	6.11 (P<0.001)
HDL-cholesterol [#]	1.30 ± 0.36 (50.4 ± 13.8)	1.33 ± 0.36 (51.3 ± 14.0)	1.11 (n.s.)
LDL-cholesterol [#]	3.18 ± 0.99 (122.8 ± 38.1)	2.95 ± 0.83 (113.9 ± 31.9)	4.69 (P<0.001)
Total minus HDL-cholesterol [#]	3.91 ± 1.11 (151.1 ± 42.9)	3.54 ± 0.95 (136.8 ± 36.9)	17.35 (P<0.001)
Male 40-59 y	n = 2405	n = 9024	
BMI	23.9 ± 2.9	22.9 ± 2.7	15.89 (P<0.001)
BMI > 25.2	31.3 %	17.2 %	
Total cholesterol	5.33 ± 0.97 (206.0 ± 37.4)	5.11 ± 0.92 (197.7 ± 35.5)	10.07 (P<0.001)
Triglyceride	1.69 ± 1.45 (150.6 ± 129.4)	1.35 ± 1.05 (120.4 ± 93.7)	12.87 (P<0.001)
HDL-cholesterol	1.33 ± 0.39 (51.6 ± 15.2)	1.30 ± 0.39 (50.2 ± 15.2)	4.01 (P<0.001)
LDL-cholesterol	3.27 ± 0.93 (126.3 ± 35.9)	3.21 ± 0.88 (124.2 ± 34.2)	2.65 (P<0.01)
Total minus HDL-cholesterol	3.99 ± 1.00 (154.4 ± 38.8)	3.81 ± 0.97 (147.5 ± 37.6)	7.99 (P<0.001)

BMI > 25 and > 25.2 correspond to the top quintile of the total subjects of this group

[#]mmol/L (mg/dl): average ± standard deviation

*Statistical analysis was performed with Student's t test.

comparable to those of the EUROASPIRE study for almost every risk factor (Table 2). The peculiar feature of the Japanese patients was a relatively low BMI; the prevalence rate of overweight with BMI at or above 25 in the Japanese patients was still lower than that of obesity with BMI at or above 30 in New Zealand, even though the rates of both obesity and overweight, especially the former, in ACS patients were considerably higher than in the general population in Japan.

It is universally recognized that the relative risk of CHD increases in a curvilinear manner with an increase in serum cholesterol (16-18), while the number of events is markedly different in different cultures (7). A tendency for serum cholesterol to increase with an increase in BMI has also been demonstrated in epidemiological studies (11). The ratio of the prevalence rate of hypercholesterolemia in ACS patients versus the general population was relatively small (only about twice as much) in Japan, probably because the distribution of cholesterol towards the

higher range was not as remarkable as in Western countries.

The ratio of the prevalence rate of hypertriglyceridemia with serum triglyceride at or above 2.3 mmol/L (204 mg/dl) in the ACS patients versus the general population was much higher than that of hypercholesterolemia. In this context, it is important to note that the subjects with hypertension had hypertriglyceridemia at a rate significantly high as hypercholesterolemia in the general population in Japan; the differences in these two values between hypertensive and normotensive subjects were statistically much more significant than those in LDL- and HDL-cholesterol in the general population.

It is difficult to compare exactly the prevalence of diabetes mellitus because of the limitation of diagnosis by a simple measurement of blood glucose levels. However, even considering such a limitation, diabetes mellitus appears to be an important risk factor for CHD in Japanese patients, and its prevalence was much greater in Japanese patients than in Australia-New Zealand.

The importance of hypertriglyceridemia with a mild increase in total cholesterol as a major CHD risk factor and its association with glucose intolerance and diabetes mellitus have been suggested by many case-control studies in Japan (19-23). Increases in intermediate-density lipoprotein (IDL) or remnant particles and small-dense LDL without a remarkable difference in LDL-cholesterol were recognized as peculiar to these patients. In this context, it is important to note that the difference in total minus HDL-cholesterol values between normotensive and hypertensive subjects in the general population was more significant than the difference in LDL-cholesterol. It is also important that these patients with CHD or ACS were not necessarily obese. In the lipid survey carried out in 1990, a difference in triglyceride between hypertensive and normotensive subjects was generally seen in every class of subjects with different BMI (data not shown). The increase in CHD risk with the rise of cholesterol has been shown clearly in the Japanese population only when the serum cholesterol increases above 6.2 mmol/L (240mg/dl) according to the epidemiological study (3) and a postmarketing survey on a large number of patients under treatment with simvastatin (4). This is probably because risk factors other than LDL-cholesterol are involved more strongly in atherogenesis in the Japanese population.

The importance of diabetes mellitus as a major CHD risk factor has been widely recognized in Asian populations, especially Indians. In Singapore, a National Health Survey revealed that the prevalence of diabetes mellitus was high across all three ethnic groups; Chinese, Malays, and Indians (24). The survey also suggested that ethnic differences in the prevalence of diabetes mellitus, central obesity, hypertension, and lipid profiles could explain the differential coronary heart disease rate in the three ethnic

groups, with Indians being at the highest risk. The results of an epidemiological study on plasma insulin levels in the glucose tolerance test in Japanese and in Americans of Japanese descent living in Hawaii and Los Angeles showed that they were much lower in Japanese and even in Japanese-Americans than in Caucasians (25). It was reported that the index of coronary atherosclerosis assessed by angiogram was higher on average in patients with higher plasma insulin levels (26). It is important to note that the measurement of fasting plasma glucose is not adequate as a measure for glucose intolerance or diabetes mellitus in the Asian population compared to Caucasians as reported from a study in London (27). It seems important to look for the reason why Asian people, including Japanese, become ill with diabetes mellitus without becoming as obese as Caucasians.

The results of this study show the importance of hypertension, hypertriglyceridemia and diabetes mellitus, i.e. the importance of multiple risk factor syndrome (28,29), as underlying risk factors. A relationship between hypertension and glucose intolerance was observed regardless of the presence of obesity (30). A recent report from a multicenter, cross-sectional study carried out in the Fukuoka area on patients who underwent coronary angiography for suspect or known CHD has shown that the combination of hypertension, hypertriglyceridemia with low HDL-cholesterol, and diabetes mellitus was more important than hypercholesterolemia (31). However, the results of these studies do not deny the importance of cholesterol as a major CHD risk factor. Both epidemiological and intervention studies have shown that the increase in risk ratio due to an increase in serum cholesterol is almost equivalent to that in Europe and America (3,4,18). Life style in the Japanese population is steadily changing. Data obtained by a pathological study of atherosclerotic lesions in aorta and coronary arteries showed that coronary lesions have become greater in the last 13 years, although the lesions in the aorta did not show a remarkable change (32). Statistics on the origin of stroke also showed an increase in atherothrombosis, which had previously not been so frequent in Japan (Minematsu *et al*: personal communication). There is still scope for Euro-American type atherosclerosis to increase in the near future, even in Japan.

Conclusion

1) Hypertension, hyperlipidemia, diabetes mellitus, and smoking are involved in atherogenesis as risk factors for CHD with almost equal potentiality in the Japanese population. Diabetes mellitus is an important risk factor in Japan as well as in other ethnic Asian populations.

2) Although moderate to severe hypercholesterolemia with total cholesterol ≥ 6.5 mmol/L is an important risk factor, hypertriglyceridemia with triglyceride ≥ 2.3 mmol/L has almost the same or even greater potency as hypercho-

lesterolemia and it seems more important than the increase in LDL-cholesterol in regard to the association with hypertension.

3) Body mass index is much smaller in Japanese than in Caucasians, yet, Japanese are prone to diabetes mellitus without marked obesity.

Acknowledgements: We gratefully acknowledge the support of Merck Sharp and Dohm Asia and Banyu Co. for the ASPAC Study. The Serum Lipid Survey 1990 was supported by the HMG-CoA Reductase Study Grant of Sankyo Co. and the investigators are listed in Ref. 10.

List of Investigators and Associate Investigators of the ASPAC study

Akihiko Nozawa (Hokkaido Prefectural Hospital Kitami, Cardiology Dept), Junichi Kikuchi (Towada City General Hospital, Third Dept of Medicine), Takesatoru Fukuda (Saiseikai Maebashi Hospital, Cardiology Dept), Toshio Shibuya (National Defense Medical College, First Dept of Medicine), Kamon Imai (Ohara Cardiovascular Center Saitama), Kyoichi Mizuno (Chiba Hokuso Hospital, Nippon Medical School, Dept of Medicine), Koji Tamura (Tokyo Women's Medical College, Daini Hospital), Tetsuya Sumiyoshi (Sakakibara Memorial Hospital), Takeshi Motomiya, Yoshiki Tokuyasu (Tokyo Hiroo Hospital, Cardiology Dept), Yoichi Shimizu (New Tokyo Hospital, Cardiology Dept), Toshihiko Tochiara (Sagamihara Kyodo Hospital, Cardiology Dept), Manabu Shirotani (Shizuoka General Hospital, Cardiology Dept), Akinori Takizawa (Shizuoka City Shizuoka Hospital, Cardiology Dept), Mitsuhiro Okada (Nagoya Ekiseikai Hospital, Dept Medicine), Hiroshi Nonogi (National Cardiovascular Center, Cardiovascular Dept), Toru Hayashi (Osaka National Hospital, Cardiology Dept), Hideo Tamai, Eisho Kyo (Shiga Medical Center for Adults, Cardiology Dept), Takashi Fujii (Yamaguchi University School of Medicine, Second Dept of Medicine), Nobuaki Nakamura (Matsue Red Cross Hospital, Cardiology Dept), Masakiyo Nobuyoshi (Kokura Memorial Hospital, Cardiology Dept), Samon Koyanagi (National Hospital Kyushu Medical Center, Cardiology Dept), Takashi Honda (Saiseikai Kumamoto Hospital, Cardiovascular Center)

References

- (1) Keys A: Coronary heart disease in seven countries (AHA Monograph No 29). *Circulation*, 41 (Suppl 1): 1-211, 1970
- (2) Age standardized death rate for selected causes, by sex, latest available year. *World Health Statistics Annuals*, World Health Organization, 1970-1986
- (3) Ueshima H: Follow-up study from the National Survey of Circulatory Disorders in Japan 1980. National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged (NIPPON DATA). *J Jap Assoc Cerebro-cardio-vascul Dis Control*, 31: 231-237, 1997 (In Japanese)
- (4) Matsuzaki M, Kita T, Mabuchi H, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, Itakura H, and The J-LIT Study Group: The influence of hypercholesterolemia on the occurrence of myocardial infarction in 47, 294 Japanese hypercholesterolemic population with no prior coronary artery disease: Primary prevention in the J-LIT Study. reported at the 2001 Annual Scientific Meeting of ACC (March 19, 2001, abstract: *J Am Coll Cardiol* 37, No.2, Suppl A, abstract No. 842-6).
- (5) Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, and Packard CJ for the West of Scotland Coronary Prevention Study Group: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*, 333: 1301-1307, 1995
- (6) Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Krueger W, Gotto AM Jr, for the AFCAPS/TextCAPS Research Group: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. *JAMA*, 279: 1615-1622, 1996
- (7) Verschuren WMM, Jacobs DR, Bloemberg BPM, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Karvonen MJ, Nedeljkovic S, Nissinen A, Toshima H: Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the Seven Countries Study. *JAMA*, 274: 131-136, 1995
- (8) Richie GM and Keech AC on behalf of the ASPAC Collaborative Group: Asia-Pacific collaboration on coronary heart disease risk factor intervention: study design and methods. *Heart, Lung and Circulation*, 10: 24-29, 2001
- (9) The ASPAC Collaborative Investigators Group: Coronary heart disease risk factors in patients with acute coronary syndromes in the Asia-Pacific region- The Asia-Pacific Collaboration (ASPAC) Study on Coronary Heart Disease Risk Factor Intervention. *Lancet* submitted for publication
- (10) Research Committee on serum Lipid Level Survey 1990 in Japan: Current state of and recent trends in serum lipid levels in the general Japanese population. *J Atheroscl Thromb*, 2: 122-132, 1996
- (11) Yamamoto A, Horibe H, Mabuchi H, Kita T, Matsuzawa Y, Saito Y, Nakaya N, Fujioka T, Tenba H, Kawaguchi A, Nakamura H, and Goto Y for the Research Group on Serum Lipid Survey 1990 in Japan: Analysis of serum lipid levels in Japanese men and women according to body mass index. Increase in risk of atherosclerosis in postmenopausal women.

- Atherosclerosis, 143: 55-73, 1999
- (12) National Heart, Lung, and Blood Institute Conference Development Panel. Treatment of hypertriglyceridemia. *J Am Med Assoc* 251: 1196-1200, 1984
 - (13) NIH Consensus Development Panel on Triglyceride, High Density Lipoprotein, and Coronary Heart disease: Triglyceride, high-density lipoprotein and coronary heart disease. *JAMA*, 269: 505-510, 1993
 - (14) 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 (NECP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*, 285: 2486-2497, 2001;
 - (15) EUROASPIRE Study Group: EUROASPIRE A European Society of cardiology survey of secondary prevention of coronary heart disease; Principal results. *Eur Heart J*, 18: 1569-1582, 1997
 - (16) Stamler J, Wentworth D, and Neaton JD: Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk factor Intervention Trial (MRFIT). *JAMA*, 256: 2823-2828, 1986
 - (17) 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, 1980
 - (18) Guideline Committee of Japan Atherosclerosis Society: Guidelines for the treatment of hyperlipidemia. *J Japan Atheroscl Soc*, 25: 1-34, 1997 (In Japanese)
 - (19) Tatami R, Mabuchi H, Ueda K, Ueda R, Haba T, Kametani T, Ito S, Koizumi J, Ohta M, Miyamoto S, Nakayama A, Kanaya H, Oiwake H, Genda A, Takeda R: Intermediate-density lipoprotein and cholesterol-rich very low density lipoprotein in angiographically determined coronary artery disease. *Circulation*, 64: 1174-1184, 1981
 - (20) Kukita H, Imamura Y, Hamada M, Joh T, Kokubo T: Plasma lipids and lipoproteins in Japanese male patients with coronary artery disease and in their relatives. *Atherosclerosis*, 42: 21-29, 1982
 - (21) Kameda K, Matsuzawa Y, Kubo M, Ishikawa K, Maejima I, Yamamura T, Yamamoto A, and Tarui S: Increased frequency of lipoprotein disorders similar to type III hyperlipoproteinemia in survivors of myocardial infarction in Japan. *Atherosclerosis*, 51: 241-249, 1984
 - (22) Kugiyama K, Doi H, Motoyama T, Soejima H, Misumi K, Kawano H, Nakagawa O, Yoshimura M, Ogawa H, Matsumura T, Sugiyama S, Nakano T, Nakajima K, and Yasue H: Association of remnant lipoprotein levels with impairment of endothelium-dependent vasomotor function in human coronary arteries. *Circulation*, 97: 2519-2526, 1998
 - (23) Koba S and Hirano T: Small dense low-density lipoprotein in Japanese men with coronary artery disease. *Ann Intern Med*, 132: 762, 2000
 - (24) Tan C-E, Tan B-Y, Emmanuel SC, and Jacobs E: Prevalence of diabetes and ethnic differences in cardiovascular risk factors. The 1992 Singapore National Health Survey. *Diabetes Care*, 22: 241-247, 1999
 - (25) Egusa G, Fujikawa R, Watanabe H, Ohkubo M, and Yamakido M: Comparison of NIDDM between USA and Japan. *Mebio*, 15: 78-82, 1997 (In Japanese)
 - (26) Yamamoto A, Yamamura T, Kawaguchi A, Kameda K, and Matsuzawa Y: Triglyceride and glucose intolerance as a risk factor for coronary heart disease. *Cardiology*, 78: 185-193, 1991
 - (27) Harris TJ, Cook DG, Wicks PD, and Cappuccio FP: Impact of the new American Diabetes Association and World Health Organization diagnostic criteria for diabetes on subjects from three ethnic groups living in UK. *Nutr Metabol Cardiovasc Dis*, 10: 305-309, 2000
 - (28) Reven GM: Role of insulin resistance in human disease. *Diabetes*, 37: 1595-1607, 1988
 - (29) DeFronzo RA and Ferrannini E: Insulin resistance. A multifacted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Diabetes Care*, 14: 173-194, 1991
 - (30) Suzuki M, Hirose J, Asakura Y, Sato A, Kageyama A, Harano Y, and Omae T: Insulin sensitivity in obese, nondiabetic essential hypertension and its improvement by an alpha-1-blocker (bunazosin). *Am J Hypertension*, 5: 869-874, 1992
 - (31) Washio M, Sasazuki S, Kodama H, Yoshimasu K, Liu Y, Tanaka K, Tokunaga S, Kono S, Arai H, Koyanagi S, Hiayama K, Doi Y, Kawano T, Nakagaki O, Takada K, Nii T, Shirai K, Ideishi M, Arakawa K, Mohri M, and Takeshita A: Role of hypertension, dyslipidemia and diabetes mellitus in the development of coronary atherosclerosis in Japan. *Jpn Circ J*, 65: 731-737, 2001
 - (32) Imakita M, Yutani C, Strong JP, Sakurai I, Sumiyoshi A, Watanabe T, Mitsumata M, Kusumi Y, Katayama S, Mano M, Baba S, Mannami T, Masuda J, Sueishi K, and Tanaka K: Second nation-wide study of atherosclerosis in infants, children and young adults in Japan. *Atherosclerosis*, 155: 487-497, 2001