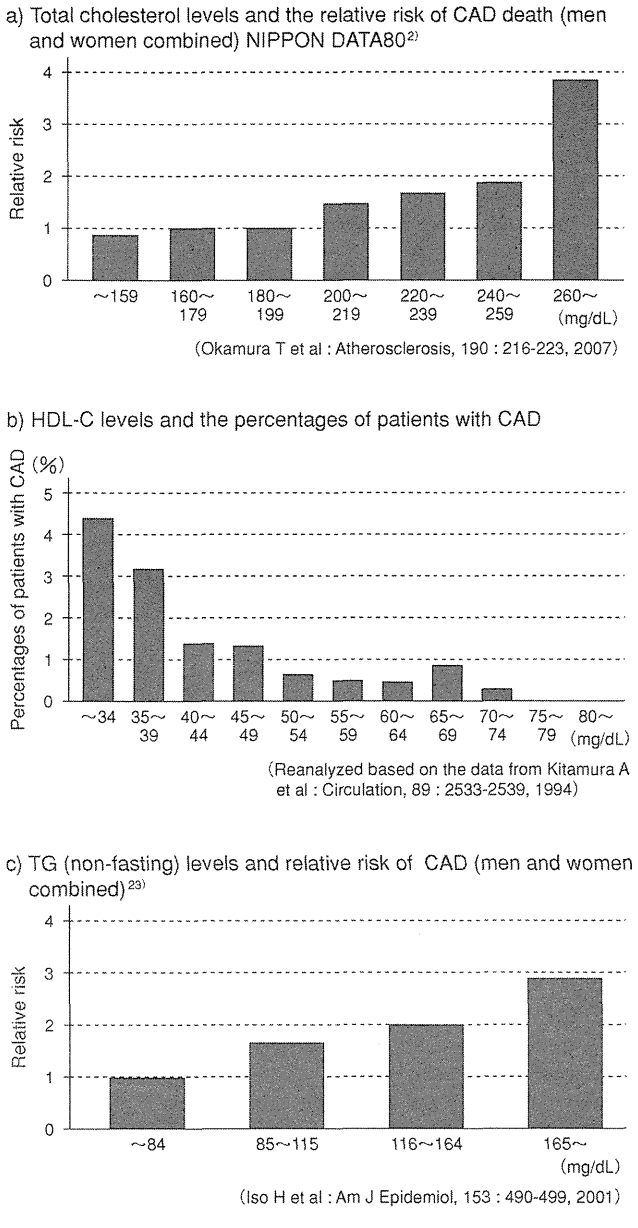

Fig. 1. Serum Lipids and Risk for CAD

intervention significantly decreases the incidence of CAD. In addition, in Japan, the results of large-scale clinical studies have recently shown that treatment for hyper-LDL cholesterolemia is clinically beneficial for Japanese individuals[28-31].

In the U.S. guidelines NCEP-ATP Ⅲ, based on the relationship between the TC levels and CAD mortality reported in the MRFIT[32], the cutoff value for hypercholesterolemia is a TC level of 240 mg/dL, the level at which the relative risk is 2-fold higher than that observed at a TC level of 200 mg/dL[33]. As described above, the absolute risk of CAD in Japanese individuals is much lower than that observed in Westerners. In order to maintain this low risk, the use of early prevention measures is needed.

Based on the above findings, a TC level of 220 mg/dL, the level at which the relative risk shown in the NIPPON DATA80 is approximately 1.5-fold higher than that observed at a TC level of <180 mg/dL, was used as the cutoff value for screening Japanese individuals in terms of the prevention and treatment of CAD, and the corresponding LDL-C level of 140 mg/dL was defined as the cutoff value for the diagnosis of hyper-LDL cholesterolemia.

The CIRCS, an epidemiological study recently conducted in Japan[1], showed that the incidence of CAD in subjects with an LDL-C level of 80 to 99 mg/dL, 100 to 119 mg/dL, 120 to 139 mg/dL and ≥140 mg/dL is 1.4-, 1.7-, 2.2- and 2.8-fold higher, respectively, than that observed in subjects with a LDL-C level of <80 mg/dL. In the presence of multiple risk factors, the incidence of and mortality from CAD also increase in Japanese individuals. Since the incidence of and mortality from CAD in patients with multiple risk factors were found to be higher than those observed in patients without such factors, even at the same LDL-C levels, and patients with diabetes mellitus (DM) developed CAD at lower LDL-C levels of approximately 30 to 40 mg/dL as frequently as patients without DM in a subanalysis of primary prevention in the J-LIT study[34], it has been suggested that the degree of the increased risk of CAD associated with the LDL-C level changes depending on comorbidities. As a result of these concerns, these guidelines define an LDL-C level of 120-139 mg/dL as the borderline level at which the effects of other risk factors should be carefully considered when screening Japanese individuals for dyslipidemia.

2. Hypo-HDL Cholesterolemia

Having a low level of HDL-C places a patient at risk for developing CAD. Conversely, a higher HDL-C level is associated with a decreased risk of CAD (**Fig. 1b**)[11, 35]. In the NIPPON DATA90, the HDL-C level was found to be significantly inversely correlated with overall mortality and stroke mortality during the 9.6-year observation period[36]. Community and worksite-based cohort studies have shown that an HDL-C level <40 mg/dL is associated with an increased risk of CAD[11, 37-39]. In the J-LIT, a cohort study, simvastatin-treated primary prevention patients[12] and secondary prevention patients[13] with an HDL-C level <40 mg/dL were found to have a

Table 1. Dyslipidemia: Diagnostic Criteria for Screening (Fasting*)

Low-density lipoprotein cholesterol (LDL-C)	≥ 140 mg/dL	Hyper-LDL cholesterolemia
	120-139 mg/dL	Borderline hyper-LDL cholesterolemia**
HDL-C	< 40 mg/dL	Hypo-HDL cholesterolemia
Triglycerides (TGs)	≥ 150 mg/dL	Hypertriglyceridemia

• The LDL-C level is calculated using the Friedewald formula (TC − HDL-C − TG/5) (if TG < 400 mg/dL).
• If the TG level is ≥ 400 mg/dL or non-fasting blood is used, the non HDL-C (TC − HDL-C) level should be used. The cutoff value is LDL-C + 30 mg/dL.
*A "fasting state" is defined as having fasted for ≥ 10 to 12 hours. The consumption of liquids with no calories, such as water and tea, is permitted.
**If borderline hyper-LDL cholesterolemia is diagnosed during screening, the presence of high-risk conditions should be assessed and the need for treatment should be considered.

1.3- and 1.6- fold higher relative risk of CAD, respectively, than those with an HDL-C level of 40-49 mg/dL. Based on these findings, these guidelines define an HDL-C level of < 40 mg/dL as the cutoff value for screening for hypo-HDL cholesterolemia. In general, women exhibit higher HDL-C levels than men[36, 39, 40]; however, there is currently insufficient evidence to support the existence of a relationship between sex differences in the HDL-C levels and the incidence of CAD. Therefore, these guidelines used the same cutoff value for both women and men.

3. Hypertriglyceridemia

Many reports have shown that a high TG level is associated with a risk of developing CAD in Asia, Oceania[41] and Japan[9, 10, 39, 42, 43] as well as in Western countries[44]. In some of these studies, the TG level was found to be associated with the risk of CAD even when the HDL-C level was corrected[9, 41, 42, 44]. In the U.S., hypertriglyceridemia is defined as a fasting TG level of ≥ 150 mg/dL based on the Framingham study[45]. Traditionally, the TG level has been measured using fasting blood; however, one report indicates that the non-fasting TG level more accurately predicts cardiovascular events[46]. Epidemiological studies conducted in Japan have shown that the incidence of CAD increases when the fasting TG is ≥ 150 mg/dL[10, 39, 43] and that the incidences of myocardial infarction, exercise-induced angina and sudden death increase when the non-fasting TG level is ≥ 165 mg/dL (**Fig. 1c**)[9]. Moreover, many reports have also shown that hypertriglyceridemia is a risk factor for cerebral infarction, although this association is weaker than that observed for CAD[39, 41, 47-49]. Considering these findings, these guidelines define a TG level of ≥ 150 mg/dL as the cutoff value for screening for hypertriglyceridemia; however, hypertriglyceridemia often reflects other pathological conditions, such as increased levels of remnant lipoproteins or small, dense LDL, complications of hypo-HDL cholesterolemia and the presence of metabolic syndrome. Therefore, other conditions associated with increased TG levels should be carefully assessed.

4. Non HDL Cholesterol

If hypertriglyceridemia exists, especially when the TG level is ≥ 400 mg/dL, the correct LDL-C level cannot be calculated because the Friedewald formula is not applicable and the direct measurement method is problematic. In such cases, the non HDL-C level is a useful and simple index calculated by subtracting the HDL-C level from the TC level. Some investigators consider the non HDL-C level to be superior to the LDL-C level in terms of predicting the development of atherosclerotic diseases because the non HDL-C level incorporates all atherogenic lipoproteins, including remnant lipoproteins[50, 51]. Recently, many epidemiological studies have examined the relationship between the non HDL-C level and the risk of CAD in Japan[8, 24, 25, 49, 52]. The non HDL-C level exhibits the same relationship with the incidence of myocardial infarction as the LDL-C level, with both parameters demonstrating comparable ability to predict the development of myocardial infarction[24]. On the other hand, one study showed that the non HDL-C level is superior to the TC level in terms of predicting the incidence of myocardial infarction[25]. The incidence and mortality of CAD and myocardial infarction markedly increase in men with a non HDL-C level of ≥ 170-180 mg/dL, while no specific tendencies have been observed in women[8, 24, 25, 52]. One study investigated the risk of myocardial infarction associated with the non HDL-C level in the presence or absence of hypertriglyceridemia[49]. In that report, the risk of myocardial infarction markedly increased in the group with both hypertriglyceridemia (TG ≥ 150 mg/dL) and a

non HDL-C level of ≥ 190 mg/dL. In a subanalysis of the JELIS that compared the groups that achieved both LDL-C and non HDL-C management goals, the other groups exhibited higher incidences of CAD[53]. Recently, it was demonstrated that the non HDL-C level in Japanese individuals is equal to LDL-C + 30 mg/dL, the same as that observed in the U.S[54, 55]. Based on these findings, these guidelines defined a non HDL-C level of ≥ 170 mg/dL as the cutoff value for screening.

Footnotes

This is an English version of the guideline from the Japan Atherosclerosis Society (chapter 3) published in Japanese in June, 2012.

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The Relationship Between Low-Density Lipoprotein Cholesterol Levels and the Incidence of Cardiovascular Disease in High-Risk Patients Treated With Pravastatin

Main Results of the APPROACH-J Study

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SUMMARY

This study aimed to evaluate the relationship between low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular disease (CVD) in high-risk patients with hypercholesterolemia without a history of CVD. Patients who were receiving or started treatment with pravastatin, were followed-up for 2 years. Patients were divided into quartiles according to on-treatment LDL-C. The maximum contrast method based on the Cox proportional hazards model was used to evaluate the relationship between achieved LDL-C and the incidence of CVD. Incidence of CVD was also compared according to whether a number of risk factor targets were achieved. A total 6,229 patients were enrolled, with 4,916 having reported LDL-C values. During the 2 years, 69 cases of CVD (6.7/1000 patient years), including 36 coronary artery disease (CAD) (3.5/1000 patient years) and 28 strokes (2.7/1000 patient years), occurred. The comparison of on-treatment LDL-C level quartiles suggested that the incidence of all CVD decreased linearly as the LDL-C levels decreased. Incidence of CAD showed a curvilinear relationship to LDL-C levels, suggesting some attenuation of risk below LDL-C of 119 mg/dL. The incidence of all CVD and CAD tended to be decreased as the number of achieved risk factor targets increased. In conclusion, through our observational study, it was shown that a linear relationship between the incidence of CVD and LDL-C was observed in high-risk hypercholesterolemic patients. The low incidence of CVD in the present study may be associated with multifactorial management of conventional risk factors including high LDL-C levels. However, prospective, randomized studies are needed to confirm these findings. (Int Heart J 2014; 55: 39-47)

Key words: Hypercholesterolemia, Primary prevention, Occlusive atherosclerotic complications, Cardiovascular disease

Dyslipidemia is a consolidated risk factor for atherosclerotic disease, which has been established by a great number of epidemiological studies in Western as well as Asian countries.[1-3] The current consensus is that statins can reduce coronary heart disease by 20-40%, with an approximately 30-50% lowering of low-density lipoprotein cholesterol (LDL-C), irrespective of setting (primary prevention or secondary prevention)[4-10] or the presence of other risk factors (eg, diabetes).[11]

Based on these findings, various guidelines for the diagnosis and treatment of dyslipidemia were conceived and updated to minimize lethal atherosclerotic disease.[12,13] In Japan, a treatment guideline for dyslipidemia was first released in 1997, and it has since been modified to become the Japanese Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia (2002, updated in 2007).[14] The current JAS guideline states that the fundamental treatment concept for primary prevention is modification of lifestyle, including diet and exercise, but if it is difficult to manage lipid levels appropriately, drug therapy including statins should be considered. The JAS guideline also shows the treatment goal for LDL-C level according to stratification by the risk level of a patient. The treatment goals for a patient without conventional risk factors, with one or two risk factors, and with three risk factors or more are set at < 160 mg/dL, < 140 mg/dL, and < 120 mg/dL, respectively, in the primary prevention setting; more intensive goals are recommended for a patient in secondary prevention, based on the findings from clinical trials.[15,16] Although the current JAS guideline has been well established based on a large amount of Japanese evidence which has been generated recently, some statements still rely on overseas data. Therefore, we need to accumulate Japanese evidence to confirm whether the recommendation of the JAS guideline is working effectively in the real world setting.

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Pravastatin is one of the statins which has firm evidence showing its beneficial effect against cardiovascular disease,[17] including studies from Japan.[18-21] Of these studies, the landmark MEGA Study clearly revealed that pravastatin significantly reduces cardiovascular disease by 30%, with an 18% decrease in LDL-C in patients without a history of cardiovascular disease,[18] and various findings of the MEGA Study have been cited in the current JAS guideline.[15] However, exactly how pravastatin works in high-risk patients in primary prevention categorized by the JAS guideline has not been well investigated to date. Therefore, we investigated the relationship between on-treatment LDL-C level and the incidence of cardiovascular disease in high-risk patients in primary prevention in the real world setting in the Affirmation Primary Prevention with Pravastatin in Reduction of Occlusive Atherosclerotic Complications in Hypercholesterolemia-Japan (APPROACH-J) Study, a prospective observational study of patients taking pravastatin.

Methods

The design of the APPROACH-J Study has been reported previously.[22] Briefly, this observational cohort study was started in February 2008 with a target of 5,000 patients to be enrolled until January 2009, and the patients were followed up for 2 years until January 2011.

The patients enrolled in the present study were initiated on or were taking pravastatin at the beginning of the study, and were men aged 20 years or older and women aged 55 years or older (or postmenopausal women) without a history of cardiovascular disease. The patients were categorized as high risk, with 3 or more major risk factors other than high LDL-C level, including being older (age ≥ 45 years in men, ≥ 55 years in women), hypertension, diabetes mellitus (including impaired glucose tolerance), smoking, a family history of coronary artery disease, and low high-density lipoprotein cholesterol (HDL-C, < 40 mg/dL), according to the JAS guideline. The number of risk factors for each patient was defined based on the physician's diagnosis at the time of enrollment. All enrolled patients were starting or continuing treatment with pravastatin and gave written informed consent. The exclusion criteria were: 1) a history of cardiovascular disease (myocardial infarction, MI; unstable angina; coronary revascularization; or stroke); 2) serious arrhythmia; 3) familial hypercholesterolemia; 4) poorly controlled blood pressure or blood glucose; 5) serious hepatic dysfunction or serious renal dysfunction; 6) other serious diseases, such as malignant tumors; 7) contraindications to pravastatin therapy; and 8) other reasons judged by the investigator to render the patient inappropriate for long-term administration of pravastatin.

Written informed consent was obtained from all eligible patients. Follow-up was continued for 24 months after initiation of the study, irrespective of whether administration of pravastatin continued, and the investigators contacted patients who failed to visit the hospital at 12 and 24 months after initiation of the study to confirm their health status. No restrictions were placed on other treatments, and all treatments were recorded. The patient characteristics, blood pressure laboratory data, compliance with pravastatin therapy, concomitant medications, and presence or absence of cardiovascular events at baseline and after 6, 12, 18, and 24 months were recorded in clinical report forms every year. Adverse events were investigated throughout the study period. This study was performed in compliance with the Japanese standards for post-marketing surveillance.

The primary composite endpoint was the first occurrence of cardiovascular disease, which included fatal or nonfatal myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, fatal or nonfatal stroke (except transient ischemic attack), arteriosclerosis obliterans, and sudden and unexpected death. The secondary endpoints were subsets of the primary endpoint, laboratory findings, and safety. All cardiovascular disease reported by the investigators was assessed by the Endpoint Committee.

The study was conducted as a post-marketing study of Daiichi Sankyo Co., Ltd. and fully adhered to the regulations of the Japanese Ministry of Health, Labor and Welfare.

Statistical analysis: The patients who had an on-treatment LDL-C level measured by direct methods were divided into quartiles according to their on-treatment LDL-C levels. All on-treatment LDL-C levels were averaged during follow-up except for those measured before the initiation of pravastatin treatment. Incidence of cardiovascular disease was compared between the quartiles by using the multivariable Cox proportional hazards model, adjusted by sex, age, baseline HDL-C, prior use of antihyperlipidemic agents, family history of coronary artery disease, hypertension, diabetes (including impaired glucose tolerance), body mass index, and smoking status. Furthermore, the maximum contrast method[23,24] based on the Cox proportional hazards model was used to investigate the relationships between achieved LDL-C levels and the incidence of cardiovascular events. The maximum contrast method is used to determine the contrast pattern which best fits the observed data with the largest contrast statistic (the smallest *P*-value).[24] This method was originally proposed to identify a dose-response pattern, however, it can be also applied to survival data using contrast statistics with several contrast coefficient vectors.[25] In this analysis, we evaluated contrast statistics for a regression coefficient vector of the Cox proportional hazards model. The details are described in the Appendix. Additionally, the incidence of cardiovascular disease was compared according to the number of achieved targets for the following factors: LDL-C level, blood pressure, hemoglobin (Hb) A1c, and smoking status. The patients who had mean LDL-C < 120 mg/dL, blood pressure < 130/80 mmHg, HbA1c (US National Glycohemoglobin Standardization Program, NGSP) < 6.5%, and smoking cessation during the follow-up period were defined as having achieved the target for each factor. The mean values during the follow-up period were taken for the achieved values of LDL-C, blood pressure, and HbA1c (NGSP). The blood pressure and HbA1c (NGSP) values measured at each institution by their own methods were used in this study. Smoking status was defined using the baseline data. All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

A total of 6,229 patients were enrolled during a year of

entry period, and followed up for 2 years. Data from 4,916 patients were used as the final analysis set, after excluding data from 302 patients (including 6 patients who received no pravastatin treatment, 53 patients who did not have any follow-up data, and 38 patients who withdrew consent), and the 930 patients who did not have on-treatment LDL-C values measured by direct methods. In the follow-up, 95.2% and 89.3% of the patients visited the hospital at 12 months and 24 months, respectively. The patients whose data were used in the final analysis (Table I) had a mean age of 66 years; 42.2% were men and 63.6% were taking antihyperlipidemic agents, including pravastatin, at enrollment. The baseline LDL-C and HDL-C levels were 219.5 and 57.5 mg/dL. Most of the patients were older (95.4%) (≥ 45 years in men, ≥ 55 years in women) and had hypertension (72.9%); and/or diabetes, including impaired glucose tolerance (78.1%). The mean LDL-C during follow-up was 119.5 mg/dL, and there was no apparent change in blood pressure or glucose status (data not shown).

Table I. Baseline Characteristics

	Final analysis set (n = 4,916)
Men, %	42.2
Age, years	66.3 ± 9.9
BMI, kg/m^2	24.6 ± 3.9
Prior hypercholesterolemic medication, %	63.6
Prior pravastatin treatment, %	58.8
Target LDL-C,* mg/dL	120.8
Receiving dietary instruction, %	70.5
Receiving exercise therapy, %	59.2
TC, mg/dL	219.5 ± 35.1
LDL-C, mg/dL	135.4 ± 31.1
HDL-C, mg/dL	57.5 ± 15.2
Non HDL-C, mg/dL	162.0 ± 35.5
Triglycerides, mg/dL (median IQR)	123.0 (90.0-167.0)
SBP, mmHg	133.8 ± 16.1
DBP, mmHg	76.1 ± 10.9
Fasting plasma glucose, mg/dL	120.3 ± 36.1
HbA1c (NGSP), %	6.8 ± 1.1
Conventional risks,** %	
Older age[§]	95.4
Hypertension	72.9
Diabetes (including IGT)	78.1
Smoking	19.7
Family history of coronary disease	19.8
Low HDL-C (< 40 mg/dL)	10.6
Number of risks 3	83.7
4	14.5
5	1.7
6	0.2

*Target LDL-C levels were set by patients' physicians. **Conventional risk factors were defined based on physicians' reports. [§]≥ 45 years for men, ≥ 55 years for women. BMI indicates body mass index; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c (NGSP), hemoglobin A1c (US National Glycohemoglobin Standardization Program); and IGT, impaired glucose tolerance.

As shown in Table II, a total of 69 cases of cardiovascular disease (6.7/1000 patient years, py), including 36 cases of coronary artery disease (3.5/1000 py), 28 cases of stroke (2.7/1000 py), 3 cases of arteriosclerosis obliterans (0.3/1000 py), and 2 cases of sudden/cardiac death (0.2/1000 py), occurred during the 2-year follow-up in patients with LDL-C values in the efficacy analysis set. In the 4 groups generated based on the quartiles of on-treatment LDL-C level (Q1, ≤ 104.9 mg/dL; Q2, 105.0 to < 119.0 mg/dL; Q3, 119.0 to < 133.0 mg/dL; and Q4, ≥ 133.0 mg/dL), the incidence of all cardiovascular disease decreased as the LDL-C levels decreased. The lowest incidence of all cardiovascular disease was found in group Q1, with the lowest on-treatment LDL-C (hazard ratio, HR, against Q4, 0.431; P = 0.0210) (Table III).

In testing the suitability for the shapes of L1 to L6 (Figure 1) by the maximum contrast method for all cardiovascular disease, the largest Wald statistic (the smallest P-value, 0.0229) was found in the L4 type, suggesting that there is a linear relationship between the incidence of all cardiovascular disease and the LDL-C level (Figure 2A). A curvilinear relationship was found for coronary artery disease and was determined to be of the L2 type, with the largest Waldχ^2 (P = 0.0049) in the maximum contrast method (Figure 2B). This resulted in the significantly lower incidence of coronary artery disease in group Q2 (HR, 0.348; P = 0.0292) and group Q1 (HR, 0.283; P = 0.0157), shown in Table III. No significant relationship was found between LDL-C and stroke by using the maximum

Table II. Incidences of Events

Variables	Final analysis set (n = 4,916)
	No. of events* (no. of events/1,000 patient years)
All cardiovascular diseases	69 (6.7)
Coronary artery disease	36 (3.5)
Myocardial infarction	12 (1.1)
Unstable angina	7 (0.7)
Revascularization	35 (3.4)
Stroke	28 (2.7)
Ischemic stroke	9 (0.9)
Cardioembolic stroke	1 (0.1)
Lacunar stroke	9 (0.9)
Hemorrhagic stroke	9 (0.9)
Subarachnoid hemorrhage	1 (0.1)
Other strokes	0
Arteriosclerosis obliterans	3 (0.3)
Sudden /cardiac death	2 (0.2)

*First event for each variable.

Table III. Incidence of Events in Each Quartile Group

Group: LDL-C, mean (range), mg/dL	No. of events/ no. of patients	Incidence (/1,000py)	Hazard ratio (95%CI)	*P*
All cardiovascular diseases				
Q1: 92.9 (44.0 - 104.9)	12/1,214	4.6	0.431 (0.211, 0.353)	0.0210
Q2: 112.2 (105.0 - 118.8)	17/1,240	6.5	0.667 (0.353, 1.258)	0.2106
Q3: 125.5 (119.0 - 132.9)	17/1,222	6.6	0.732 (0.390, 1.375)	0.3324
Q4: 147.5 (133.0 - 230.0)	23/1,240	8.9	1.00	-
Coronary artery disease				
Q1: 92.9 (44.0 - 104.9)	5/1,257	1.9	0.283 (0.102, 0.788)	0.0157
Q2: 112.2 (105.0 - 118.8)	6/1,243	2.3	0.348 (0.135, 0.899)	0.0292
Q3: 125.5 (119.0 - 132.9)	9/1,224	3.5	0.582 (0.256, 1.320)	0.1948
Q4: 147.5 (133.0 - 230.0)	16/1,238	6.2	1.00	-
Stroke				
Q1: 93.0 (44.0 - 104.9)	6/1,222	2.3	0.588 (0.191, 1.807)	0.3538
Q2: 112.1 (105.0 - 118.7)	9/1,230	3.4	1.068 (0.393, 2.903)	0.8977
Q3: 125.5 (118.8 - 132.9)	6/1,237	2.3	0.769 (0.257, 2.302)	0.6389
Q4: 147.0 (133.0 - 230.0)	7/1,233	2.7	1.00	-

LDL-C indicates low-density lipoprotein cholesterol; CI, confidence interval; and py, patient years.

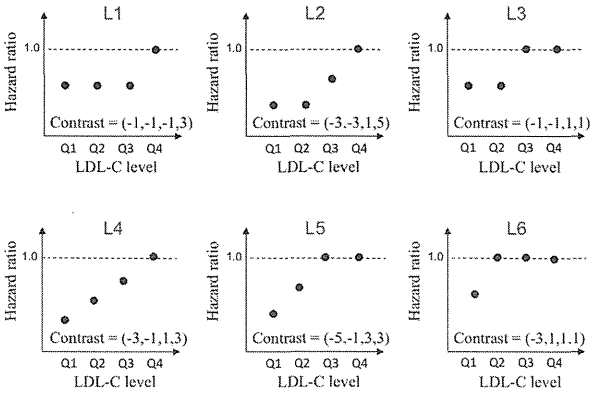
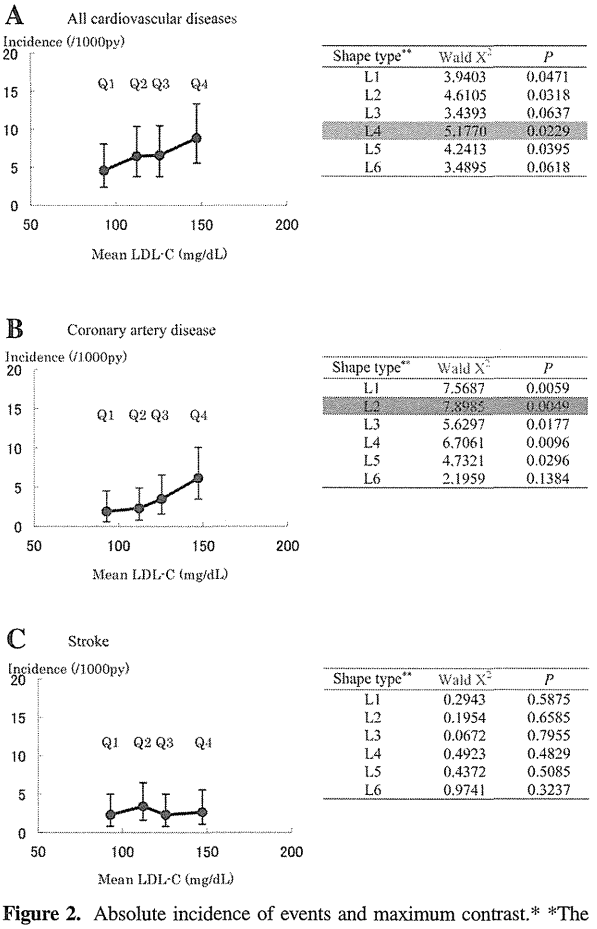


Figure 1. Statistical concepts underlying the maximum contrast method, a statistical method to evaluate the shape of curves which are likely to fit into one of six patterns (L1-L6). LDL-C indicates low-density lipoprotein cholesterol.



Shape type**	Wald X^2	*P*
L1	3.9403	0.0471
L2	4.6105	0.0318
L3	3.4393	0.0637
L4	5.1770	0.0229
L5	4.2413	0.0395
L6	3.4895	0.0618

Shape type**	Wald X^2	*P*
L1	7.5687	0.0059
L2	7.8985	0.0049
L3	5.6297	0.0177
L4	6.7061	0.0096
L5	4.7321	0.0296
L6	2.1959	0.1384

Shape type**	Wald X^2	*P*
L1	0.2943	0.5875
L2	0.1954	0.6585
L3	0.0672	0.7955
L4	0.4923	0.4829
L5	0.4372	0.5085
L6	0.9741	0.3237

Figure 2. Absolute incidence of events and maximum contrast.* *The maximum contrast was evaluated by the Cox proportional hazard model, based on logarithmic LDL-C value. **Shape types: refer to Figure 1. LDL-C indicates low-density lipoprotein cholesterol; and py, patient years.

contrast method (Figure 2C).

To evaluate the effect of risk factors other than the on-treatment LDL-C level, we compared the baseline features of each quartile. A favorable lipid profile was found in the group with a low on-treatment LDL-C level at baseline. Although the number of patients in each quartile who had hypertension and diabetes mellitus (including impaired glucose tolerance) increased from Q4 to Q1, blood glucose and blood pressure were relatively well controlled within the ranges 118.2-121.7 mg/dL and 132.9/74.7-134.8/77.7, respectively, between the 4 groups (Table IV). Moreover, antithrombotic agents, in addition to antiplatelet and anticoagulant agents, were used most frequently (26.4%) in the group with the lowest LDL-C levels.

As shown in Table V, fewer cases of cardiovascular disease occurred in groups with a greater number of achieved risk factor targets (LDL-C < 120 mg/dL, blood pressure < 130/80 mmHg, HbA1c [NGSP] < 6.5%, and no smoking during follow-up), but this result was not statistically significant (P = 0.239). However, the number of cases of coronary artery disease was significantly related to the number of risk factor targets achieved (P = 0.021); significantly fewer cases of coro-

Table IV. Baseline Characteristics According to Quartile Group

Variables	Q1	Q2	Q3	Q4
Men, %	46.0	40.3	39.9	42.7
Age, years	68.7	66.9	65.9	63.8
BMI, kg/m^2	24.1	24.4	24.7	25.1
Prior hypercholesterolemic medication	67.9	65.8	62.8	58.1
Prior pravastatin treatment	64.4	61.3	58.5	51.0
Target LDL	117.8	120.3	121.8	123.3
Receiving dietary instruction, %	69.5	71.9	70.6	70.0
Receiving exercise instruction, %	59.9	61.0	58.3	57.7
TC, mg/dL	198.2	214.4	223.6	240.0
LDL-C, mg/dL	113.3	128.9	140.3	157.7
HDL-C, mg/dL	59.5	58.6	56.7	55.4
Non HDL-C, mg/dL	139.1	156.0	167.1	180.4
Triglycerides, mg/dL (median)	109.0	113.0	124.0	138.5
SBP, mmHg	132.9	133.5	133.9	134.8
DBP, mmHg	74.7	75.5	76.7	77.7
Fasting glucose, mg/dL	120.1	121.7	118.2	121.5
HbA1c (NGSP), %	6.7	6.8	6.8	6.9
Conventional risk factor,** %				
Age§	97.4	96.8	95.3	92.1
Hypertension	76.5	72.5	71.7	71.1
Diabetes (including IGT)	83.0	79.2	75.1	74.9
Smoking	19.1	18.3	19.3	22.1
Family history of coronary disease	15.2	18.1	22.1	23.6
Low HDL-C (< 40 mg/dL)	9.2	10.5	10.9	11.7
Medication, %				
Antihypercholesterolemic agents	10.9	11.3	11.4	14.0
Statins	5.5	6.6	5.8	8.5
Simvastatin	0.1	0	0.2	0.1
Fluvastatin	0	0	0.1	0.4
Atorvastatin	1.6	2.2	0.9	1.5
Pitavastatin	1.4	1.1	1.8	2.8
Rosuvastatin	2.8	3.5	3.2	4.0
Fibrates	1.3	1.2	1.1	1.0
Others	4.7	4.4	4.9	5.5
Antihypertensive agents	74.3	69.8	67.4	63.6
Antidiabetic agents	60.0	56.7	48.9	47.4
Antithrombotic agents	26.4	18.1	16.9	14.3

**Conventional risk factors were defined based on physicians' reports. §≥ 45 years for men, ≥ 55 years for women. BMI indicates body mass index; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c (NGSP), hemoglobin A1c (US National Glycohemoglobin Standardization Program); and IGT, impaired glucose tolerance.

nary artery disease were found in patients who achieved targets for 3 risk factors (HR, 0.216, $P = 0.031$). No relationship was found between the number of risk factor targets achieved and the incidence of stroke ($P = 0.561$).

In the 6,053 patients who had pravastatin at least once during the 2-year follow-up, 320 (5.3%) experienced severe adverse events, including cancer (95 patients, 1.6%), pneumonia (9 patients, 0.1%), and atrial fibrillation (8 patients, 0.1%). Frequent reports of nonsevere adverse events included increased creatine phosphokinase (62 patients, 1.0%) and muscle ache (38 patients, 0.6%). There were also 175 adverse drug reactions, 6 of which were serious (thrombocytopenia, adult-onset Still's disease, breast cancer, VIIth nerve paralysis, urinary calculus, and hospitalization), which were judged by physicians as being possibly related to pravastatin.

Discussion

There is a paucity of information in Japan on the evaluation of the relationship between LDL-C and cardiovascular disease in high-risk patients in the primary prevention setting, such as those with 3 or more cardiovascular risk factors other than high LDL-C. For these high-risk patients, the JAS guideline recommends the reduction of LDL-C level to < 120 mg/dL by improving their lifestyle. However, a large number of patients allocated to this category receive a statin to achieve their target LDL-C in general practice. Therefore, it is still important to investigate the relationship between on-treatment LDL-C level after taking statin treatment and the onset of cardiovascular disease.

The APPROACH-J Study provides some important findings. First, the incidence of cardiovascular disease was low even though > 70% of the patients had diabetes, hypertension,

Table V. Relationship Between Incidence of Vascular Disease and Number of Risk Factor Targets Achieved

No. of targets achieved*	All cardiovascular diseases: No. of events/ no. of patients (no. of events/1,000 py)	Hazard ratio (95%CI)	*P*	Coronary artery disease: No. of events/ no. of patients (no. of events/1,000 py)	Hazard ratio (95%CI)	*P*	Stroke**: No. of events/ no. of patients (no. of events/1,000 py)	Hazard ratio (95%CI)	*P*
0	3/125 (11.3)	-	0.239§	3/125 (11.3)	-	0.021§	0/124 (0.0)		
1	15/867 (8.2)	0.725 (0.210-2.504)	0.611	10/868 (5.4)	0.482 (0.133-1.751)	0.267	4/868 (2.2)	-	0.561§
2	23/1,573 (6.9)	0.611 (0.184-2.037)	0.423	12/1,573 (3.6)	0.318 (0.090-1.126)	0.076	10/1,574 (3.0)	1.383 (0.434-4.408)	0.584
3	14/1,148 (5.7)	0.505 (0.145-1.758)	0.283	6/1,150 (2.5)	0.216 (0.054-0.866)	0.031	6/1,151 (2.4)	1.122 (0.317-3.976)	0.859
4	2/302 (3.1)	0.271 (0.045-1.624)	0.153	0/303 (0.0)	-	-	2/302 (3.1)	1.413 (0.259-7.717)	0.690

*Achievement of risk factor targets was defined by using mean values during follow-up according to the following criteria: low-density lipoprotein cholesterol < 120 mg/dL, blood pressure < 130/80 mmHg, hemoglobin A1c (US National Glycohemoglobin Standardization Program) < 6.5%, and no smoking during follow-up. **The hazard ratio was calculated in relation to the combination group consisting of groups 0 and 1, because there were no events in group 0. py indicates, patient years; and CI, confidence interval. §The *P* value is for the number of risk factor targets achieved, included as a quantitative variable in the multivariable Cox proportional hazards model.

or both. In the present study, only 69 cardiovascular events occurred in 4,916 patients during the 2 years (6.7/1000 py), corresponding to approximately 0.7% per year. This incidence is one-third that of estimates derived from data used in the subanalysis of the MEGA Study for diabetes,[26] whose participants had similar background characteristics to those of patients enrolled in the present study. Although it is necessary to take into account major differences in dealing with angina between the two studies (only unstable angina was included as the primary endpoint in APPROACH-J; in contrast, all angina events, including stable ones, were included in the MEGA Study), the incidence of MI and stroke was still low in APPROACH-J compared with in the MEGA diabetic population (1.1 versus 1.9/1000 py for MI and 2.7 versus 4.1/1000 py for stroke). The difference in the incidence of cardiovascular disease between the two studies may suggest that there are some differences between the clinical trial and general practice settings. In fact, other epidemiological data from Japan similarly showed a low incidence of cardiovascular disease even though the studies involved high-risk patients.[27-29] It should also be considered that recent clinical practice tends to involve treating patients more aggressively, through the popularization of several guidelines, which might have reduced event rates in the Japanese population.

The second point is that the results of this study clearly show that the achievement of low levels of LDL-C is highly associated with a low incidence of cardiovascular disease in these patients. Even though other conventional risk factors were well-controlled, the influence of LDL-C clearly remains. This finding suggests that an aggressive LDL-C-lowering strategy could be applied to high-risk patients, although the absolute event rate appears to be low even in this group.

When looking at coronary events and cerebral events separately, a significant relationship with LDL-C level was found for coronary events, reaching some attenuation of risk and a plateau in Q2 and Q1, in which the LDL-C level was < 119 mg/dL, but not for cerebral events. The relationships between LDL-C and coronary events and stroke observed in this study are similar to those reported for coronary events[27,30-32] and cerebral events.[33-35] The Japan Lipid Intervention Trial (J-LIT), an observational study with simvastatin, similarly showed that the incidence of coronary artery disease reaches a plateau level at LDL-C around 120-140 mg/dL in a primary prevention setting.[26] Also, the post-hoc analysis of the MEGA Study, which investigated the relationship between on-treatment LDL-C level and coronary heart disease and stroke, showed a similar curvilinear shape in relation to on-treatment LDL-C levels and coronary artery disease and stroke. The results of these studies also showed that the curve levels out around LDL-C 120 mg/dL in coronary artery disease, and they showed no relationship between LDL-C levels and stroke, consistent with the results of the present study.[32] Therefore, these findings are consistent with the LDL-C target for primary prevention recommended by the 2007 JAS guideline.[14] However, the efficacy of LDL-C lowering for stroke prevention and target levels of LDL-C for coronary artery disease prevention in the Japanese population, especially in high-risk patients, should be further investigated.

Generally, risk for cardiovascular disease is not only related to LDL-C levels but also to blood pressure, hyperglycemia, and smoking. Recent research has revealed that a greater number of cardiovascular health metrics are associated with a lower risk of cardiovascular disease mortality, the 7 cardiovascular health metrics being not smoking, being physically active, having normal blood pressure, having normal blood glucose, having low total cholesterol, having an ideal weight, and eating a healthy diet.[36] The present study revealed that blood pressure and HbA1c value decrease as LDL-C levels decrease. Therefore, we attempted to determine the relationship between cardiovascular disease and control of these 4 factors (blood pressure, HbA1c, smoking, and LDL-C level). The results showed that the incidence of cardiovascular disease decreases as more risk factor targets are achieved. (The targets are defined by the guidelines of the JAS,[14] Japan Society of Hypertension,[37] and Japan Diabetes Society[38]). These results indicate that patients who achieve low LDL-C and concurrently have good blood pressure and glucose control, as well as good

management of conventional factors, may have the associated low incidence of cardiovascular disease in the lowest LDL-C group. Furthermore, the use of antithrombotic agents, which has widely been recognized for providing a beneficial effect in the prevention of cardiovascular disease, was greater in the lower LDL-C group (Table IV). Moreover, we have evaluated adherence to lipid-lowering treatment as another objective in this study, and we found that good adherence to drug therapy is associated with lower LDL-C level.[39] In this study, about 90% of the patients had good adherence to drug therapy including pravastatin. These two facts may explain the low incidence of cardiovascular disease.

The present study had some limitations related to its design. The population of this study was not selected randomly. Patients invited to participate in the study were considered to be in sufficiently good condition to tolerate the long-term follow-up. This may result in an event rate lower than that in the actual population who are at high risk in primary prevention. In addition, the inclusion criteria of the present study allowed patients to be enrolled who were continuing pravastatin at initiation of the study, resulting in a mixture of pravastatin-naïve and non-naïve patients. In fact, about half of the patients had taken pravastatin at enrollment. However, we believe that these facts do not affect the interpretation of the study results, because there were no apparent differences in baseline characteristics or in the incidence of events between pravastatin-naïve and non-naïve patients (data not shown). This belief is supported by the fact that there was little impact with adjustment for pre-pravastatin treatment (HR for group with pre-hypercholesterolemic drugs against those without them, 0.94; $P = 0.83$ in the multivariable Cox proportional hazards model).

The LDL-C values that we used in this analysis were all obtained by direct methods, and there was no distinction as to the types of kit which were included in the analysis. Recently, it was reported that the Friedewald method is more appropriate for determining LDL-C values than direct methods, because of the great variability between different measuring kits.[40] However, we decided to adopt direct methods in this analysis because of the lack of a great number of total cholesterol values, which is related to the reimbursement policy in some regions. Many institutions were not allowed to measure both total cholesterol and LDL-C by direct methods during the study period. Moreover, blood samples were not taken while patients were fasting, which also had an effect on the lack of Friedewald LDL-C values. Only 33.5% of samples provided enough data for the Friedewald method in this study setting. However, although we only used LDL-C values obtained by direct methods, the results of the study could apply irrespective of measurement methods, because the correlation between the values obtained by direct methods and those obtained by Friedewald's methods was high ($r = 0.90$) in the analysis of 3,769 LDL-C values in 1,681 patients who had both LDL-C and Friedewald's values.

The follow-up period was rather short; 2 years may not reflect the actual treatment period in general practice. Moreover, we did not obtain information about the duration of patients' high LDL-C condition, and how long they had been receiving lipid-lowering treatment before enrollment; these data would be different for individual patients. A long-term state of high LDL-C before enrollment may affect the incidence of cardiovascular disease, and it should be taken into account when interpreting the findings of the present study, especially in this kind of short-term observation. The multiplicity adjustment is generally essential for confirmatory studies conducted with the purpose of proving a certain hypothesis from among many statistical tests in order to maintain the total alpha error within the statistical significance level. Since this study is an observational study mainly to identify the relationships between achieved LDL-C and the incidence of cardiovascular events, there was no multiplicity adjustment in the analysis. Finally, since this study was an observational study, we did not consult the physicians and patients about not only lipid levels but also other risk factors. In the analysis for the number of risk factors for which target levels were achieved, the achievement of targets was defined under natural conditions in the clinical setting, meaning that a naturally low-risk population may be included in the achievement group who might have had different characteristics compared with treated patients.

In conclusion, through our observational study design, it was shown that high-risk patients in the primary prevention setting receiving pravastatin treatment have a low incidence of cardiovascular disease, which may be associated with good control of conventional risk factors. It also shows that a lower LDL-C level is associated with a lower incidence of cardiovascular disease. Pravastatin is used broadly in the primary prevention setting based on consolidated evidence,[18] and the findings from the present study show that it should still be considered for high-risk hypercholesterolemic patients in a primary prevention setting, along with managing blood pressure and HbA1c according to the guidelines, and abstaining from smoking. The updated JAS guideline for 2012 has been released,[41] and it emphasizes the importance of managing multiple risk factors, including hypertension, diabetes, and smoking, along with lipid management, as a total risk management concept. The findings of the present study support the idea that total risk management could be associated with a low incidence of cardiovascular disease. However, prospective, randomized studies are needed to confirm these findings.

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APPENDIX

Maximum contrast method based on the Cox proportional hazards model

The Cox proportional hazards model with a regression parameter vector β is expressed as follows:

$$\lambda(t) = \lambda_0(t) \exp(\beta' Z))$$

where $\lambda(t)$ is the hazard for an event at time t, $\lambda_0(t)$ is an arbitrary and unspecified baseline hazard function, and Z is a vector of explanatory variables (quartiles of achieved LDL-C). The regression parameter vector β is estimated using a partial likelihood method.

In order to detect a response pattern which best fits observed data among candidate patterns, contrast coefficient vectors corresponding to the candidate patterns are specified. Let l_i be the ith contrast coefficient vector to test the null hypothesis H_0: $l'_i\beta = 0$. Then, the covariance matrix of a contrast function $l'_i\beta$ is given by $l'_i V(\beta) l_i$, where $V(\beta)$ is a model-

based covariance matrix of β. The contrast statistic for the contrast coefficient vector l_i is formalized as follows:

$$\chi^2 = (l'_i\beta)'(l'_iV(\beta)l_i)^{-1}l'_i\beta.$$

The maximum contrast method identifies a response pattern as the corresponding one which achieves the maximum of the contrast statistics.[24] The contrast statistic is approximated by a chi-square distribution with 1 degree of freedom where $(l'_iV(\beta)l_i)^{-1}$ is an inverse matrix of $l'_iV(\beta)l_i$ for large samples under the null hypothesis H_0.[42]

A list of the participating physicians is available on the website. (https://www.jstage.jst.go.jp/article/ihj/55/1/55_13-002/_article)

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脂質異常症
—基礎・臨床研究の最新知見—

I 総　　論

動脈硬化性疾患の絶対リスクの評価と脂質管理目標

岡村智教　　杉山大典

動脈硬化性疾患の絶対リスクの評価と脂質管理目標

Absolute risk of atherosclerotic disease and lipid management goals

岡村智教　　杉山大典

Key words：絶対リスク，フラミンガムスコア，SCOREチャート，NIPPON DATA，動脈硬化性疾患予防ガイドライン2012

はじめに

従来から個人の疾病リスクの評価として相対リスクが用いられてきた．相対リスクでは，1,000人に1人の死亡率が5人に増えても，10人に1人の死亡率が5人に増えても同じように5.0である．しかし実際には，前者は0.1％から0.5％への増加，後者は10％から50％への増加となり，もしこれが死亡率などであれば非常に大きな違いとなる．欧米では診療ガイドラインに絶対リスクの概念を取り入れ，それに基づいて患者の管理指針を決定してきた経緯がある．日本では動脈硬化性疾患予防ガイドライン2012(以下ガイドライン2012)が我が国初の試みとして，絶対リスク別の脂質管理目標値を導入した．

1 海外における絶対リスク評価

予防を目的とした診療ガイドラインに役立てるためには，危険因子から絶対リスクを予測するツールが必要である．これには大きく2種類があり，スコアリングテーブル(危険因子を得点化して合計する方式)とリスクチャート(縦軸と横軸に別々の危険因子をレベル別に配して交点のマス目を絶対リスク別に色分けして表示する方式)に大別される．いずれもコホート研究から危険因子保有別やそのレベル別の動脈硬化性疾患の罹患率や死亡率を算出して作成されている．代表的なものとして米国のフラミンガムスコア[1]と欧州のSCORE(Systematic Coronary Risk Evaluation)プロジェクト[2]がある．ガイドラインに用いるためには，そのコホート研究が当該集団を代表している必要性がある．国民一般を代表しているとはいえない集団(大企業の勤務者，離島や山奥の住民など)のコホート研究に基づいて，国民全体の治療方針を決めるのは危険である．

フラミンガムスコアは，その名のとおりスコアリングテーブル方式であり，性別(男女で各危険因子の重みづけが異なる)，年齢，総コレステロール，喫煙，高比重リポ蛋白コレステロール(HDLコレステロール)，収縮期血圧を得点化し，その合計得点で10年以内の冠動脈疾患(冠動脈性死亡と非致死性心筋梗塞)の発症率を求めるようになっている．一方，SCOREはリスクチャート式であり，性別，年齢，総コレステロール，喫煙，収縮期血圧を用いて脳卒中を含む全動脈硬化性疾患による10年以内の死亡率を求める(**図1**)．なお同じ危険因子レベルの患者でも国によって死亡率が異なるため，SCOREは死亡率の低い国(フランス，イタリア，スペインなど)で用いるものと高い国(イギリス，ドイツなど)で用いるものに分かれている．

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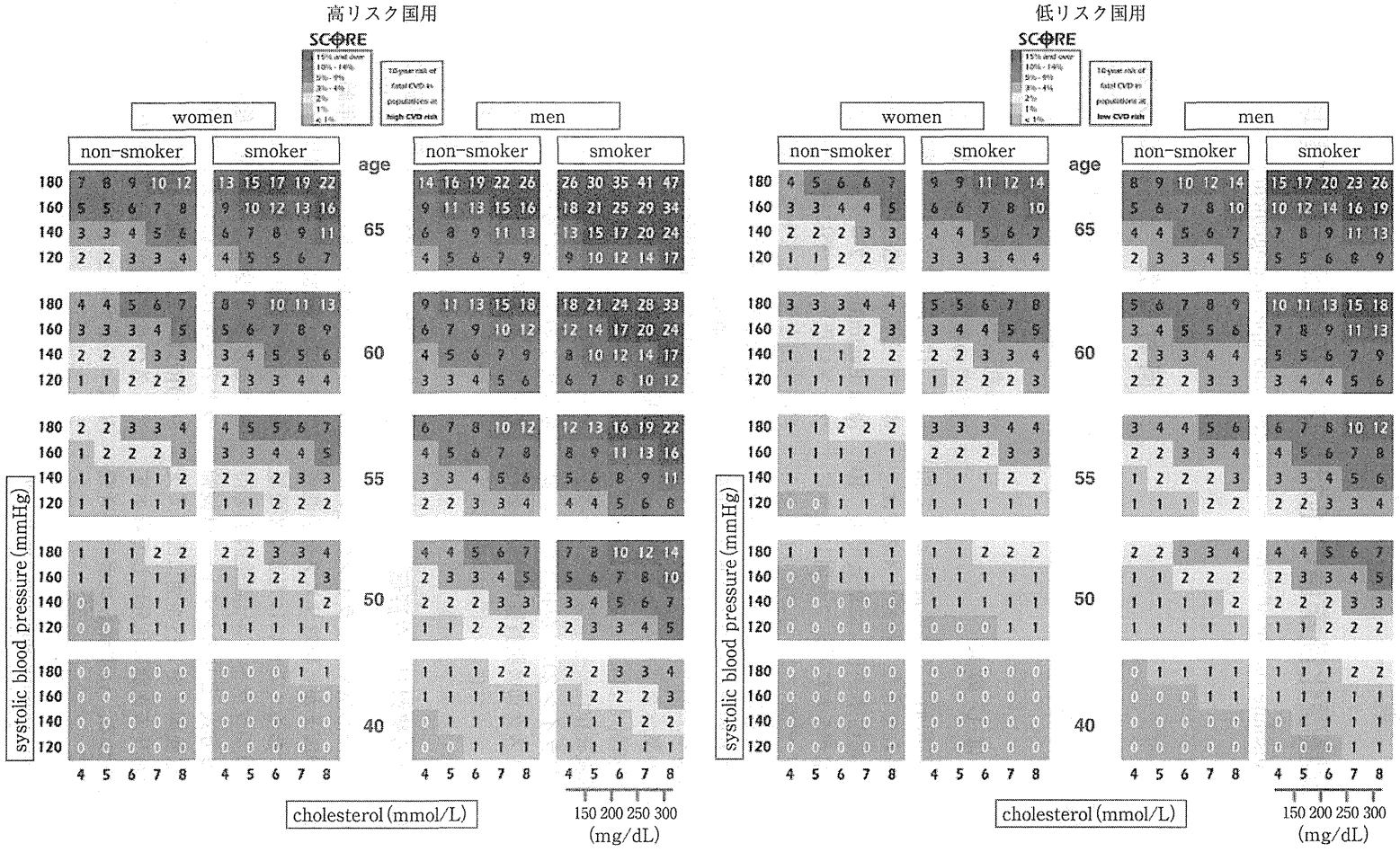

図 1　SCORE チャート（文献[2]より引用）

表1 日本の絶対リスク予測ツールの一覧

コホート名	評価方式	リスク評価期間	予測に用いる危険因子	予測対象としているイベント
NIPPON DATA80[3]	リスク評価チャート	10年	(性別のテーブル), 年齢, 総コレステロール, 喫煙, 収縮期血圧, 随時血糖	冠動脈疾患死亡/脳卒中死亡/全循環器疾患死亡
久山町[4]	スコアリングテーブル	10年	性別, 年齢, LDLコレステロール, HDLコレステロール, 糖尿病, 喫煙	心筋梗塞の発症, 心突然死, 冠血行再建術, 脳卒中の発症
JMSコホート(心筋梗塞)[5]	リスク評価チャート	10年	(性別のテーブル), 年齢, 総コレステロール, 収縮期血圧, 喫煙(男性のみ), 糖尿病(女性のみ)	心筋梗塞の発症
JMSコホート(脳卒中)[6]	リスク評価チャート	10年	(性別のテーブル), 年齢, 収縮期血圧, 喫煙, 糖尿病	脳卒中の発症
JALS-ECC[7]	スコアリングテーブル	5年	性別, 年齢, 総コレステロール(またはnon-HDLコレステロール), HDLコレステロール, 高血圧(グレード1と2), 喫煙, 糖尿病	心筋梗塞の発症
茨城県コホート[8]	ウェブサイト[注1)]	5-15年	性別, 年齢, 体重, 収縮期血圧, HDLコレステロール, トリグリセライド, AST, 血糖値(治療状況含む), 採血条件, 喫煙, 飲酒	死因別死亡(脳卒中, がん, 冠動脈疾患, 全循環器疾患, 総死亡)

注1)http://www.hsc-i.jp/03_seikatsu/nousochu/top.htm

2 日本における絶対リスク評価

ガイドラインに絶対リスク評価を導入するためには, 前述のように母集団を代表性するコホート研究が不可欠である. また絶対リスクに最も大きな影響を与えるのは年齢である. したがって絶対リスク評価の原資料となるコホート研究は, 年齢別に分けても十分な信頼性が得られるくらいのサンプルサイズが必要である. これは単に参加者の人数が多いというだけではなく, 十分なイベント数があることも意味している. 欧米では多くのコホート研究が行われてきたが日本ではそうではなかった. 日本ではコホート研究で最も重要な長期追跡を実施するための環境整備が不十分であり, 一般市民の動脈硬化性疾患の発症を登録する制度がなく, 死因情報でさえ所定の条件を満たしたうえで人口動態統計の目的外利用申請を行わないと入手できない. またそれ以前の問題として, 非患者集団では追跡対象者が生きているのか死んでいるのか, 引き続き同じ場所に居住しているのか転居しているのかさえ把握することは困難である. そのため日本でコホート研究を設定して長期間にわたって維持することは非常に難しく, またできたとしても追跡調査がやりやすい非都市的な地域にコホートが集中する傾向がみられた.

しかしながら絶対リスクの導入という世界的潮流の中, ここ数年で複数の絶対リスク推計のためのツールが日本のコホート研究から提示されている[3-8]. 主なもののリスク評価方式, リスク評価期間, 予測に用いる危険因子, 予測対象としているイベントを**表1**に示す. 同一人物のリスクの評価をこれら別々のツールで実施すると, 予測結果に大きなばらつきが出ることが指摘されている[9]. これは評価ツールの正確性の問題ではなく, 主に予測対象としているエンド

ポイントの違いによる．例えば久山町のツールでは冠動脈疾患と脳卒中の両方を合わせた発症率を予測している．ここでもし9％という絶対リスク(10年以内の発症確率)が算出されたとすると，このうち冠動脈疾患は1/3くらいなので3％程度の発症率となり，更に冠動脈疾患の死亡率だとこの1/3くらいの1％程度と予測される．すなわち久山町の9％(脳・心疾患発症率)とNIPPON DATA80の1％(冠動脈疾患死亡率)は同じ予測結果の範疇に属している．

ガイドライン2012ではNIPPON DATA80リスクチャート[3]を絶対リスク設定に用いている．NIPPON DATA80は，厚生省の1980年の循環器疾患基礎調査受検者の追跡調査である．今回，NIPPON DATA80を用いた主な理由は，①全国から無作為抽出された300地区の住民を対象としており地域的な偏りがない，②自然歴を観察できている(コレステロール測定時にスタチンなどがないため)，③参加率・追跡率が高い，等が指摘されているが，最大の理由は①の偏りのなさ，すなわち日本人集団の代表性を有する点である．

3 絶対リスク評価と診療ガイドライン

診療ガイドラインで絶対リスクを用いる理由は，危険度の高い人により手厚い治療を行い，危険度の低い人に不要な治療を行わないという点にある．**表2**に欧州のガイドライン(2011年)に記載されているSCOREによるリスク評価に基づく脂質管理戦略を示した[2]．縦軸にはSCOREチャートで求めた10年以内の動脈硬化性疾患死亡確率が，横軸にはLDLコレステロールのレベルが示されている．例えばLDLコレステロールが100-155 mg/dLの場合，SCOREによる絶対リスクが1％未満の場合は生活習慣の改善のみ，1-5％未満はコントロール不良なら服薬，5％以上だと直ちに服薬と，それぞれ対応が異なり，'必要性'に応じた対応が推奨されている．

ガイドライン2012では，対象者を二次予防，カテゴリーI-IIIの4グループに分類する[10]．まず対象者の冠動脈疾患の既往を確認し，二次予防の対象かどうかをチェックする．二次予防の場合，LDLコレステロールの管理目標値は最も厳しいレベルになる(<100 mg/dL未満)．次に自動的にカテゴリーIIIとなるハイリスク状態(糖尿病，慢性腎臓病，非心原性脳梗塞，末梢動脈疾患)があるかを確認する．これらがない場合は，**図2**に示したガイドライン2012用のNIPPON DATA80リスクチャートに進み，絶対リスク(10年以内の冠動脈疾患死亡確率)のレベルに応じてカテゴリーI-IIIに分類される(それぞれ0.5％未満，0.5-2.0％未満，2.0％以上)．なお低HDLコレステロール血症，早発性冠動脈疾患の家族歴，耐糖能異常のいずれか，または複数がある場合は，それぞれ一段階上のカテゴリーに変更される(ただしカテゴリーIIIはそのまま)．なおガイドライン2012で提示した10年以内の冠動脈疾患死亡率2％以上という値は，欧州のガイドラインの動脈硬化性疾患死亡5％にほぼ相当する．なぜなら日本人で冠動脈疾患死亡率が2％だと，全循環器疾患死亡率(これはSCOREの動脈硬化性疾患死亡率とほぼ同じ)は5％程度になると考えられるからである．

そしてガイドライン2012では分類区分ごとの脂質管理目標を**表3**のように定めている[10]．すなわち二次予防を含めた4グループで異なるLDLコレステロールの管理目標値が設定されている．欧州のガイドラインと異なり治療法の選択までは言及していないが，"いずれのカテゴリーにおいても管理目標達成の基本はあくまでも生活習慣の改善である"こと，"カテゴリーIにおける薬物療法の適用を考慮するLDLコレステロールの基準は180 mg/dL以上とする"など，一部治療方針にも言及している．

おわりに

ガイドライン2012は，現時点での日本人集団を対象とした最良のエビデンスから構築されており，我が国の動脈硬化性疾患の実態に適切に対処していると考えられる．動脈硬化性疾患の予防のためには，脂質異常だけでなく様々な

表2　SCOREによるリスク評価に基づく脂質管理戦略（文献[2]より引用）

SCOREチャートによる動脈硬化性疾患死亡確率（%）	LDLコレステロールのレベル（mg/dL）				
	<70 mg/dL	70 to <100 mg/dL	100 to <155 mg/dL	155 to <190 mg/dL	>190 mg/dL
<1%	治療不要	治療不要	生活習慣の改善	生活習慣の改善	生活習慣の改善，コントロール不良なら服薬治療を考慮
≧1% to <5%	生活習慣の改善	生活習慣の改善	生活習慣の改善，コントロール不良なら服薬治療を考慮	生活習慣の改善，コントロール不良なら服薬治療を考慮	生活習慣の改善，コントロール不良なら服薬治療を考慮
>5% to <10%，or high risk*	生活習慣の改善，服薬治療も考慮	生活習慣の改善，服薬治療も考慮	生活習慣の改善に加えてただちに服薬治療を開始	生活習慣の改善に加えてただちに服薬治療を開始	生活習慣の改善に加えてただちに服薬治療を開始
≧10% or very high risk*	生活習慣の改善，服薬治療も考慮	生活習慣の改善に加えてただちに服薬治療を開始	生活習慣の改善に加えてただちに服薬治療を開始	生活習慣の改善に加えてただちに服薬治療を開始	生活習慣の改善に加えてただちに服薬治療を開始

* very high risk: CVDの既往，糖尿病（2型，1型で臓器障害あり），CKD（eGFR<60 mL/mim/1.73 m^2），high risk: 1つの危険因子のレベルが極端に高い場合（家族性脂質異常や重症高血圧）．