that observed in the women without these healthy lifestyle factors[9]. There are few reports of large-scale studies on lifestyle and CAD in women in Japan; however, the Japanese Acute Coronary Syndrome Study (JACSS), a multicenter study of acute coronary syndrome, revealed that smoking significantly increases the risk of CAD in women and that the odds ratio in women is 8.2, which is much higher than the 4.0 observed in men[10]. The Japan Public Health Center-based Prospective Study (JPHC Study) Cohort I, which included subjects 40 to 59 years of age, also reported that the risk of CAD in female smokers is significantly high, with a value of 3.1, which is comparable to 2.9 observed in male smokers. Among men who quit smoking, the multivariate relative risk of CAD abruptly decreases to 0.1 within two years[11]. Although the effects of smoking cessation in women were not investigated due to a lack of heavy female smokers, the effects of smoking cessation in women are expected to be the same as those observed in men.

Increasing the level of physical activity, promoting healthy dietary habits and encouraging smoking cessation are important measures for preventing CAD not only in men, but also in women.

Lifestyle modification is also important for the prevention and management of cerebrovascular disease. The NIPPON DATA80 study demonstrated that smoking more than two packs of cigarettes a day increases the relative risk of stroke 4-fold in women[12] and that the risk of stroke decreases to the same level as that observed in nonsmokers following smoking cessation[12]. It has been reported that Japanese women who walk and participate in sports tend to have lower rates of mortality from cerebral infarction[13]. The Nurses' Health Study, a prospective study of 71,000 women, showed that women with one or more of five factors (a negative history of smoking, a nonobese status, appropriate exercise habits, moderate alcohol intake and healthy dietary habits) have a lower risk of developing cerebral infarction and that women with all five factors have a significantly lower risk, with a value of 0.2, compared to that observed in women with none of the five factors[14].

Therefore, lifestyle modification is important for the prevention and management of CVD in women and helps individuals avoid the need for excess doses of drugs, while also enhancing the efficacy of drugs.

4. Risk Factors and CVD in Women

A relationship between the TC levels and the risk of CAD has been reported in Japanese women, although it is slightly weaker than that observed in men[15]. The Japan Lipid Intervention Trial (J-LIT), in which women accounted for 68% of the subjects, reported that higher LDL-C levels following simvastatin treatment are associated with an increased relative risk of CAD[16]. On the other hand, the JACSS study showed that the TC level is not a significant risk factor for the development of CAD in women, although hypercholesterolemia is a risk factor for the development of CAD in both men and women <65 years of age[10].

As reported by the NIPPON DATA80 and JACSS studies[10, 17], hypo-HDL cholesterolemia, diabetes mellitus (DM) and hypertension are also important risk factors for CAD in women. Another report found that a high level of TGs also increases the risk of CAD in women[18].

Hypertension is an important risk factor for cerebrovascular disease in women as well as men. In the NIPPON DATA80 study, women with a systolic blood pressure of ≥ 180 mmHg had a 5.4-fold higher age-adjusted relative risk of stroke[19] compared with women with a systolic blood pressure of <120 mmHg. Women with DM exhibit an increased risk of cerebral infarction up to 2-fold that observed in women with normal glucose tolerance[20]. The J-LIT study demonstrated that subjects with an LDL-C level of ≥ 160 mg/dL have a ≥ 2-fold higher relative risk of cerebral infarction compared to subjects with an LDL-C level of <120 mg/dL and that higher TG levels and lower HDL-C levels are associated with an increased risk of cerebral infarction[21]. The risk factors for cerebral infarction in Japanese women are similar to those for CAD.

Hormone replacement therapy (HRT) has been reported to affect the risk of CVD in postmenopausal women. The results of the Heart and Estrogen/progestin Replacement Study (HERS) showed that the use of HRT in women with CAD is not effective in decreasing the risk of CAD or cerebral infarction[22, 23]. In the Women's Health Initiative (WHI), those who received HRT (conjugated estrogen at a dose of 0.625 mg/day + medroxyprogesterone acetate at a dose of 2.5 mg/day) exhibited a relative risk of developing CAD of 1.2 [24] and a relative risk of developing cerebral infarction of 1.4 [25], rates that were significantly higher than those observed in the women treated with a placebo. HRT containing conjugated estrogen alone was found to significantly increase the risk of cerebral infarction 1.6-fold[26].

Based on the results of the WHI, the Japan Society of Obstetrics and Gynecology states that, in order to prevent CVD, the use of HRT with the continuous administration of the above prescription is not recommended in women with risk factors (obesity, hyper-

tension, a smoking habit, etc.)[27]. However, since estrogen is apparently effective in improving lipid metabolism and the vascular function, this recommendation does not deny the efficacy and safety of HRT (the type and dose of hormones used, route of administration, etc.) other than that administered in the WHI. Therefore, these issues require further investigation[27].

5. Primary and Secondary Prevention of CAD and Cerebrovascular Disease in Women

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) found that lipid-lowering therapy containing lovastatin is more effective in inhibiting the development of CAD in women than in men. However, no statistically significant differences were observed due to the low number of events[28].

A subanalysis of women in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study, in which postmenopausal women ≤70 years of age accounted for 68% of the subjects, showed that the hazard ratio for CAD in women ≥55 years of age was 0.6 (p=0.10), with no significant differences between the women treated with pravastatin and those treated with dietary therapy alone. However, the hazard ratio for CAD + cerebral infarction in women ≥55 years of age was 0.6 (p=0.04), with a significantly lower incidence in the pravastatin group[29].

With respect to secondary prevention, the results of a subanalysis of the Scandinavian Simvastatin Survival Study (4S) showed that lipid-lowering therapy is effective in preventing CAD events in women at an equal level to that observed in men[30]. Similarly, the Cholesterol and Recurrent Events Trial (CARE) showed that lipid-lowering therapy with pravastatin is more effective in preventing CAD events in women than in men[31]. Although there were no statistical differences, the relative risk of death from CAD associated with lipid-lowering therapy in women calculated from three studies (the Scottish Society of Physicians, Newcastle upon Tyne and 4S) was 0.4 [32], thus indicating that appropriate treatment is required for secondary prevention in women as well as men.

In Japan, there is little evidence of a risk for CAD among premenopausal women with dyslipidemia. This is because quite a small number of cases of CAD occur in premenopausal women. Previous studies conducted in Japan have shown that even if a diagnosis of CAD is suspected in premenopausal women, no significant stenosis is observed on coronary angiography in many cases and that CAD caused by vasculitis or aortitis due to systemic lupus erythematosus (SLE), not atherosclerosis, may be detected[33].

On the other hand, the results of the Chicago Heart Association Detection Project Industry study conducted in the U.S. found that, among women with no risk factors (a TC level of <200 mg/dL, a blood pressure of <120/80 mmHg and a current nonsmoking status), the relative risk of CAD is 0.27, even among middle-aged women 40 to 59 years of age, which is significantly lower than that observed in women with these risk factors, and that total mortality is also significantly decreased[34]. The results of this cohort study showed that even premenopausal women with three healthy lifestyle factors, including proper dietary habits, appropriate exercise habits and a nonsmoking status, can decrease their risk of developing CAD to less than half of that observed in women without these habits[9].

The most important risk factor for cerebrovascular disease is hypertension, regardless of sex[19, 35], and controlling hypertension is essential for preventing cerebrovascular disease. The NIPPON DATA80 study reported that the estimated decrease in mortality from stroke associated with a decrease in the mean blood pressure of 1 mmHg is 4.3% in men and 2.2% in women[19].

A subanalysis of the MEGA Study revealed that statins are effective in the primary prevention of stroke in Japanese women. In that study, the risk of developing cerebral infarction in women ≥55 years of age in the pravastatin group significantly decreased by 53% compared with that observed in the women who received dietary therapy alone[29]. The effectiveness of high-dose statins in the secondary prevention of stroke was investigated in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study. No efficacy was observed in preventing the recurrence of nonfatal cerebral infarction; however, the risk of recurrence of fatal cerebral infarction significantly decreased by 73% in women[36].

The incidence of CAD in women in Japan is much lower than that observed in Western countries[37]. Moreover, controlling hypertension has been reported to decrease the incidence of cerebrovascular disease[37]. On the other hand, new concerns are emerging regarding the increasing risk of CVD due to the Westernization of dietary habits, lack of exercise and a gradual increase in the number of female smokers in their 20s and 30s. Taking into consideration further aging, it is important to introduce healthy lifestyle and control risk factors for the development of atherosclerosis from a younger age, even in women.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 16) published in Japanese in June 2012.

Acknowledgements

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Committee Report 17

Diagnosis of Atherosclerosis

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan—2012 Version

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Committee for Epidemiology and Clinical Management of Atherosclerosis

From the perspective of preventing atherosclerotic cardiovascular disease (CVD), it is essential to determine the presence or absence and degree of atherosclerosis before the development of clinical symptoms and to manage or treat risk factors in order to prevent progression or achieve regression of disease. It is necessary to diagnose whether atherosclerosis is present, and if so, to what extent. The diagnostic techniques for atherosclerosis employed in the primary prevention of CVD should be noninvasive. In secondary prevention, however, the use of invasive diagnostic techniques, including angiography, is necessary. Currently, morphological imaging tests are predominantly used to assess the presence and degree of atherosclerosis.

1. Ultrasonography

Noninvasive imaging tests include body surface ultrasonography (a high-frequency probe of ≥7 MHz), which enables observation of the degree of stenosis and plaque formation (localized atherosclerotic lesions) in the peripheral arteries, such as the carotid arteries and arteries of the lower extremities. In particular, in the carotid arteries, ultrasonography is used to determine the degree of stenosis quantitatively and detect vulnerable plaques that could cause cerebral embolism, thereby assessing the degree of systemic atherosclerosis and/or functioning as an alternative predictor of the presence or development of CVD (e.g., coronary artery disease (CAD), peripheral arterial disease (PAD) or cerebrovascular disease)[1,2]. The existence of plaques and intima-media complex thickness (IMT) is often used as a measurement index on carotid ultrasonography[3]. Ultrasonography is also useful for making the diagnosis of atherosclerotic renal artery stenosis[4].

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2. Computed Tomography (CT)

Multidetector row CT (MDCT) offers superior imaging speed and spatial resolution and enables visualization of the coronary arteries following the injection of contrast medium into peripheral veins. This technique is starting to replace coronary angiography as a diagnosing test for CAD. In particular, it is superior in specificity[5-8], and if no abnormalities are detected using this technique, the existence of organic coronary stenosis can be almost completely ruled out. In addition, this technique allows for visualization of coronary plaques, and the degree of calcification and fat and fiber content can also be estimated to some extent based on the CT number.

3. Magnetic Resonance Imaging (MRI) and MR Angiography (MRA)

MRA is used to visualize the cerebral/carotid arteries, aorta and renal arteries and enables the visualization of coronary stenotic lesions.

4. Angiography

Invasive diagnostic imaging techniques include angiographic evaluations of the degree of stenosis, which remains a central diagnostic technique for assessing arterial stenosis. The degree of arterial stenosis (the stenosis rate) is represented by the formula $(D-S)/D \times 100\%$, where D is the intravascular luminal diameter at the site proximal to the site of stenosis that appears to be normal and S is the luminal diameter at the site of stenosis. However, because intimal thickening is more or less observed even at sites that appear to be normal, the stenosis rate is underestimated considering the amount of the plaque volume. Because

plaques are usually eccentric and the intravascular luminal diameter is therefore not a precise circle, there are limitations in the ability to determine the stenosis rate based on one cross-section. If there is compensatory vascular remodeling, the blood vessel may not be considered to exhibit luminal stenosis even if the plaques are well-formed; thus, there are severe limitations in establishing the plaque volume using this technique.

5. Intravascular Ultrasound (IVUS)

IVUS is a technique used to observe the arterial wall from the arterial lumen using an ultrasound device. It enables the evaluation of both the plaque volume and the properties of the plaques.

6. Angioscopy

Angioscopy is a technique used to observe the color of the plaque surface and estimate the properties of plaques.

7. Physiological Tests

Diagnostic techniques other than morphological tests include physiological tests, such as the brachial-ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI). Although these parameters are easily determined by measuring the pulse wave in the extremities using a dedicated device, it should be noted that the values function as indices of artery stiffness and do not always reflect the presence of atherosclerosis. The ankle-brachial blood pressure index (ABI), can be used to diagnose PAD in the lower extremities (<0.9 or ≥ 1.3). The techniques used to measure the vascular endothelial function impaired in the early stage of atherosclerosis include flow-mediated vasodilation (FMD), which measures and calculates changes in the vascular diameter following ischemic reactive hyperemia of the extremities using ultrasound, and strain gauge plethysmography, which electrically observes and measures changes in the volume of the arterial blood flow in the extremities as changes in the circumference using a strain gauge. However, the use of these techniques is quite limited in general practice.

If a diagnosis of CAD, particularly effort angina, is suspected, the following noninvasive tests are useful.

8. Exercise Electrocardiography

Exercise electrocardiography has been shown to have a sensitivity of approximately 70% and a specificity of approximately 75% for detecting significant coronary stenosis[9], neither of which are superior; however, since the procedure can be easily performed at a low cost, it is widely used. Because myocardial ischemia can be induced, it is important to keep in mind the risk of possible cardiac events, including ventricular fibrillation and sudden death, when performing this technique.

9. Myocardial Perfusion Scintigraphy

This technique is widely used in the diagnosis of CAD to assess disease severity, myocardial viability and the prognosis and aids in decision making concerning therapeutic strategies. It is also used to screen for significant coronary stenosis, is relatively minimally invasive and may be a useful monitoring test for preventing atherosclerosis. Stressors include exercise stress, dipyridamole stress and adenosine stress. This technique has been shown to have a sensitivity of 80% to 90% and a specificity of 70% to 95% for detecting significant coronary stenosis[10].

At present, ultrasonography is a minimally invasive, simple and easy-to-use test for diagnosing atherosclerosis. Coronary CT, exercise electrocardiography and myocardial perfusion scintigraphy are noninvasive and useful diagnostic techniques in cases in which a diagnosis of CAD is suspected.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 17) published in Japanese in June 2012.

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Committee Report Appendix

Statements

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Committee for Epidemiology and Clinical Management of Atherosclerosis

J Atheroscler Thromb, 2014; 21:299-303.

Comprehensive Risk Management for the Prevention of Cardiovascular Disease

J Atheroscler Thromb, 2013; 20:603-615.

1. In order to prevent cardiovascular disease (CVD), major risk factors, including dyslipidemia, hypertension and diabetes mellitus (DM), should be managed comprehensively from the initial stage of the disease.
2. Lifestyle modification, such as encouraging healthy dietary habits, exercise and the cessation of smoking, constitutes the basis for preventing CVD. It is important to continue to provide guidance on lifestyle modification after initiating drug therapy.

Diagnostic Criteria for Dyslipidemia

J Atheroscler Thromb, 2013; 20:655-660.

1. The incidence of coronary artery disease (CAD) increases in association with increases in LDL-C.
2. The incidence of CAD increases in association with decreases in HDL-C.
3. The incidence of CAD increases in association with increases in TG.
4. The incidence of CAD increases in association with increases in non HDL-C.

Absolute Risk of Cardiovascular Disease and Lipid Management Targets

J Atheroscler Thromb, 2013; 20:689-697.

1. In primary prevention, the management targets for LDL-C should be determined according to categories based on the absolute risk of CAD. [Recommended level IIa, evidence level C]
2. In secondary prevention, an LDL-C level of <100 mg/dL should be targeted. [Recommended level IIa, evidence level C]
3. The target for the TG level should be <150 mg/dL. [Recommended level IIa, evidence level C]

4. The target for the HDL-C level should be ≥ 40 mg/dL. [Recommended level IIa, evidence level C]
5. The target for the non HDL-C level should be < management target for the LDL-C level + 30 mg/dL. [Recommended level IIa, evidence level C]

Cardiovascular Disease Risk Factors Other than Dyslipidemia

J Atheroscler Thromb, 2013; 20:733-742.

1. Hypertension is a risk factor for cerebrovascular disease and CAD.
2. DM is a risk factor for CVD, such as CAD, cerebrovascular disease and peripheral artery disease (PAD).
3. Smoking is a risk factor for CAD, cerebrovascular disease and PAD.
4. Passive smoking is a risk factor for CAD and cerebrovascular disease.
5. Aging is a risk factor for cerebrovascular disease and CAD.
6. A family history of premature CAD is a risk factor for the development of CAD.

Other High-Risk Conditions

J Atheroscler Thromb, 2013; 20:785-789.

1. A history of CAD is a risk factor for CAD and cerebrovascular disease.
2. A history of non-cardiogenic cerebral infarction is a risk factor for cerebrovascular disease and CAD.
3. CKD is a high-risk condition for CAD and cerebrovascular disease.
4. PAD is a high-risk condition for CAD and cerebrovascular disease.

Treatment—Lifestyle Modification

J Atheroscler Thromb, 2013; 20:835-849.

1. Avoid smoking and passive smoking to prevent atherosclerosis. [Recommended level I, evidence level B]
2. For the management of obesity, reduce the total energy intake and increase physical activity in order to reduce the body weight to the ideal level. [Recommended level I, evidence level B]
3. Increase the intake of vegetables, fruit, unrefined grains, seaweed, soy products, etc. [Recommended level I, evidence level B]
4. In order to reduce the LDL-C level, reduce the intake of saturated fatty acids and increase the intake of unsaturated fatty acids. In addition, limit the intake of cholesterol and increase the intake of dietary fiber. [Recommended level I, evidence level B]
5. In order to reduce the TG level, reduce the intake of carbohydrates and alcohol and increase the intake of n-3 polyunsaturated fatty acids. [Recommended level I, evidence level B]

6. In order to increase the HDL-C level, engage in moderate aerobic exercise, reduce body weight and avoid the intake of trans fatty acids. [Recommended level I, evidence level B]
7. Sustained physical activity or aerobic exercise is effective for preventing atherosclerosis. [Recommended level I, evidence level B]

Treatment—Drug Therapy

J Atheroscler Thromb, 2013; 20:850-860.

1. If a patient cannot achieve the management target for LDL-C after adequate lifestyle modification in the setting of primary prevention, drug therapy should be considered according to the weight of the patient's risk. [Recommended level IIa, evidence level B]
2. If a patient persistently has an LDL-C of ≥ 180 mg/dL in category I, drug therapy should be considered. [Recommended level IIa, evidence level C]
3. Statin therapy is recommended for the treatment of hyper-LDL cholesterolemia. [Recommended level I, evidence level A]
4. In patients with high-risk hyper-LDL cholesterolemia, the use of ezetimibe in combination with a statin should be considered. [Recommended level IIa, evidence level B]
5. In patients with high-risk hyper-LDL cholesterolemia, the use of ethyl icosapentate (EPA) in combination with a statin should be considered. [Recommended level IIa, evidence level A]
6. In patients with hypertriglyceridemia accompanied by hypo-HDL cholesterolemia, drug therapy with fibrates or nicotinic acid derivatives should be considered according to the level of the patient's risk. [Recommended level IIa, evidence level B]

Metabolic Syndrome

J Atheroscler Thromb, 2014; 21:1-5.

1. Metabolic syndrome is a high-risk condition for CVD.
2. For the treatment of metabolic syndrome, lifestyle modification is recommended. [Recommended level I, evidence level C]

Familial Hypercholesterolemia

J Atheroscler Thromb, 2014; 21:6-10.

1. Familial hypercholesterolemia is a frequent autosomal dominant disease associated with a high risk of CAD. Early diagnosis and rigorous treatment are recommended. [Recommended level I, evidence level B]
2. For the treatment of heterozygous FH, strict lipid management, primarily with statin

therapy, is recommended. [Recommended level I, evidence level B]
3. For the treatment of homozygous FH and drug therapy-resistant severe heterozygous FH, LDL apheresis therapy is recommended. [Recommended level I, evidence level B]

Other Types of Primary Hyperlipidemia

J Atheroscler Thromb, 2014; 21:82-85.

1. Patients with familial combined hyperlipidemia or familial type Ⅲ hyperlipidemia are likely to develop CVD. As such patients respond well to dietary therapy, providing strict dietary therapy is essential. [Recommended level I, evidence level C]
2. Familial lipoprotein lipase deficiency and familial apoprotein C-Ⅱ deficiency are only slightly related to atherosclerosis, although they are associated with a high risk of acute pancreatitis. Fat intake should be strictly restricted. [Recommended level I, evidence level C]

Coronary Artery Disease

J Atheroscler Thromb, 2014; 21:86-92.

1. In patients with acute coronary syndrome, strict LDL-C-lowering therapy is recommended from the initial stage of the disease. [Recommended level I, evidence level B]
2. In patients with CAD who are smokers or exhibit DM, CKD, non-cardiogenic cerebral infarction/PAD, metabolic syndrome or more than one major risk factor other than LDL-C, stricter LDL-C-lowering therapy is recommended together with management of risk factors other than LDL-C. [Recommended level Ⅱa, evidence level B]

Diabetes Mellitus

J Atheroscler Thromb, 2014; 21:93-98.

1. Patients with DM require strict, comprehensive management of the lipid levels and blood pressure, as well as the blood glucose level, from the early stage of the disease. [Recommended level I, evidence level B]
2. In patients with DM complicated by microvascular complication such as retinopathy or nephropathy, non-cardiogenic cerebral infarction/PAD, smoking, metabolic syndrome, persistently poor glycemic control and more than one major risk factor stricter management of LDL-C is recommended together with management of risk factors other than LDL-C. [Recommended level Ⅱa, evidence level B]

Chronic Kidney Disease

J Atheroscler Thromb, 2014; 21:173-174.

1. CKD is a high-risk condition. Comprehensive risk management, including reducing the LDL-C level to <120 mg/dL, is recommended. [Recommended level IIa, evidence level C]

Cerebrovascular Diseases

J Atheroscler Thromb, 2014; 21:175-179.

1. Statin therapy may prevent the development of cerebral infarction. [Recommended level I, evidence level A]

The Elderly

J Atheroscler Thromb, 2014; 21:180-185.

1. In the young-old (≥65 and <75 years of age), as well as adults, hyper-LDL cholesterolemia is an important risk factor for CAD.
2. Statin therapy for hyper-LDL cholesterolemia in the young-old may be effective for the secondary prevention of CAD. [Recommended level IIa, evidence level B]
3. Statin therapy for hyper-LDL cholesterolemia in the young-old may be effective for the primary prevention of CAD and cerebral infarction. [Recommended level IIa, evidence level B]
4. Statin therapy for hyper-LDL cholesterolemia in the old-old may be effective for the secondary prevention of CAD. [Recommended level IIa, evidence level B]
5. The significance of lipid-lowering therapy for hyper-LDL cholesterolemia in the old-old in the primary prevention of CAD is not clear at present. Patients should be individually treated at the discretion of their attending physician. [Evidence level C]

Women

J Atheroscler Thromb, 2014; 21:291-295.

1. Premenopausal women with dyslipidemia should be primarily treated with non-drug therapy, such as lifestyle modification. [Recommended level I, evidence level B]
2. Drug therapy should be considered in high-risk premenopausal women with familial hypercholesterolemia or those requiring secondary or primary prevention of CAD. [Recommended level I, evidence level C]
3. In postmenopausal women with dyslipidemia, lifestyle modification is given priority; however, drug therapy should also be considered, taking due account of the patient's risk factors. [Recommended level IIa, evidence level B]

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.

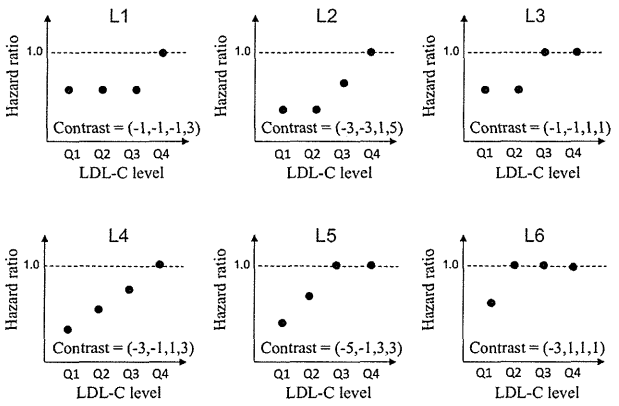
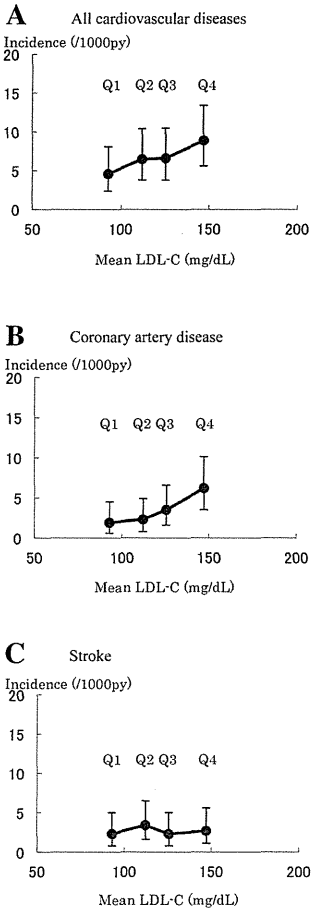


Figure 1. Statistical concepts underlying the maximum contrast method, a statistical method to evaluate the shape of curves which are likely to fit into one of six patterns (L1-L6). LDL-C indicates low-density lipoprotein cholesterol.



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)	All cardiovascular diseases: Hazard ratio (95%CI)	All cardiovascular diseases: *P*	Coronary artery disease: No. of events/ no. of patients (no. of events/1,000 py)	Coronary artery disease: Hazard ratio (95%CI)	Coronary artery disease: *P*	Stroke**: No. of events/ no. of patients (no. of events/1,000 py)	Stroke**: Hazard ratio (95%CI)	Stroke**: *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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