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Committee Report 9

Familial Hypercholesterolemia

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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This is a collaborative work to describe the guidelines for familial hypercholesterolemia issued by the Committee for Epidemiology and the Clinical Management of Atherosclerosis, the Committee for the Diagnosis and Treatment of Familial Hypercholesterolemia and the Research Committee for Primary Hyperlipidemia, Research on Measures against Intractable Diseases.

Heterozygous Familial Hypercholesterolemia

1. Condition and Clinical Picture of FH

Familial hypercholesterolemia (FH) is an autosomal dominant disease caused by abnormal LDL receptors or LDL receptor-related genes, characterized by the triad of (1) hyper-LDL cholesterolemia, (2) premature coronary artery disease (CAD) and (3) tendon/cutaneous xanthoma. Arcus corneae is also characteristic of FH; however, the rate is approximately 30%.

FH by itself is a very high-risk condition for CAD. Untreated men 30 to 50 years of age and women 50 to 70 years of age are likely to develop CAD, such as myocardial infarction and angina pectoris[1]. Early diagnosis and appropriate treatment result in the prevention of premature death. Heterozygous FH exists in approximately one in 500 people, and it is estimated that there are approximately 300,000 patients in Japan. Therefore, heterozygous FH is one of the genetic diseases most frequently encountered by general practitioners.

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2. Diagnosis of Heterozygous FH

1) LDL-C Cutoff Value

Table 1 shows the diagnostic criteria. Using data obtained from a total of 1,397 untreated dyslipidemic patients, including 439 patients with FH and 958 patients without FH, an analysis was performed of

Table 1. Diagnostic Criteria for Heterozygous FH in Adults (15 Years of Age or Older)

1. Hyper-LDL cholesterolemia (an untreated LDL-C level of ≥ 180 mg/dL)
2. Tendon xanthoma (tendon xanthoma on the backs of the hands, elbows, knees, etc. or Achilles tendon hypertrophy) or xanthoma tuberosum
3. Family history of FH or premature CAD (within the patient's second-degree relatives)

- The diagnosis should be made after excluding secondary hyperlipidemia
- If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In cases of suspected FH, obtaining a diagnosis using genetic testing is desirable.
- Xanthoma palpebrarum is not included in xanthoma tuberosum.
- Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is ≥ 9 mm on soft X-ray imaging.
- An LDL-C level of ≥ 250 mg/dL strongly suggests FH.
- If a patient is already receiving drug therapy, the lipid level that led to treatment should be used as the reference for diagnosis.
- Premature CAD is defined as the occurrence of CAD in men < 55 years of age or women < 65 years of age.
- If FH is diagnosed, it is preferable to also examine the patient's family members.

major items, including an LDL-C level of ≥ 180 mg/dL, the presence of Achilles tendon hypertrophy or cutaneous xanthoma and a history of FH or premature CAD in relatives within the second degree. The results showed a sensitivity of 94.3% and a specificity of 99.1%. In cases involving an LDL-C level of ≥ 190 mg/dL, the sensitivity was 92.1% and the specificity was 99.1%. Therefore, 180 mg/dL, the level at which the specificity was the same and the sensitivity was higher than that observed at 190 mg/dL, was adopted as the LDL-C cutoff value[2]. Because this analysis showed that 5% of patients with an LDL-C level of ≥ 250 mg/dL do not have FH, a diagnosis of FH is thus strongly suspected in the presence of an LDL-C level of ≥ 250 mg/dL alone[3].

2) Soft X-Ray Radiography of the Achilles Tendon

Achilles tendon hypertrophy should be evaluated using soft X-ray radiography. Positioning is performed so that the lower leg bones and sole of the foot form a 90-degree angle, and radiation is administered so that the X-ray enters the center of the lateral malleolus from the side of the foot. The imaging distance should be 120 cm, and the imaging conditions should be 50 kV and 5.0 mA. When the greatest dimension is ≥ 9 mm, hypertrophy is diagnosed. Conducting the evaluations using ultrasonography is possible, although it has not yet been standardized.

3) Differential Diagnosis

Diseases that must be distinguished from FH include conditions that cause secondary hyperlipidemia (e.g., diabetes mellitus, hypothyroidism and nephrotic syndrome) and a similar disease, familial combined hyperlipidemia (FCHL). FCHL is distinguished by the absence of tendon xanthoma, the presence of small, dense LDL, the presence of other types of dyslipidemia (types IIa, IIb and IV) in the patient's family and, in children, a lower degree of increase in the LDL-C level compared with that observed in FH.

3. Management Targets for LDL-C in Heterozygous FH

Because FH is a disease associated with a very high risk of CAD, FH should be considered to correspond to secondary prevention, and it is desirable to set a management target for the LDL-C level at < 100 mg/dL. However, in many cases, it is difficult to achieve a management target for an LDL-C level of < 100 mg/dL in FH patients in clinical practice. Therefore, it is acceptable to aim for < 50% of the pretreatment level if the management target for LDL-C is not achieved. The achievement of the management target does not always assure the absence of future cardiovascular events. In the treatment of FH, risk assessment cannot be applied using the risk charts provided in these guidelines. This management target should be applied to patients with FH ≥ 30 years of age, and it is desirable to administer the treatment under the direction of a specialist, in principle. Treatment for FH in patients 15-29 years of age must be administered under the direction of a specialist.

4. Treatment of Heterozygous FH

1) Lifestyle Modification

Lifestyle modification should be performed in FH patients after diagnosis and continued as described in committee report 7A[4]. However, due to the high risk of cardiovascular disease (CVD), screening for CVD before administering exercise therapy is essential. CVD should be evaluated using patient interviews to determine the presence or absence of effort angina, and exercise electrocardiography and echocardiography should be performed. If the existence of ischemic heart disease is suspected, administering treatment for ischemic heart disease before initiating exercise therapy is thus preferred. Smoking cessation and obesity management are also important.

2) Drug Therapy

Statins are the first-line drugs for FH treatment. A retrospective analysis of 329 patients with heterozy-

gous FH conducted in Japan revealed that the use of statins delayed the onset of CAD[5]. If the patient does not respond to monotherapy with statins, other lipid-lowering drugs should be concomitantly used. Such concomitant drugs include ezetimibe, bile acid-binding resins (cholestyramine and colestimide), probucol, fibrates and nicotinic acid derivatives. Although there is no evidence that these combination therapies inhibit cardiovascular events in patients with FH more effectively than statin monotherapy, strict management of the LDL-C level is recommended in patients with FH. A retrospective investigation suggested that probucol delays the recurrence of CAD in patients with heterozygous FH[6].

3) Indications for LDL Apheresis

In heterozygous FH patients, LDL apheresis should be considered if the total cholesterol (TC) level does not decrease to ≤250 mg/dL following intensive drug treatment in the presence of CAD. If LDL apheresis is indicated, it is desirable to consult a specialist.

5. FH in Children

1) Diagnosis of Heterozygous FH in Children

The initial finding of heterozygous FH is hyper-LDL cholesterolemia. In childhood, many patients do not develop physical signs associated with hyper-LDL cholesterolemia, such as Achilles tendon xanthoma and arcus corneae. Therefore, FH in children is primarily diagnosed based on the presence of hyper-LDL cholesterolemia and family history. In the diagnosis of FH in children, if the parent(s) has/have hyper-LDL cholesterolemia, a diagnosis of FH in the parent(s) should be established. The diagnostic criteria for heterozygous FH in children are shown in **Table 2**. Because 95% of healthy children have an LDL-C level of ≤140 mg/dL[7], the cutoff value for screening is defined as 140 mg/dL.

2) Treatment for Heterozygous FH in Children

• **Nutritional Guidance and Lifestyle Modification**

If heterozygous FH is diagnosed, the affected child and their guardians should be directed to modify their lifestyle as soon as possible. Affected children with a smoking habit should be directed to stop smoking. In addition, they should be directed to avoid smoking throughout their life and receive an explanation of the risk of passive smoking; their family members should also be directed to stop smoking.

• **Drug Therapy**

Evidence pertaining to the age from which treatment should be administered in patients with heterozygous FH has not yet been established in Japan. Because atherosclerotic changes in the coronary arteries are observed from an earlier age in heterozygous FH patients, appropriate LDL-C management is recommended at an earlier age. According to the proposal of the American Academy of Pediatrics, if a patient has an "LDL-C level of ≥190 mg/dL" or an "LDL-C level of ≥160 mg/dL and a family history of premature CAD or at least two risk factors," lipid-lowering treatment should be initiated, even in children, and if lifestyle modification is inadequate, drug therapy should also be considered in boys aged 8 to 10 years or older and in girls after menarche[8]. Among patients who are at a very high risk, such as patients with tendon xanthoma or aortic stenosis or those with a family history of remarkable atherosclerosis, a differential diagnosis of heterozygous FH should be performed. With respect to drug therapy, in terms of safety for growth and development, bile acid-binding resins, which are not absorbed from the gastrointestinal tract, are typically used and are the first-line drugs. Drug therapy for children should be administered under the direction of a specialist.

Table 2. Diagnostic Criteria for Heterozygous FH in Children

1. Hypercholesterolemia: an untreated LDL-C level of ≥140 mg/dL (measure the LDL-C level if the TC level is ≥220 mg/dL)
2. Family history of FH or premature CAD within the patient's second-degree relatives

• Pediatric patients exhibit few symptoms, such as tendon xanthoma. Therefore, diagnosing FH in the patient's family members is important.
• The LDL-C level may vary during development. Providing careful follow-up is necessary.
• Premature CAD is defined as the occurrence of CAD in men <55 years of age or women <65 years of age.

6. Heterozygous FH in Women

Drug therapy, other than bile acid-binding resins, during pregnancy should be carefully considered due to concerns regarding the risk of fetal malformations. According to the National Institute for Health and Clinical Excellence[9], if pregnancy is diagnosed during drug therapy, lipid-lowering drugs other than bile acid-binding resins should be immediately discontinued, and, if there is a possibility of pregnancy, pregnancy after the discontinuation of drug treatment for three months should be recommended.

Homozygous Familial Hypercholesterolemia

1. Diagnosis of Homozygous FH

Homozygous FH is characterized by the presence of a TC level of ≥600 mg/dL, xanthoma and CVD from childhood, with both parents being heterozygous for FH. Therefore, making a clinical diagnosis is possible. If homozygous FH is suspected even when the TC level is <600 mg/dL, obtaining the diagnosis and therapeutic decisions from a specialist is essential.

2. Drug Therapy for Homozygous FH

Similar to that recommended for patients with heterozygous FH, lifestyle modification, including diet therapy, exercise therapy, smoking cessation and obesity management, provides the basis for treatment in patients with homozygous FH, although intensive LDL-C-lowering treatment is required at an earlier age because patients with homozygous FH face a considerable risk with respect to the development and progression of CAD. However, homozygous FH is much less responsive to drug treatment than heterozygous FH. Therefore, the administration of LDL apheresis once every one to two weeks is necessary. Probucol exerts LDL-C-lowering effects on homozygous FH and may cause the regression or disappearance of xanthoma in the skin or Achilles tendon. For patients with homozygous FH who wish to have children, screening for CAD and the presence of aortic stenosis and supravalvular stenosis should be performed, and appropriate measures should be taken as required to ensure the safe continuation of pregnancy and delivery[10].

3. LDL Apheresis for Homozygous FH

In patients with homozygous FH, it is difficult to decrease the LDL-C level sufficiently using existing drug therapies, and many patients require continued LDL apheresis with extracorporeal circulation starting in childhood. Considering the inhibition of the progression of CVD, the earlier LDL apheresis is initiated, the better; however, it is difficult to perform LDL apheresis until the affected child can be kept in bed during apheresis. Realistically, the timing of treatment initiation is 4 to 6 years of age, when children can lie in bed and extracorporeal circulation can be performed; however, it is recommended that the treatment be initiated as early as possible.

4. Pregnancy and Delivery of Patients with Homozygous FH

It is important to permit patients with homozygous FH to become pregnant as planned. Before pregnancy, screening for atherosclerosis should be performed using carotid ultrasonography, echocardiography and exercise tolerance tests to assess the status of atherosclerosis. By three months before the planned pregnancy, treatment with lipid-lowering drugs other than bile acid-binding resins should be discontinued. Because the cardiovascular system is greatly stressed during late pregnancy, particularly at delivery, performing LDL apheresis during pregnancy is desirable. LDL apheresis can also be safely administered during pregnancy.

5. Homozygous FH Designated as a Specified Disease

In October 2009, homozygous FH was designated as a specified disease in the Specified Disease Treatment Research Program. The criteria for designation are as follows: patients with homozygous FH definitively diagnosed using a genetic analysis of genes involved in the LDL metabolic pathway or measurement of the LDL receptor activity are definitively designated, and patients with remarkable hypercholesterolemia and those with cutaneous xanthoma starting in childhood who are refractory to drug treatment should be designated.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (chapter 9) published in Japanese in June, 2012. The details of this Committee Report 9 on Familial Hypercholesterolemia have been previously published as an original manuscript[11]; this is a brief summary.

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Committee Report 10

Other Types of Primary Hyperlipoproteinemia (Hyperlipidemia)

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

1. Primary Hyperlipoproteinemias (Hyperlipidemias) Other Than Familial Hypercholesterolemia

There are various types of primary hyperlipoproteinemias (hyperlipidemias) other than familial hypercholesterolemia (FH). These types are clinically important and classified according to their associated pathophysiology and genetic abnormalities (**Table 1**)[1]. Familial lipoprotein lipase (LPL) deficiency manifests as severe hyperchylomicronemia and may present with eruptive cutaneous xanthomas or acute pancreatitis, although it does not necessarily accompany atherosclerotic cardiovascular disease (CVD). On the other hand, familial type Ⅲ hyperlipoproteinemia and familial combined hyperlipidemia (FCHL) are often associated with CVD; therefore, providing early diagnosis and treatment is mandatory. Patients suspected of having these abnormalities must be investigated for the underlying causes of disease and evaluated for lifestyle and diet improvement, drug therapy and the presence of atherosclerosis. The major clinical types of this condition are described below.

2. Familial Combined Hyperlipidemia (FCHL)

1) Genetic and Environmental Background

The basic phenotype of FCHL is type Ⅱb hyperlipoproteinemia, although it varies from type Ⅱa to Ⅳ depending on secondary factors, such as dietary effects. This is a genetic hyperlipoproteinemia, and the first degree relatives of affected patients may develop hyperlipoproteinemias of type Ⅱa, Ⅱb or Ⅳ. This condition used to be considered an autosomal dominant disease caused by a single gene mutation; however, more recently, it has been found to be associated with enhanced hepatic apolipoprotein (apo) B-100 synthesis, decreased LPL activity, increased very-low-density lipoprotein (VLDL) secretion from the liver and the accumulation of visceral fat as factors for the development of symptoms and has been reported to be related to abnormalities of the *LPL* and *APOC-Ⅱ* genes or *APOA-Ⅰ/C-Ⅲ/A-Ⅳ* gene cluster. However, none of these findings have been proven to be definitive. It has also been suggested that FCHL is caused by a polygenic background that tends to induce hyperlipoproteinemia due to environmental factors, such as overnutrition and a low level of physical activity. The prevalence of this disease is as high as 1/100 in the general population.

2) Clinical Manifestations

In patients with FCHL, hyperlipoproteinemia appears after puberty, and the increase in the serum LDL-cholesterol (LDL-C) levels is relatively mild compared with that observed in patients with FH. In contrast to FH, Achilles tendon thickening is not observed in patients with FCHL. The frequency of coronary artery disease (CAD) is high, although not as high as that observed in FH patients[2, 3]. In Japan, among patients with FCHL, myocardial infarctions are observed in men ≥35 years of age and women ≥55 years of age[4]. FCHL is detected in 32% of patients ≤65 years of age with myocardial infarctions in Japan[5], indicating that FCHL is the most common primary hyperlipoproteinemia in CAD patients.

3) Laboratory Findings and Diagnosis

Insulin resistance frequently develops in patients with FCHL, and the synthesis and excessive secretion of VLDL occur due to the increased input of free fatty acids to the liver. As a result, the serum apo B levels

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Table 1. Classification of Primary Hyperlipoproteinemia (Hyperlipidemia) According to the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases Established by the Japanese Ministry of Health, Labour and Welfare

Primary hyperchylomicronemia	Familial lipoprotein lipase deficiency Apolipoprotein CII deficiency Primary type V hyperlipoproteinemia Unexplained hyperchylomicronemia
Primary hypercholesterolemia	Familial hypercholesterolemia Familial combined hyperlipidemia Idiopathic hypercholesterolemia
Endogenous hypertriglyceridemia	Familial type IV hyperlipoproteinemia Idiopathic hypertriglyceridemia
Familial type III hyperlipoproteinemia	
Primary hyper-HDL cholesterolemia	

(The 1987 report of the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases established by the Japanese Ministry of Health, Labour and Welfare (issued in March 1988). Classification and diagnostic criteria of primary hyperlipidemia (pp. 26-34, 1988).

are relatively high in affected patients, and the amount of apo B is relatively more excessive than that of LDL-C. LDL becomes small, dense LDL, which is rich in triglycerides (TGs), has a smaller particle size and is easily oxidized and likely to transform macrophages into foam cells, thereby promoting atherosclerosis.

Small, dense LDL is diagnosed using polyacrylamide gel (PAG) electrophoresis of lipoproteins. The diagnosis should be made according to the diagnostic criteria of the Research Committee for Primary Hyperlipidemia, Research on Measures against Intractable Diseases established by the Japanese Ministry of Health, Labour and Welfare (**Table 2**)[6, 7]. It is desirable to determine the presence of hyperlipoproteinemia of mixed phenotypes IIa, IIb and IV using a family survey. If it is difficult to conduct a family survey or the LDL particle size cannot be measured, an apo B/LDL-C ratio of >1.0 or the presence of small, dense LDL on PAG electrophoresis should be established. It is also important to rule out FH.

4) Treatment

Treatment for FCHL is similar to that for FH. Lifestyle modification and obesity management achieved via dietary and exercise therapy are most important. Patients with FCHL respond well to dietary therapy, and the effects of drugs are greater than those observed in patients with FH. With respect to drug therapy, statins, fibrates and nicotinic acid derivatives are effective. The presence or absence of CVD, such as CAD, is a prognostic factor.

3. Familial Type III Hyperlipoproteinemia

1) Cause

Familial type III hyperlipoproteinemia, a hereditary type of hyperlipoproteinemia also called broad β disease, is a disease in which remnant lipoproteins, such as intermediate-density lipoprotein (IDL), chylomicron remnants and β-VLDL (cholesterol-rich VLDL that migrates in the β position on electrophoresis), accumulate. Familial type III hyperlipoproteinemia is caused by abnormalities in apo E (apo E2/E2 or apo E deficiency). Apo E is an important apolipoprotein in the uptake of IDL and chylomicron remnants by the liver. Variants include wild-type E3 and isoforms E2 and E4. The proportion of the population with the *APOE2/E2* genotype is estimated to be approximately 0.2% in Japan, while very few individuals are diagnosed with familial type III hyperlipoproteinemia (0.01% to 0.02% of the general population).

Abnormalities in apo E result in the impaired uptake of chylomicron remnants and IDL by the liver, leading to the accumulation of these lipoproteins in the blood. However, in many cases, remarkable hyperlipoproteinemia does not occur in the presence of apo E2/E2 only, as this condition usually develops in association with other abnormalities [e.g., diabetes mellitus (DM), obesity or hypothyroidism]. The reported abnormalities of APOE include the *APOE2/E2* genotype in addition to other gene mutations, such as *APOE1*, abnormal *APOE3* and *APOE* deficiency.

2) Clinical Manifestations

Xanthoma striatum palmare and/or xanthoma

Table 2. Diagnostic Criteria for Familial Combined Hyperlipidemia According to the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases Established by the Japanese Ministry of Health, Labour and Welfare

Criteria	(1) Familial combined hyperlipidemia is associated primarily with phenotype IIb and possibly with phenotypes IIa or IV. (2) An apoprotein B/LDL-C ratio of >1.0 or the presence of small, dense LDL (particle size <25.5 nm) should be established. (3) Secondary hyperlipidemia, such as familial hypercholesterolemia or DM, should be excluded. (4) One or more of the first-degree relatives have phenotype IIb, IIa or IV hyperlipoproteinemia and at least one of such relatives, including the patient himself/herself, has phenotype IIb or IIa.
Diagnosis	The diagnosis is confirmed if all of the above criteria ((1) to (4)) are met. However, in daily practice, a diagnosis may simply be made if criteria (1) to (3) are met.

(Cited from the 2000 report of the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases established by the Japanese Ministry of Health, Labour and Welfare)

Table 3. Diagnostic Criteria for Familial Type III Hyperlipoproteinemia According to the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases Established by the Japanese Ministry of Health, Labour and Welfare

Major criteria	(1) Both the serum cholesterol and serum TG levels are high. (2) Electrophoresis of plasma lipoproteins shows a continuous broad β pattern from VLDL to LDL. (3) Abnormalities in apolipoprotein E (E2/E2, E deficiency, etc.) are established by electrophoresis of apolipoproteins.
Minor criteria	(1) Xanthoma (particularly xanthoma striatum palmare) (2) An increased serum apolipoprotein E concentration (apolipoprotein E/TC ratio ≥ 0.05) (3) A VLDL-C/serum TG ratio of ≥ 0.25 (4) A decreased level of LDL-C (5) The presence of cardiovascular disease, such as arteriosclerosis obliterans or ischemic heart disease
Diagnosis	The diagnosis is confirmed if all three major criteria are met. Familial type III hyperlipoproteinemia is suspected if two of the three major criteria and at least one of the minor criteria are met.

(Cited from the 1987 report of the Research Committee for Primary Hyperlipidemia, Research on Measures Against Intractable Diseases established by the Japanese Ministry of Health, Labour and Welfare)

tuberosum may appear in patients with this disease. Patients with familial type III hyperlipoproteinemia are likely to develop premature CVD [e.g., CAD, carotid atherosclerosis, renal arteriosclerosis or peripheral arterial disease (PAD)] and may have renovascular hypertension or intermittent claudication due to PAD. The incidence of CAD in patients with familial type III hyperlipoproteinemia is high in both Japan and Western countries[8].

3) Laboratory Findings and Diagnosis

Both the serum TC and TG levels are raised in this patient population. However, the ranges of these parameters vary from slightly increased in patients with normal TC or TG levels to up to 500 mg/dL or 2,000 mg/dL, respectively. The diagnosis is made based on the diagnostic criteria of the Specific Disease Primary Hyperlipidemia Research Group of the Ministry of Health and Welfare (**Table 3**)[6, 7]. For patients with both increased TC and TG levels, a lipoprotein analysis is performed to establish the presence of phenotype III. Patient screening can be performed in daily practice using lipoprotein electrophoresis to establish the presence of a broad β pattern and an apo E/TC ratio of ≥ 0.05. In lipoprotein analyses using ultracentrifugation or high-performance liquid chromatography (HPLC), the level of LDL-C does not increase, but instead decreases. Since the amount of cholesterol in the IDL fraction ($1.006 < d < 1.019$) dramatically increases, the presence of a high cholesterol/TG ratio (≥ 0.42) in the VLDL fraction ($d < 1.006$) should also be assessed. Next, the existence of any abnormalities in the apo E isoforms should be established according to the apo E phenotype or genotype.

4) Treatment

Dietary fat restriction is essential. Patients with familial type III hyperlipoproteinemia respond relatively well to lifestyle modification resulting from dietary and exercise therapy; thus, early diagnosis and

treatment are extremely important. Treatment of complications, such as DM, obesity or hypothyroidism, that occur in such patients is also effective for treating dyslipidemia. With respect to drug therapy, fibrates are the first-line drugs; however, nicotinic acid derivatives and statins are also effective. Early detection and treatment can prevent a poor prognosis, while conducting periodic examinations is essential for preventing the development of CAD, carotid atherosclerosis and PAD. Consultations with specialists are also desirable.

4. Other Types of Primary Hyperlipoproteinemia

Other types of primary hyperlipoproteinemia include familial LPL deficiency and familial apolipoprotein C-II deficiency. These deficiencies can take the form of remarkable hyperchylomicronemia or hypertriglyceridemia, although they usually present as type I hyperlipoproteinemia. While the relationship between marked hyperchylomicronemia and CVD is weak, caution should be exercised because hyperchylomicronemia is a frequent cause of acute pancreatitis. It is important to inhibit any increases in the levels of chylomicrons by enforcing strict fat restriction (≤ 20 g per day), and referring affected patients to specialists is recommended.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 10) published in Japanese in June 2012.

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Committee Report 11

Coronary Artery Disease

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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Epidemiological and interventional studies conducted in Western countries and the results of a meta-analysis have revealed that the incidence of cardiovascular events in patients with coronary artery disease (CAD) is higher than that observed in primary prevention patients. In Japan, the incidence of cardiovascular events in patients who receive dietary therapy was found to be 2.1/1,000 person-years in the MEGA study[1], while that in primary prevention patients using statins was found to be 0.9/1,000 person-years in the J-LIT study[2]. In contrast, the incidence of cardiovascular events in patients with CAD was found to be 4.5/1,000 person-years in the J-LIT study[3] and 6.8/1,000 person-years in the JELIS study[4]. The JCAD[5] and CREDO-Kyoto studies[6], registry studies of patients with CAD, both reported a high incidence of cardiovascular events of ≥15/1,000 person-years. Moreover, among patients with CAD, those with the conditions listed in **Table 1** are at higher risk. It has been reported that such patients have a clearly higher incidence of coronary events, even when the LDL-cholesterol (LDL-C) level is managed to the same extent as in patients without complications.

Table 1. Patient Conditions Requiring More Strict Management for Secondary Prevention

- Acute coronary syndrome
- Smoking
- DM
- CKD
- Noncardiogenic cerebral infarction/PAD
- Metabolic syndrome
- Multiple risk factors

1. Acute Coronary Syndrome

Patients with acute coronary syndrome (ACS) have a higher risk of recurrence of cardiovascular events than patients with stable CAD. The OACIS-LIPID study investigated the inhibitory effects of early statin treatment on cardiovascular events in Japanese patients with acute myocardial infarction (MI)[7]. In that study, the incidence of total mortality and nonfatal MI in patients who received lipid-lowering therapy other than statins was 40/1,000 person-years, while that among patients who received statins was 30/1,000 person-years, thus revealing a remarkably high incidence of cardiovascular events.

Meanwhile, it has been reported that the administration of LDL-C-lowering therapy from the early stage of ACS is effective in preventing cardiovascular events[8] and that more intensive LDL-C-lowering therapy decreases the incidence of cardiovascular events more significantly than typical LDL-C-lowering therapy[9]. A meta-analysis of randomized controlled trials (RCTs) of statin treatment started within 14 days after the onset of ACS demonstrated no protective effects on cardiovascular events in a short period of four months[10]; however, the incidence of cardiovascular events was significantly reduced during an observation period of ≥2 years[11]. These results suggest that the beneficial effects of providing early, intensive LDL-C-lowering therapy in preventing cardiovascular events are observed from four to 12 months after the onset of ACS.

In Japan, the effectiveness of early LDL-C-lowering therapy in patients with ACS has been investigated by observing coronary artery plaque using intravascu-

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lar ultrasonography (IVUS). In the ESTABLISH study, the administration of early, intensive LDL-C-lowering therapy after the onset of ACS decreased the mean LDL-C level to 70 mg/dL after six months, resulting in a decrease in the plaque volume of 13.1%[12]. The changes in plaque volume were found to be significantly and positively correlated with the LDL-C level after treatment and the rate of decrease in the LDL-C level. The ESTABLISH study followed up (mean: 4.2 years) additional patients and reported that the administration of early, intensive LDL-C-lowering therapy after the onset of ACS significantly decreased cardiovascular events[13]. Furthermore, the JAPAN-ACS study demonstrated that providing early, intensive LDL-C-lowering therapy using statins in patients with ACS was effective in inhibiting plaque progression[14]; however, that study found no significant relationships between the changes in the LDL-C level during treatment or the LDL-C level observed after treatment and the rate of plaque regression.

2. Smoking

In patients with CAD who continue to smoke, the risk of recurrence of cardiovascular events is higher than that observed in nonsmokers and the risk of fatal cardiovascular events, including total mortality, cardiac death and sudden cardiac death, is significantly increased[15-19]. In the REACH Registry, a registry study of patients with cardiovascular disease [CAD, cerebrovascular disease and peripheral arterial disease (PAD)] or more than one risk factor for atherosclerosis, the incidence of cardiovascular events in patients who continued to smoke was approximately 1.3-fold higher than that observed in lifelong nonsmokers[20]. In the OACIS study, even after adjusting for age, sex, diabetes mellitus (DM), hypertension, dyslipidemia, and therapeutic drugs, the risk of total mortality in patients who continued to smoke after the onset of MI was 2.3-fold higher than that observed in lifelong nonsmokers. In contrast, the risk of total mortality in patients who stopped smoking after the onset of MI was as low as that observed in lifelong nonsmokers and was significantly decreased (by 61%) compared with that observed in patients who continued to smoke[21]. Many epidemiological studies have reported that the risk of recurrence of cardiovascular events decreases after approximately half a year following the cessation of smoking and reaches almost the same level as that observed in lifelong nonsmokers approximately 10 years after smoking cessation, regardless of age and sex[15-22].

A subanalysis of the secondary prevention studies, TNT and IDEAL[23], showed that the risk of cardiovascular events in continued smokers is higher than that observed in lifelong nonsmokers, even among those receiving intensive LDL-C-lowering therapy with statins. Therefore, providing smoking cessation instructions to patients who continue to smoke is extremely important.

3. Multiple Risk Factors and Metabolic Syndrome

The results of a meta-analysis revealed that patients with CAD complicated by metabolic syndrome have a higher risk of total mortality and cardiovascular events[24].

A subanalysis of the TNT study of patients with stable CAD and metabolic syndrome demonstrated the risk of cardiovascular events to increase in association with the presence of each additional component of metabolic syndrome. In particular, patients with three or more major risk factors have a higher incidence of cardiovascular events. However, high-dose statin treatment has been shown to significantly decrease the rate of cardiovascular events (by 29%) compared with usual-dose statin treatment[25].

The JCAD, an observational study conducted in Japan, demonstrated that the risk of cardiovascular events in patients with three or more major risk factors is 1.3-fold higher than that observed in patients with two or less risk factors[5]. In a study in which patients who underwent percutaneous coronary intervention (PCI) were followed up for a long period, the relative risk of cardiovascular events in the patients with metabolic syndrome was 2.1-fold[26]; however, statin treatment resulted in a significant decrease in total mortality of 44% and coronary death of 47%[27].

4. Diabetes Mellitus (DM)

It has been reported that the risk of recurrence of cardiovascular events is increased in the presence of DM in patients with a history of MI[28-31]. Epidemiological studies of Japanese patients with CAD have also reported that the risk of total mortality and cardiovascular events in patients with DM is high[5, 32, 33]. Moreover, an analysis of patients with CAD in the J-LIT study showed that the relative risk of cardiovascular events is increased approximately 2.5-fold in the presence of DM[3, 7].

According to the CTT, a meta-analysis of 14 RCTs of statins, the beneficial effects of statins on cardiovascular events are observed regardless of the presence or absence of DM or CAD[34]. A subanalysis of the TNT study of patients with CAD and DM showed that high-dose statin treatment significantly decreases cardiovascular and cerebrovascular events by 25% and 31%, respectively, compared with usual-dose

statin treatment[35].

A meta-analysis of clinical studies using IVUS conducted in Western countries reported that DM is an independent risk factor in patients whose coronary plaque volume is ≥5% despite having a decreased LDL-C level of ≤70 mg/dL with treatment[36]. It has also been reported that there is a significant positive relationship between an increase in the coronary plaque volume, as well as the LDL-C level, and the incidence of cardiovascular events after treatment. This suggests that the use of intensive LDL-C-lowering therapy is important in patients with CAD complicated by DM. Furthermore, in a subanalysis of the JAPAN-ACS study conducted in patients with ACS in Japan[37], DM was found to be a strong negative risk factor for plaque regression. In addition, although the LDL-C-lowering effects of statins were equivalent to those observed in patients without DM, the effects on plaque volume regression were significantly decreased in patients with DM. However, it has been reported that significant plaque regression effects can be obtained if the LDL-C level is maintained at <75 mg/dL[38].

5. Noncardiogenic Cerebral Infarction and Peripheral Arterial Disease (PAD)

Cardiovascular diseases, such as CAD, cerebrovascular disease and PAD, which commonly occur in patients with atherosclerosis, interact, leading to a risk of systemic vascular complications. The REACH registry revealed that approximately 16% of patients have two or more cardiovascular diseases[39]. In a comparison of the results of the CREDO-Kyoto study conducted in Japan with those of a registry study conducted in the U.S.[33], the complication rate of cerebrovascular disease was significantly higher in Japan (16.4% vs. 5.0%), while the complication rate of PAD was significantly higher in the U.S.; however, both complications were confirmed to be high risk factors for cardiovascular events in Japan and the U.S.

1) Noncardiogenic Cerebral Infarction

Secondary prevention studies of CAD conducted in Western countries, such as the 4S, LIPID and CARE studies, have reported that patients with CAD with a history of cerebrovascular disease have a high risk of recurrence of cerebrovascular and cardiovascular events, although LDL-C-lowering therapy with statins decreases the risk of recurrence of both cerebrovascular and cardiovascular events[40-42].

2) Peripheral Arterial Disease (PAD)

Although patients with PAD with a history of CAD have an extremely high risk of total mortality and fatal cardiovascular events[43-48], there are no lipid intervention studies focusing only on patients with PAD complicated by CAD. In a meta-analysis of the effectiveness of lipid intervention in patients with PAD, lipid-lowering therapy was found to decrease the incidence of cardiovascular events by 20% and total mortality by 14%[49]. Subanalyses of cohort studies and RCTs have reported the effectiveness of statins in patients with PAD[50-54].

A meta-analysis of clinical studies in which the progression of coronary plaque lesions was analyzed using IVUS showed that effects on the inhibition of the progression and regression of plaque are observed when the LDL-C level is maintained at <70 mg/dL, regardless of the presence or absence of PAD, and that plaque regression is related to cardiovascular events[55].

6. Chronic Kidney Disease (CKD)

Analyses of long-term observational studies of patients with ACS and those who have undergone PCI stratified according to the estimated glomerular filtration rate (eGFR) have reported that the risk of cardiovascular events, including cerebrovascular disease, cardiac death and total mortality, in patients with mild chronic kidney disease (CKD) increases by 2- to 3-fold compared with patients with a normal renal function, and the risk further increases in association with the severity of renal dysfunction[56, 57], The CREDO-Kyoto study reported that, among patients with CKD who have undergone PCI, the risk of cardiovascular death is increased by 2.9-fold and the risk of total mortality is increased by 2.1-fold. In particular, patients ≤55 years of age were found to have an increased risk of cardiovascular events, including cerebrovascular disease (by 3.7-fold)[58]. Furthermore, patients with CKD and a serum creatinine level of ≥2.0 mg/dL were found to have a 7.0-fold increased risk of total mortality. This suggests that patients with CKD who have undergone PCI have an increased risk of cardiovascular events[33].

The protective effects of lipid-lowering therapy on cardiovascular events in patients with CKD complicated by CAD have been investigated in a post hoc analysis of early secondary prevention studies using statins. The results showed that statins provide significant beneficial effects on cardiovascular events, but not cerebrovascular disease, in patients with mild CKD and an eGFR of <75 mL/min/1.73 m^2 [59, 60]. Furthermore, a post hoc analysis of secondary prevention studies reported that high-dose statin treatment significantly decreases the incidence of cardiovascular events by approximately 30% in patients with moderate

CKD compared with usual-dose statin treatment[61, 62].

Footnotes

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Committee Report 12

Diabetes Mellitus

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

1. Importance of Diabetes Mellitus as a Risk Factor for Cardiovascular Disease

Diabetes mellitus (DM) is an important risk factor for cardiovascular disease (CVD)[1-3]. A meta-analysis of data from Western countries showed that the risks of coronary artery disease (CAD) and cerebral infarction due to DM after adjustment for multiple factors, including sex, age and blood pressure, are 2.0 and 2.3, respectively[4]. In Japan, the NIPPON DATA80 showed that the risk of death from CAD in patients with DM is 2.8, which is significantly higher than it is for non-DM subjects[5]. The Hisayama study showed that the risks of CAD and cerebral infarction after adjustment for multiple factors, including patient sex and age, in patients with DM are 2.6 and 3.2, respectively, both of which are higher than those of patients with normal glucose tolerance[6]. In terms of relative risk, DM is an important risk factor for CVD regardless of race. However, the absolute risk of CAD in Japanese subjects with DM is approximately 30 to 70% of the risk in Western subjects with DM[7, 8]. Although there have been few investigations in Japan, the incidence of CAD in Western patients with type 1 DM is higher[9], especially in patients with nephropathy[10].

CAD in patients with DM is characterized by (1) a higher prevalence of silent myocardial ischemia[11], (2) multivessel lesions, (3) high-grade and diffuse lesions[12, 13] and (4) calcified lesions[14]. Cerebral infarction is characterized by increased lacunar infarction and atherothrombotic cerebral infarction[15, 16]. The CVD prognosis in diabetic subjects is poor relative to nondiabetic subjects[17-19], and the recurrence rate of cerebral infarction in patients with DM is higher[20, 21].

Patients with DM are at a higher risk of peripheral arterial disease (PAD), and 20% of patients with PAD symptoms are diabetic. Furthermore, one report found that the risk of intermittent claudication is 2.6-fold higher in patients with DM[22].

Although the risk of CVD in women is lower than in men, women with DM have a higher relative CVD risk than men with DM[23, 24]. The results of the Japan Diabetes Complications Study (JDCS) showed that the absolute risks of CAD in Japanese patients with DM were 11.2/1,000 person-years for men and 7.9/1,000 person-years for women, which is still higher in men than in women[8].

The risk of CVD increases after reaching the stage of impaired glucose tolerance (IGT), even before the onset of DM[25, 26]. The Hisayama study showed that the relative risk of CVD in patients with IGT compared to normal subjects is 1.9, although it is lower than the risk of 2.6 in diabetic subjects[6]. Instead of the fasting blood glucose level, the blood glucose levels at 2 hours after a glucose load have been reported to be significantly associated with the risk of CVD in subjects with IGT[27, 28], showing that postprandial hyperglycemia is a risk factor for atherosclerosis. Thus, patients with IGT have an increased risk of CVD, but it is not obvious whether the degree of risk is equal to that of patients with DM. In this guideline, IGT is distinguished from DM and is considered to be one among many risk factors, such as hypo-high density lipoprotein (HDL) cholesterolemia and a family history of CAD.

2. Cardiovascular Disease Risk Factors and Their Comprehensive Management in Patients with DM

The risk factors for CAD in patients with DM

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include hyperglycemia, hypertension, smoking, the male sex, hyper-low density lipoprotein (LDL) cholesterolemia, hypo-HDL cholesterolemia, hypertriglyceridemia[8, 29] and high Lp(a) levels[30]. Diabetic nephropathy[31, 32] and retinopathy[33] are predictors of CAD. The risk factors for cerebral infarction include hypertension, the male sex and atrial fibrillation[29, 34]. The concentration of homocysteine in the blood is also reportedly associated with the severity of PAD[35].

The comprehensive and early management of risk factors such as hyperglycemia, hypertension and dyslipidemia has been shown to be effective for inhibiting cardiovascular events[36, 37]. Additionally, comprehensive and intensive therapy to mitigate these risk factors has been reported to suppress the progression of CVD in Japan[38].

The antithrombotic effects of low-dose aspirin and the antioxidant effects of vitamin E for primary prevention in DM patients are not evident[39, 40].

3. Lipid Management in Patients with DM

It is clear that lifestyle modifications, including dietary therapy, increased physical activity and smoking cessation, are fundamental for the management of CVD and these factors contribute to a decrease in disease incidence and mortality[41-46]. In patients with DM, dietary therapy and exercise decrease the risk of atherosclerosis, hyperglycemia, dyslipidemia and hypertension[47-49]. Several reports have shown that smoking cessation and increased physical activity decrease the risk of CVD in DM patients[50, 51].

Patients with DM are likely to have hyper-LDL cholesterolemia, hypertriglyceridemia and hypo-HDL cholesterolemia. A sub-analysis of the HPS[52] and the CARDS[53] has already shown the effectiveness of statins in preventing CVD in DM patients. A recent meta-analysis of a large-scale clinical trial revealed that statins decreased LDL-cholesterol(C) levels by 38.6 mg/dL, resulting in a decrease in total mortality risk by 9% ($p=0.02$), death from CAD by 12% ($p=0.03$), major coronary events [myocardial infarction or death from CAD] by 22% ($p<0.0001$) and cerebral infarction by 21% ($p=0.002$); these rates are similar to those in nondiabetic subjects[54].

The FIELD study investigated the effects of fibrates on CVD in patients with DM and mild dyslipidemia and showed a decrease in coronary events (nonfatal myocardial infarction or death from CAD) as a consequence of primary prevention[55]. A sub-analysis of the ACCORD trial demonstrated that combination therapy of statins with fibrates in patients with hypertriglyceridemia and hypo-HDL cholesterolemia may significantly reduce the risk of cardiovascular events even after statin treatment[56, 57]. It was also reported that adding eicosapentaenoic acid (EPA) treatment for patients with impaired glucose metabolism complicated by hypercholesterolemia and already under statin treatment can reduce coronary events by 22% (the JELIS study)[58] and that combination therapy with statins and ezetimibe in patients with DM complicated by chronic kidney disease (CKD) decreases the development of cardiovascular events by 22% compared to a placebo treatment (the SHARP study)[59].

In previous guidelines, a TG <150 mg/dL and HDL-C ≥ 40 mg/dL have been recommended as target values regardless of the presence or absence of DM[60]. This new guideline adopts non HDL-C as a secondary management target if hypertriglyceridemia is present after controlling LDL-C. It has been reported that increased non HDL-C levels are significantly associated with the risk of death from CVD in patients with DM[61].

4. LDL-C Management for the Prevention of CAD

DM is considered to be a "coronary risk equivalent" by the NCEP-ATP Ⅲ, and an LDL-C level of <100 mg/dL is the recommended target[62]. These concepts were introduced by ADA clinical practice recommendations[63]. The ESC/EAS guidelines also recommend that LDL-C levels of <100 mg/dL should be the primary goal in all patients with type 2 DM[64].

In Japan, the J-LIT chart was used to investigate the incidence of CAD by stratifying the presence of risk factors in patients with DM[65, 66]. This chart shows that the risk of CAD in patients with DM alone is clearly lower than the risk of recurrence in secondary prevention patients without DM for both men and women, indicating that there is an insufficient rationale for considering DM alone as a "coronary risk equivalent" among the Japanese. However, a sub-analysis of the J-LIT study showed that even if the number of subjects with newly diagnosed CAD does not differ between diabetic and nondiabetic patient groups, the LDL-C levels are lower by approximately 30 to 40 mg/dL in diabetic subjects[67]. This result suggests that stricter management of LDL-C is needed in diabetic patients.

DM conditions vary for each patient. It is practical to find patients who are at high risk of CAD, and then attempt to strictly control their risk factors. Previous reports revealed that patients at a high risk of CAD or death from CAD are characterized by conditions including (1) microangiopathy (e.g., retinopathy, nephropathy)[31-33, 68-70], (2) persistently poor glycemic control[71-73], (3) smoking[65, 66, 74], (4) noncardiogenic