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

Table 1. Diabetic Patients with a Higher Risk of Developing CAD

• Microangiopathy (retinopathy, nephropathy, etc.)
• Persistent poor glycemic control*
• Smoking
• Non-cardiogenic cerebral infarction/PAD
• Metabolic syndrome
• More than one major risk factor

*; HbA1c ≥ 8.4% (NGSP)

cerebral infarction/PAD[75], (5) metabolic syndrome[76] and (6) more than one major risk factor (**Table 1**)[65, 66, 74].

All patients with DM should aim for LDL-C levels of < 120 mg/dL as part of their primary CAD prevention. In patients with the previous characteristics, it is essential to follow intensive and strict management measures to reach the target values. Patients with DM who have more than one of these characteristics are expected to be at an extremely high risk of CAD, and the secondary prevention target values could be considered.

Lipid management in secondary prevention patients with DM is described in Chapter 11 of "Coronary Artery Disease."

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 12) published in Japanese in June 2012.

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Committee Report 13

Chronic Kidney 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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The results of a meta-analysis of 26 clinical studies using statins demonstrated that statins significantly decreased the total mortality by 19% and the cardiovascular mortality by 20% in patients with chronic kidney disease (CKD), excluding dialysis patients, and also demonstrated that statins can be safely used with the same incidence of adverse events compared with placebo[1]. Furthermore, the SHARP study, which compared combination treatment with a statin and ezetimibe with placebo in patients with CKD, including dialysis patients, demonstrated that lipid-lowering therapy significantly decreased the cardiovascular risk in patients with CKD by 17%[2]. It should be noted that the mean LDL-cholesterol (LDL-C) level before treatment was 108 mg/dL, and patients with relatively low LDL-C levels were included in the SHARP study. A sub-analysis of patients with CKD in the MEGA study conducted in patients with hypercholesterolemia in Japan showed that the cardiovascular risk decreased in patients who received lipid-lowering therapy using a statin[3]. However, in randomized controlled trials (4D, AURORA) conducted exclusively in dialysis patients, the decreases in cardiovascular events in a broad sense, including heart failure and cerebral hemorrhage, were not significant[4, 5]. Nevertheless, the analyses in these studies using the endpoint of only atherosclerotic cardiovascular disease (CVD) in patients with diabetes mellitus (DM)[4, 6] and an analysis of only patients with high LDL-C levels before intervention (>145 mg/dL)[7] have shown significant risk reduction.

There is no evidence indicating the optimal lipid management targets in patients with CKD. On the other hand, the sub-analyses of the SHARP and 4D studies showed that the inhibitory effects of lipid-lowering therapy on CVD were greater in patients with high LDL-C levels before intervention. Because the cardiovascular risk in patients with CKD was similar to or even higher than that in patients with DM[8], it is appropriate to consider CKD as a high-risk condition for CVD, and to establish lipid management targets, comparable to DM. Whether the management targets should be subdivided according to the CKD stage classification will be discussed in the future, because a new CKD stage classification is being investigated in Japan and overseas[9].

In order to decrease the cardiovascular risk in patients with CKD, comprehensive management of various risk factors is as important as it is for patients with other diseases. The significance of the lipid management in patients with CKD is summarized in a recent review by the Committee of Renal and Peripheral Arteries of the Japan Atherosclerosis Society[10].

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Footnotes

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Committee Report 14

Cerebrovascular Diseases

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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1. Frequency

Cerebrovascular disease is classified into three types: cerebral hemorrhage, cerebral infarction and subarachnoid hemorrhage. According to the Japanese Stroke Data Bank, the frequency of cerebrovascular disease according to type in Japan is reported to be approximately 18% for cerebral hemorrhage and approximately 7% for subarachnoid hemorrhage, with the remainder for cerebral infarction[1]. Compared with the frequency of cerebrovascular disease according to type observed in Western countries, the frequency of cerebral hemorrhage is higher in Japan, while the frequency of cerebral infarction is lower[2].

Cerebral infarction is further classified into three clinical types: lacunar infarction, atherothrombotic cerebral infarction and cardiogenic cerebral embolism. According to the Hisayama study, lacunar infarction accounts for approximately 50% of cases of cerebral infarction, whereas the incidence of atherothrombotic cerebral infarction and cardiogenic cerebral embolism is slightly less than 30% and slightly more than 20%, respectively[3]. The frequency of cerebral infarction (with obvious causes) in Western countries (Caucasians) has been reported to be approximately 30% for both lacunar and atherothrombotic cerebral infarction and approximately 40% for cardiogenic cerebral embolism[4]; lacunar infarction occurs more frequently in Japan[5].

2. Risk Factors for the Development of Cerebrovascular Disease

The results of the NIPPON DATA80 indicate that the factors affecting mortality from stroke in Japan include age, systolic blood pressure, smoking and hyperglycemia and that the lipid levels, such as that of total cholesterol (TC), are not considered to be risk factors[6]. Similarly, the results of 61 observational studies conducted in Western countries (approximately 0.9 million subjects) indicated no relationships between the TC level and mortality from stroke[7]. The results of a meta-analysis of 18 cohort studies in Japan and China showed that blood pressure is the most important risk factor for stroke and that the TC level is much less frequently involved than the blood pressure[8].

In terms of individual cerebrovascular diseases, hypertension is clearly a risk factor for cerebral hemorrhage, and the presence of a cerebral aneurysm is a risk factor for subarachnoid hemorrhage. With respect to cerebral infarction, the major risk factors for cardiogenic cerebral embolism are hypertension and intracardiac thrombi[9, 10].

The results of epidemiological studies conducted in Japan have indicated no significant relationships between the serum cholesterol levels (TC, LDL-cholesterol (LDL-C) and non HDL-cholesterol) and the incidence of noncardiogenic cerebral infarction[11-17]. In Western countries, however, epidemiological studies, such as the MRFIT, have reported that an increased TC level is associated with an increased risk of cerebral infarction[18-20]. The results of seven cohort studies (approximately 0.69 million subjects) reported that the incidence of cerebral infarction is significantly decreased by 15% in patients with a decrease in the TC level of 1 mmol/L (38.6 mg/dL)[21], although, other reports have found that the TC level either is not a risk factor for cerebral infarction or is less involved[22, 23].

The results of the Hisayama study, which investi-

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gated the risk of cerebral infarction according to type, demonstrated that the LDL-C level is a risk factor for the development of atherothrombotic cerebral infarctions; however, it is not associated with the development of other types of cerebral infarction[15]. Furthermore, the Hisayama study reported that blood pressure is strongly associated with lacunar infarction, atherothrombotic cerebral infarction and, in women, cardiogenic cerebral embolism[24]. Reports published in foreign countries indicate that the major risk factor for cerebral infarction, including cardiogenic cerebral embolism, is hypertension[22, 23]. In other words, the cholesterol level is recognized to be a risk factor only for atherothrombotic cerebral infarction, and the major risk factor for all types of cerebral infarction, including atherothrombotic cerebral infarction, is hypertension[9].

Many reports in various countries, including Japan, have stated that hypocholesterolemia is a risk factor for cerebral hemorrhage[16, 25]. A meta-analysis of cohort studies found that a decrease in the cholesterol level by 1 mmol/L (38.6 mg/dL) is associated with an increase in the frequency of cerebral hemorrhage of 19%[21]. In Japan, an LDL-C level of ≤80 mg/dL has been reported to increase the frequency of cerebral hemorrhage[16]. However, as described later, the results of a meta-analysis of prevention studies of coronary artery disease (CAD) do not indicate that cholesterol-lowering therapy leads to an increased frequency of cerebral hemorrhage[26].

There have been many reports in a number of countries, including Japan, stating that a lower HDL-cholesterol level is associated with an increased incidence of cerebral infarction[27-30].

There are also many reports indicating no certain relationships between the triglyceride (TG) level and stroke[23, 31, 32]. However, the results of a meta-analysis of epidemiological studies conducted in the Asia-Pacific region, in which the fasting TG level was divided into four groups, reported that the patients with the highest TG levels had an increased risk of ischemic stroke of 50% compared with that observed in the patients with the lowest TG levels[33]. The results of cohort studies of approximately 14,000 subjects indicate that the frequency of ischemic stroke is increased in both men and women when postprandial hypertriglyceridemia is present[34]. These results show that an increase in the postprandial TG level of 1 mmol/L (88.5 mg/dL) is associated with an increase in the frequency of ischemic stroke of 15%.

3. Lipid-Lowering Therapy and Cerebrovascular Disease

Although many prevention studies of CAD using statins have been conducted to date, only the SPARCL study employed the development of stroke as the primary end point, with most studies using stroke as the secondary end point. The results of a meta-analysis of prevention studies conducted in Western countries showed that cholesterol-lowering therapy with statins significantly decreases the incidence of cerebral infarction by 19%. Additionally, in that study, the incidence of cerebral hemorrhage did not vary significantly (**Table 1**)[26]. It is unclear why statin treatment decreases the incidence of stroke because the cholesterol level has not been considered to be a risk factor for stroke in observational studies.

As mentioned above, the SPARCL study employed the recurrence of stroke as the primary end point[35]. In that study, high-dose statins were administered in patients with a history of stroke, and the recurrence rate of stroke in these patients was compared with that observed in patients who received placebo treatment. Consequently, the recurrence of stroke significantly decreased (−16%, $p=0.03$), while the incidence of CAD was markedly lower (−35%, $p=0.003$). Therefore, statin treatment is also effective in the secondary prevention of stroke. A post hoc analysis of the breakdown of stroke as an end point found that the incidence of cerebral infarction was significantly decreased (hazard ratio=0.78), whereas that of cerebral hemorrhage was significantly increased (hazard ratio=1.66). These results are inconsistent with the findings of the meta-analysis mentioned above, in which statin treatment did not increase the incidence of cerebral hemorrhage[26]. To determine the risk of cerebral hemorrhage associated with cholesterol-lowering therapy, performing further prevention studies is warranted.

Among the various studies conducted in Japan, the MEGA study showed that statin treatment tends to decrease the incidence of stroke, with hazard ratios of 0.66 and 0.63 for men and women, respectively[36]. In particular, in that study, the incidence of ischemic stroke in men and stroke in women ≥55 years of age was significantly decreased[36, 37]. The results of a subanalysis of the JELIS showed that treatment with statins and ethyl icosapentate (EPA) in patients with a history of stroke significantly inhibits the recurrence of stroke by approximately 20% compared with statin monotherapy[38].

4. Measures to Prevent Cerebrovascular Disease

Because the greatest risk of cerebrovascular dis-