Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017

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Preamble

Every 5 years, the JAS publishes guidelines for the treatment of dyslipidemia and atherosclerosis. To date, this society has released four such guidelines. Since 2007, the JAS has included objectives that consider all the risk factors for atherosclerotic cardiovascular diseases (ASCVD) and has accordingly been publishing manuals, such as the "Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases." Because guidelines should be based on evidence of diagnoses and treatments that have already been validated, regular revisions are necessary to administer medical care of high quality.

Apart from age, gender, and family history, for which clinical intervention is not possible, the major risk factors for ASCVD include diabetes, hypertension, smoking, and dyslipidemia. Dyslipidemia is a huge risk factor for coronary artery disease (CAD), a form of ASCVD, and in the current set of guidelines, we will be dealing with CAD as the main disease of interest. Nevertheless, other risk factors also ought to be thoroughly managed as part of the efforts for preventing ASCVD.

In 1987, a consensus conference on hyperlipidemia was held at the JAS, and reference values for diagnosing hyperlipidemia were proposed. Although the reference values were established when there was a lack of evidence in Japan, it was an unprecedented proposal that provided the clinical limits of lipids for the prevention of ASCVD. In 1988, the evidence-based National Cholesterol Program (NCEP) was announced in the United States, and since then, the reference values have undergone several revisions. At that time, there was a strong momentum for the creation of a set of Japan-specific guidelines; therefore, the "Guidelines for Diagnosis and Treatment of Hyperlipidemia" were established in 1997. Following the publication of epidemiological studies, such as the Hisayama study, and observational studies, such as J-LIT, we gradually gathered sufficient evidence in our country. Subsequently, the "Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases", which took risk factors into consideration, were established in 2002.

The "Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2007" were later published in 2007. A change of terms from "hyperlipidemia" to "dyslipidemia" and replacement of total cholesterol with LDL cholesterol (LDL-C) as the major risk factor were features of this guideline. Establishing LDL-C as the major risk factor has led to an even more direct approach toward managing the risk factors for ASCVD. Furthermore, raising the topic on the importance of measures against metabolic syndrome and smoking, which have gained considerable attention, serves as a reminder to pay attention also to measures for the prevention of ASCVD in our daily lives. For healthy individuals, the risk of ASCVD has traditionally been assessed through the relative risk; however, this was replaced by the use of absolute risk in the guidelines released in 2012. This change resulted in a higher awareness of the importance of combined risk factors. Considering the need to comprehensively manage the wide range of atherosclerotic risks, we have compiled information on the "Comprehensive Management of Atherosclerotic Cardiovascular Diseases" and have created charts, which incorporate the guidelines of various scientific societies.

We have striven to include more updated information in the current revision; hence, you will find several newly introduced Clinical Questions (CQs), which are the mainstream of recent guidelines.

Shizuya Yamashita
President, the Japan Atherosclerosis Society

Key Revisions

1. CQs and Systematic Review (SR)

In the subsections on dyslipidemia in the assessment of risk factors, absolute risk of ASCVD, lipid management targets as well as drug therapy and diet therapy in improving lifestyle habits, we created CQs and performed an SR based on the MINDS method. For our SR, we essentially chose the literature published before the end of 2015.

2. Calculation of Absolute Risk

Following the 2012 version, the assessment of risk has been performed using the absolute risk calculation described in this set of guidelines. The NIPPON DATA80, which was used to calculate the absolute risk in the 2012 version, was the result of baseline surveys conducted when statins were not available. It is suited to the observation of the natural course of disease, and the data are highly useful; however, using death instead of disease onset as the outcome and the absence of information on LDL-C and HDL-C are major issues, in addition to some others. SR indicated that the Suita study, which used CAD as its outcome, is most suitable for risk calculation in this set of guidelines. We believe that the determination of the incidence rate of CAD instead of the overall risk assessment has enabled a clearer demonstration of the importance of each risk.

3. Addition of High-Risk Conditions

In view of the plan to compile an extensive list of risks for atherosclerosis, we included hyperuricemia and sleep apnea syndrome (SAS) as conditions to be considered. Although these conditions may contribute to atherosclerotic lesions to different extents, it is necessary to consider them from the perspective of comprehensive management.

4. Stricter LDL-C Control in High-Risk Conditions for Secondary Prevention

For the secondary prevention of high-risk conditions, such as familial hypercholesterolemia (FH) and acute coronary syndrome (ACS), we proposed an even stricter LDL-C control level than the current LDL-C control level of <100 mg/dL.

5. Elaborating on FH

In conjunction with the launch of new drugs, the addition of pediatric FH as an indication for statins, and so on, we have provided a detailed description of the diagnosis and treatment of FH. To facilitate easy comprehension, we have used a flow chart for describing the treatment methods.

6. Evidence Levels and Recommendation Levels

Similar to the previous guidelines, we have included statements at the beginning of each section. The evidence levels and recommendation levels have also been provided (**Tables below**).

The evidence levels are separately presented as evidence from therapeutic interventions and that from epidemiological studies. The evidence in Japan was regarded as the core of the evidence levels; however, please note that important data from various other countries may have been used wherever the data from Japan was insufficient.

Classification of Evidence Levels in Relation to Treatment and Diagnosis

1+	High-quality RCT[*] and their MA/SR
1	Other RCT[*] and their MA/SR
2	Prospective cohort studies, their MA/SR, and (pre-determined) RCT sub-analysis
3	Non-randomized comparative studies, before–after comparative studies, and retrospective cohort studies, case–control studies, their MA/SR, and RCT post hoc sub-analysis
4	Cross-sectional studies and case series

RCT: Randomized controlled trial, MA: Meta-analysis, SR: Systematic review

[*]A high-quality RCT is defined as a study that (1) involves a large number of subjects (high statistical power), (2) is double-blinded and independently assessed, (3) has a high follow-up rate (low drop-out rate) and few of protocol deviations, (4) includes a clear method for random allocation, etc.

Classification of Evidence Levels of Epidemiological Studies

E-Ia:	Meta-analysis of cohort studies
E-Ib:	Cohort studies
E-II:	Case-control studies and cross-sectional studies
E-III:	Descriptive studies (case series)

Recommendation Levels

A	Strong recommendation
B	Weak recommendation

Recommendations made according to consensus are indicated by the word "consensus."

Conflict of Interest

In accordance with the "COI Management Guidelines for Clinical Research" established by the Japan Association of Medical Sciences' COI committee, a conflict of interest (COI) statement has been obtained from each member of the committee involved in drafting the Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. The names of the enterprises disclosed in the COI statement are provided below. The applicable period is January 01, 2013, to December 31, 2015.

Amgen Astellas BioPharma K.K., Astellas Pharma Inc., AstraZeneca plc, Abbott Japan Co., Ltd., Izumisano city, Eisai Co., Ltd., Aegerion Pharmaceuticals, Inc., MSD K.K., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Omron Healthcare Co., Ltd., Curves Japan Co., Ltd., Kaizuka city, Kaneka Medix Corp., Kissei Pharmaceutical Co., Ltd. Kyowa Hakko Kirin Co., Ltd., Kyowa Medex Co., Ltd., Kirin Company, Limited, Quintiles Transnational Japan, GlaxoSmithKline K.K., Kowa Company, Ltd., Kowa Pharmaceutical Co., Ltd., Signpost Corporation, Sanofi K.K., Sanwa Chemistry Co., Ltd, Sanwa Kagaku Kenkyusho Co., Ltd., JCR Pharmaceuicals Co., Ltd., Shionogi & Co., Ltd. Skylight Biotech, Inc. Zuyou Co., Ltd., Daiichi Sankyo Company, Limited., Taisho Pharmaceutical Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Takeda Pharmaceutical Company Limited., Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co., Ltd., Teijin Home Healthcare Limited., Teijin Pharma Limited., Terumo Corporation, Tomiyama Scientific Industry Co., Ltd., Eli Lilly Japan K.K., Japan Blood Product Organization, Nippon Boehringer Ingelheim Co ., Ltd., Medtronic Japan Co., Ltd., Novartis Pharma K.K., Novo Nordisk Pharma Ltd., Bayer Yakuhin, Ltd., Biogen Idec, Inc., PPD Japan, K.K., Lake Biwa Consortium of Health and Welfare, Pfizer Japan Inc., Philips Respironics GK, Fukuda Denshi Co., Ltd. Bristol-Myers Squibb Company, Boston Scientific Corporation Japan, Maruha Nichiro Corporation, Meiji Seika Pharma Co., Ltd., Medical Review Co., Ltd., Merck & Co., Mochida Pharmaceutical Co., Ltd., Rinku General Medical Center, ResMed Inc.

Chapter 1. Summary of the Guidelines

1. Clinical Diagnosis of Atherosclerosis

To prevent ASCVD, it is essential to identify the presence of atherosclerotic lesions and understand their severity before the clinical symptoms appear. The risk factors need to be managed and treated, with consideration for the prevention of progression and regression of such lesions. Therefore, it is necessary to diagnose the extent to which atherosclerosis has progressed.

Angiography, intravascular ultrasound, and invasive diagnostic methods involving a vascular endoscope are occasionally used for diagnosis in patients who present symptoms and for the secondary prevention of ASCVD. Conversely, non-invasive methods are mainly used for assessing atherosclerosis for the primary prevention of ASCVD in patients who do not present with any symptoms. These non-invasive methods of assessment are generally classified into either morphological examinations [ultrasound, multi-detector computed tomography (MDCT), and magnetic resonance imaging/magnetic resonance angiography (MRI/MRA)] or vascular function tests [ankle–brachial index (ABI), brachial–ankle pulse wave velocity (baPWV), cardio–ankle vascular index (CAVI), and flow-mediated vasodilation (FMD)]. We anticipate that carotid intima–media thickness (IMT)/plaque, ABI, baPWV, CAVI, and FMD will be useful means for predicting the future risks of ASCVD. In addition, MDCT is a simple and highly specific examination method, which can easily detect coronary lesions. Each patient should be assessed using one or a combination of methods as applicable to his or her condition.

2. Comprehensive Risk Assessment and Management

1) Risk Assessment and Management

Assessing each risk factor for atherosclerosis and managing the factors that can be resolved through interventions are important for preventing ASCVD. Evidence from numerous epidemiological studies has revealed many risk factors for atherosclerosis. They include dyslipidemia, smoking, hypertension, diabetes, chronic kidney disease (CKD), aging, male sex, family history of CAD, history of CAD, non-cardiogenic cerebral infarction, peripheral artery disease (PAD), abdominal aortic aneurysm (AAA), hyperuricemia, and SAS as well as metabolic syndromes that are caused by the accumulation of visceral fats and insulin resistance. Led by The Japanese Society of Internal Medicine, 11 scientific societies and The Japanese Association of Medical Science/Japan Medical Association published the "Comprehensive Risk Management Chart for the Prevention of Cerebro- and Cardiovascular Diseases" in 2015 as a comprehensive set of guidelines for the prevention of ASCVD. The methods of assessment and management were thoroughly explained in six steps in the guidelines, which covered topics from screening (based on the rationale behind the chart) to drug therapy.

2) Diagnostic Criteria and Management Standards for Dyslipidemia

The incidence of CAD is high when the LDL-C or triglyceride (TG) levels are high or when the HDL-C level is low. The diagnostic criteria for dyslipidemia are established in this set of guidelines (Table 1) with regard to preventive screening for ASCVD.

When employing this set of diagnostic criteria, the basis is to measure the total cholesterol (TC), TG, and HDL-C levels using blood collected in a fasting state and subsequently calculating the LDL-C using the Friedewald formula (LDL-C = TC − HDL-C − TG/5). However, this formula cannot be applied if the TG level is 400 mg/dL and greater, or when using postprandial blood. In such cases, non-HDL-C (= TC − HDL-C) shall be used. The accuracy of the LDL-C direct measurement method has improved over time, and it can therefore be used in place of the Friedewald formula.

In the 2012 version of the guidelines, for primary prevention, patients are stratified based on the absolute risk, and we had established management standards for dyslipidemia, which catered to the stratification. We followed the same plan while formulating the current guidelines and searched for methods of assessment according to absolute risk. Specifically, we formulated the CQ, "Does an assessment method that predicts the incidence of or death due to ASCVD in the Japanese exist?", and performed an SR. Although nine studies were selected by SR, we eventually chose the Suita study because (1) LDL-C and HDL-C were both included as predictive indicators, (2) the LDL-C levels were categorized in detail, (3) stroke was not included as an endpoint, and (4) the outcome was set as event onset instead of death. We performed the stratification based on the Suita score (Fig. 1). As shown in Fig. 2, due to the complexity of calculating

Table 1. Diagnostic Criteria for Dyslipidemia (Blood Collected from Patients in Fasting State)*

LDL-C	≥ 140 mg/dL	Hyper-LDL cholesterolemia
	120–139 mg/dL	Borderline hyper-LDL cholesterolemia**
HDL-C	<40 mg/dL	Hypo-HDL cholesterolemia
TG	≥ 150 mg/dL	Hypertriglyceridemia
Non-HDL cholesterol	≥ 170 mg/dL	Hyper-non-HDL cholesterolemia
	150–169 mg/dL	Borderline hyper-non-HDL cholesterolemia**

* "Fasting state" is defined as fasting for at least 10 h. However, consumption of liquids with no calories, such as water and tea without milk or sugar, is allowed.
** If screening shows borderline hyper-LDL cholesterolemia and borderline hyper-non-HDL cholesterolemia, investigate whether a high-risk condition is present and consider the need for treatment.
•LDL-C is derived using the Friedewald formula (TC−HDL-C−TG/5) or through a direct method.
•Non-HDL-C (TC−HDL-C) or a direct method is used if the TG level is 400 mg/dL and greater or if postprandial blood is collected. However, if hypertriglyceridemia is absent during screening, the risk shall be assessed with the consideration that the difference from LDL-C can possibly turn out to be smaller than +30 mg/dL.
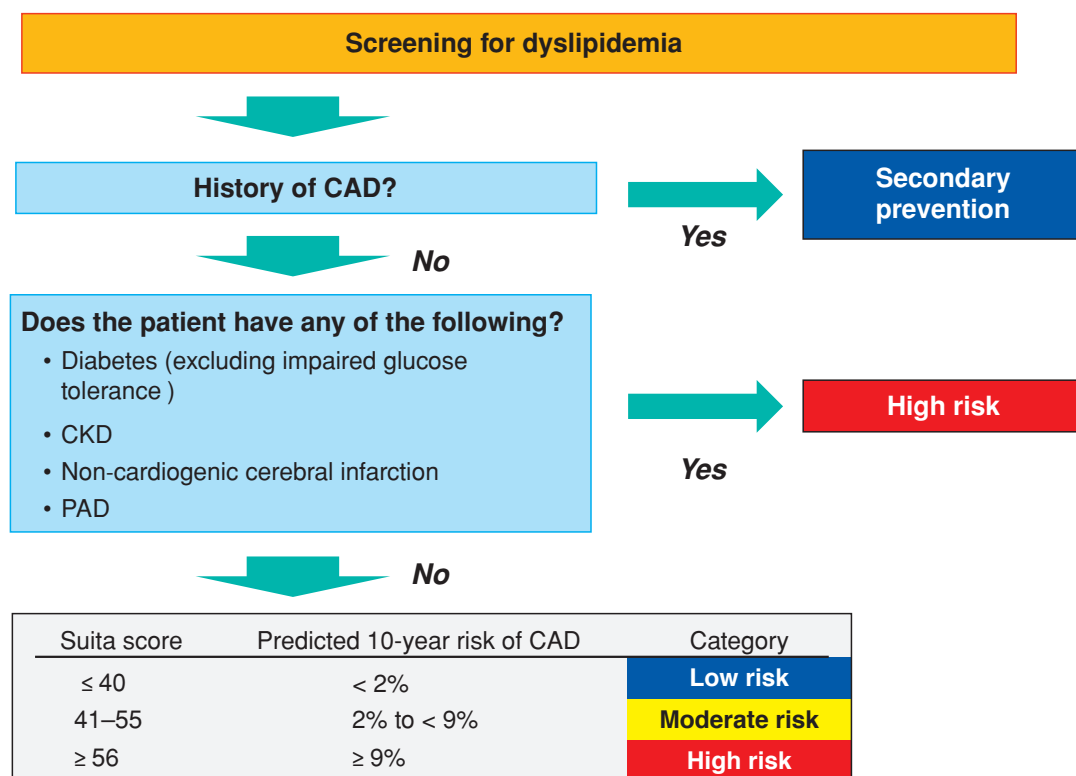
Fig. 1. Flowchart Using the Suita Score to Establish LDL-C Management Targets, from the Perspective of CAD Prevention

•The Suita score is calculated based on **Fig. 2**.
•Note: For patients diagnosed with FH and those diagnosed with familial type Ⅲ hyperlipidemia, do not use this chart and refer to Chapter 5 (Familial Hypercholesterolemia) and Chapter 6 (Other Types of Primary Dyslipidemias), respectively.

	Range	Score
1. Age	35-44	30
	45-54	38
	55-64	45
	65-69	51
	70-	53
2. Gender	Men	0
	Women	-7
3. Smoking*	Yes	5
4. Blood pressure**	SBP <120 and DBP <80	-7
	SBP =120-139 and/or DBP=80-89	0
	SBP =140-159 and/or DBP=90-99	4
	SBP ≥ 160 and/or DBP ≥ 100	6
5. HDL-C	<40	0
	40-59	-5
	≥ 60	-6
6. LDL-C	<100	0
	100-139	5
	140-159	7
	160-179	10
	≥ 180	11
7. Impaired glucose tolerance	Yes	5
8. Family history of premature CAD	Yes	5

Total score of 1-8	Probability of CAD within the next 10 years (%)	Probability range (%)		Median of probability (%)	Category
		Minimum	Maximum		
≤ 35	<1		1.0	0.5	Low risk
36-40	1	1.3	1.9	1.6	Low risk
41-45	2	2.1	3.1	2.6	Moderate risk
46-50	3	3.4	5.0	4.2	Moderate risk
51-55	5	5.0	8.1	6.6	Moderate risk
56-60	9	8.9	13.0	11.0	High risk
61-65	14	14.0	20.6	17.3	High risk
66-70	22	22.4	26.7	24.6	High risk
≥ 71	>28	28.1		≥ 28.1	High risk

Fig. 2. Model for Predicting CAD Onset Using the Suita Score

*Ex-smokers should be regarded as nonsmokers. Note that the risk of CAD decreases by almost half 1 year after smoking cessation and drops to the same level as in nonsmokers after 15 years of smoking cessation.
**The current values are used even if the patient is currently undergoing treatment or not. However, counsel the patient while keeping in mind that patients undergoing treatment for hypertension have a higher risk of CAD than those who have the same blood pressure value without undergoing treatment.

Screening for dyslipidemia (LDL-C ≥ 120 mg/dL)

History of CAD? → *Yes* → **Secondary prevention**

No

Does the patient have any of the following?
• Diabetes (excluding impaired glucose tolerance)
• CKD
• Non-cardiogenic cerebral infarction
• PAD

Yes → **High risk**

No

Count the number of the following risk factors that the patient has
(1) Smoking
(2) Hypertension
(3) Low-HDL cholesterolemia
(4) Abnormal glucose tolerance
(5) Family history of premature CAD (first-degree male family members aged <55 years and females aged <65 years at the time of disease onset; note: count as 0 if the family history is unknown)

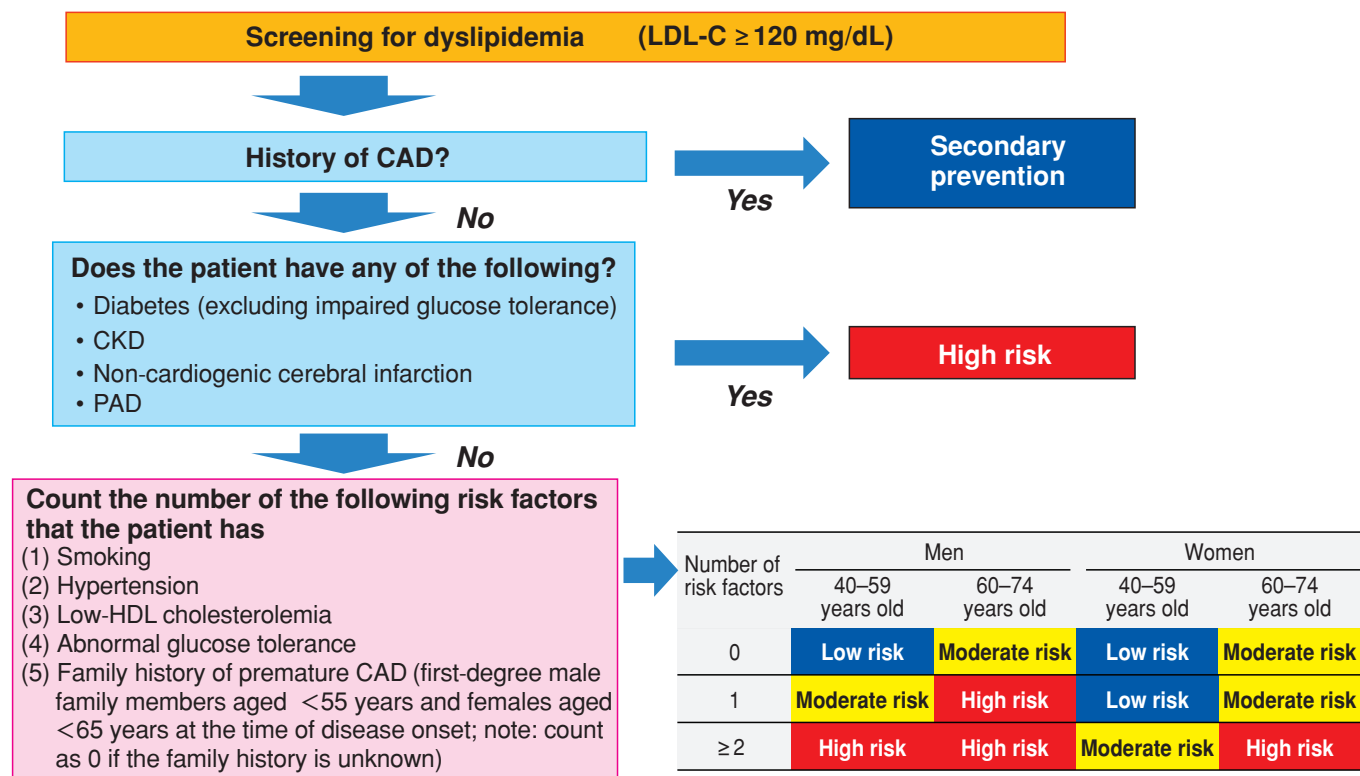| Number of risk factors	Men		Women	
	40–59 years old	60–74 years old	40–59 years old	60–74 years old
0	Low risk	Moderate risk	Low risk	Moderate risk
1	Moderate risk	High risk	Low risk	Moderate risk
≥2	High risk	High risk	Moderate risk	High risk

Fig. 3. Flowchart for Establishing LDL-C Management Targets from the Perspective of CAD Prevention (Simplified Version Using Risk Factors)

Table 2. Lipid Management Targets for Patients with Different Risk Category

Therapeutic principle	Management category	Lipid management target (mg/dL)			
		LDL-C	Non-HDL-C	TG	HDL-C
Primary prevention Drug therapy should be considered after lifestyle modification	**Low risk**	<160	<190		
	Moderate risk	<140	<170		
	High risk	<120	<150	<150	≥ 40
Secondary prevention Drug therapy should be considered together with lifestyle modification	History of CAD	<100 (<70)*	<130 (<100)*		

* For patients who are also suffering from high-risk conditions, such as FH, ACS, and diabetes complicated by other high-risk conditions shown in **Table 3b**, stricter LDL-C control should be considered, with a level of <70 mg/dL as the target.
- Although non-drug therapy is used as a standard means for achieving the management target in primary prevention, drug therapy should be considered for patients with low risk if the LDL-C level is ≥ 180 mg/dL. The possibility of FH should also be considered (refer to Chapter 5).
- Achieving the LDL-C management target should be the first goal, and reaching the non-HDL-C management target should be the next goal after the first goal has been achieved. Managing the TG and HDL-C levels is important during this process.
- These values are challenging goals by utmost effort; a 20%–30% reduction in LDL-C levels for primary prevention (low or moderate risk) and a decrease of ≥ 50% for secondary prevention are also possible targets.
- For elderly patients (aged ≥ 75 years), refer to Chapter 7.

Table 3. Patient Conditions that Require Stricter Management in Secondary Prevention

a	Familial hypercholesterolemia (FH) Acute coronary syndrome (ACS) Diabetes mellitus (DM)
b	Noncardiogenic cerebral infarction Peripheral artery disease (PAD) Chronic kidney disease (CKD) Metabolic syndrome Overlap of major risk factors Smoking

the Suita score, we created an application for categorization so that this method can be easily applied in our daily medical practice (http://www.j-athero.org/publications/gl2017_app.html). In addition, we created a chart describing the stratification by gender, age, and number of risk factors (**Fig. 3**). Categorization based on **Fig. 2** and that based on **Fig. 1** have been verified through simulation and found to be almost consistent.

The lipid management targets that catered to this categorization are shown in **Table 2**. For primary prevention, the administration of drug therapy should generally be considered after lifestyle modifications have been made for a certain period and when the effects have been ascertained. The management targets are challenging goals by utmost effort for patients with low or moderate risk. A 20-30% decrease in LDL-C also indicates a reduction in the risk of CAD by 30%; hence, we decided that a reduction of 20-30% in LDL-C levels can be considered another target for

such patients. For secondary prevention, it is advisable to initiate drug therapy, with the management targets shown in **Table 2** as the goal, along with lifestyle modifications.

3) Lifestyle Modification

As previously mentioned, lifestyle modification is required for both primary prevention and secondary prevention patients. The cessation of smoking is important for preventing atherosclerosis, and controlling the energy intake to reduce obesity would lead to improvements not just in obesity but also in other risk factors. Although a limited number of studies have followed the onset of ASCVD as an endpoint, diet therapy based mainly on the Japanese dietary pattern contributes to decrease risk factors, including improvement of lipid metabolism. In terms of exercise therapy, epidemiological studies have shown that the amount of exercise and level of physical fitness are negatively correlated with CVD, indicating the importance of appropriate exercise.

4) Drug Therapy

Given that statin therapy has been shown to be beneficial for prevention of ASCVD not just overseas but also in Japan, we believe that it is appropriate to consider statins as the first medication of choice for controlling LDL-C levels. In high-risk primary prevention patients, the management target for LDL-C should be <120 mg/dL. On the other hand, for secondary prevention, aggressive treatment with the aim of lowering LDL-C level at least <100 mg/dL should be initiated immediately after the disease onset; fur-

Table 4. Classification of Medications Used to Treat Dyslipidemia According to Their Efficacy

Category	LDL-C	NonHDL-C	TG	HDL-C	Major drug name
Statin	↓↓～ ↓↓↓	↓↓～ ↓↓↓	↓	−～↑	Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, Pitavastatin, Rosuvastatin
Intestinal cholesterol transporter inhibitor (Cholesterol absorption inhibitor)	↓↓	↓↓	↓	↑	Ezetimibe
Anion exchange resin	↓↓	↓↓	↑	↑	Colestimide, Cholestyramine
Probucol	↓	↓	−	↓↓	Probucol
PCSK9 inhibitor	↓↓↓↓	↓↓↓↓	↓～↓↓	−～↑	Evolocumab, Alirocumab
MTP inhibitor*	↓↓↓	↓↓↓	↓↓↓	↓	Lomitapide
Fibrate	↑～↓	↓	↓↓↓	↑↑	Bezafibrate, Fenofibrate, Clinofibrate, Clofibrate
Selective peroxisome proliferator-activated receptor α modulator (SPPARMα)	↑～↓	↓	↓↓↓	↑↑	Pemafibrate
Nicotinic acid derivative	↓	↓	↓↓	↑	Niceritrol, Nicomol, Tocopheryl Nicotinate
N-3 polyunsaturated fatty acid	−	−	↓	−	Ethyl icosapentate, Omega-3-acid ethyl ester

*Applicable only to patients with homozygous FH
↓↓↓↓：≤ −50%　↓↓↓：−50～30%　↓↓：−20～30%　↓：−10～−20%
↑：10～20%　↑↑：20～30%　−：−10～10%

thermore, an even lower target value should be considered when patients are complicated with other high risk clinical conditions. The application, effectiveness, and safety of oral hypolipidemic agents other than statins have already been validated; thus, before prescribing them, clinicians should always pay attention to the indications as well as clinical status of contraindication and careful administration. Ezetimibe, PCSK9 inhibitors, and EPA are the medications that have been proven to be effective for the prevention of ASCVD when used in combination with statins. When prescribing hypolipidemic agents, efforts should be made to improve adherence for medication because good adherence has proven to lead to better efficacy for prevention of ASCVD.

The effects on plasma lipids' levels of each agent are listed in **Table 4**. Taking into account of the importance for prevention of ASCVD as well as the attainability of the target level for each lipid through drug therapy, we set the order of intervention starting with LDL-C, followed by non HDL-C and TG. In the main chapter of "Drug Therapy", we also referred to the significance or meaning of management for hypertriglyceridemia.

5) Major High-Risk Conditions

A history of CAD, diabetes, and cerebrovascular diseases are observed in patients requiring more active treatment due to unsatisfactory disease management, the presence of complications, and overlapping risk factors. Therefore, we created a special subsection in this set of guidelines to provide detailed explanations on cases requiring enhanced management.

3. Primary Dyslipidemias

FH is a hereditary disease, and its heterozygote exists in 1 of 200-500 individuals. FH poses a high risk of CAD and is frequently encountered by general practitioners. Because the rate of diagnosis in Japan is still low, there is a need to accurately diagnose and treat this condition by assessing the family history, tendon xanthoma, and LDL-C levels, which are part of the diagnostic criteria for FH. In this set of guidelines, we will discuss the guiding principles for treating FH during pregnancy and childbirth and in children. In addition to the treatment methods involving LDL apheresis, we have included explanations on the types of primary dyslipidemia other than FH. Patients who are suspected to be suffering from any of these diseases should be referred to specialists for further assessment.

4. The Elderly, Women, and Children

In the elderly persons 65-74 years of age, a high LDL-C level is an important risk factor for CAD, and the effect of statin therapy on CAD prevention and primary prevention of non-cardiogenic cerebral infarction is promising. Meanwhile, because the effect of statin therapy on primary prevention in the elderly persons ≥ 75 years of age is not evident, the objective is to manage cases individually, according to the decisions of the attending physician. The treatment for women is basically lifestyle modification, but for secondary prevention patients and patients with FH or at a high risk of CAD, drug therapy shall be considered. It is also important for children to maintain the intake of proper meals and continue with exercise therapy. Similar to adults, the management of secondary dyslipidemia in children should focus on treating the primary disease. It should be kept in mind that the diagnostic criteria for pediatric cases of dyslipidemia, including FH, are different from those for adult cases.

Chapter 2. Clinical Diagnosis of ASCVD

From the perspective of preventing ASCVD, it is important to identify the presence of arteriosclerosis and atherosclerotic lesions and understand its severity before clinical symptoms appear. The management and treatment of risk factors with the prevention of progression or even regression taken into consideration is essential. Invasive diagnostic methods, such as angiography, are necessary in the secondary prevention of ASCVD. However, noninvasive methods are mainly used in primary prevention to assess arteriosclerosis and atherosclerosis. In this section, we will be discussing the methods for assessing arteriosclerosis and atherosclerosis.

1. Morphological Examinations

1) Ultrasonography

Ultrasonography is a widely used noninvasive imaging method. Lesions in the peripheral arteries, such as the carotid arteries, and arteries in the lower extremities, can be assessed using an ultrasound machine that comes with a high-frequency linear probe of ≥ 7 MHz.

The Japan Society of Ultrasonics in Medicine and The Japan Academy of Neurosonology recommend using ultrasonography as a standard method to measure the intima–media thickness (IMT), plaques (localized protruding lesions of ≥ 1.1 mm), stenosis and such for assessing the degree of arteriosclerosis, particularly in the carotid arteries[1-3]. IMT is assessed as the thickness adjusted by age[4]. It is also used to reflect the degree of systemic arteriosclerosis or as an alternative assessment factor for predicting the risk of co-existence or onset of ASCVD (e.g., CAD, PAD, cerebrovascular diseases, etc.)[5-8]. Although the presence of plaque has a stronger significance in disease prediction compared to the IMT, a high IMT value in cases where plaques are not detected is the underlying pathogenetic mechanism for the development of plaques. With reference to the Mannheim consensus, it is also necessary to assess the properties of plaques that have a maximum IMT of >1.5 mm[3, 9], and assessment is especially important for some plaques that can possibly lead to cerebral embolism (e.g., echolucent plaques, ulcers, mobile lesions, and lipid-rich plaques). If short-axis scanning shows a buildup of plaque in ≥ 50% of the vascular lumen, then the degree of stenosis needs to be assessed. When the stenosis is significant (i.e., ≥ 70%), in addition to active medical treatment, carotid endarterectomy or carotid artery stenting should also be considered.

Performing the assessment to determine the properties of the plaques and the percentage of stenosis in the same way as it is done in the carotid arteries is likewise important for arteries in the lower extremities[10]. Furthermore, confirming the presence of collateral circulation, the patterns of blood flow waveforms and the below-knee transit time of vessel flow (TVF) would make it possible to estimate where the stenotic portions are[11].

Ultrasonography is also a useful method for diagnosing atherosclerotic renal artery stenosis in the renal arteries[12, 13].

2) Computed Tomography (CT)

CT is a method of examination that can diagnose arteriosclerosis in a short amount of time. It can also determine whether aneurysm is present by measuring the size of the artery. Furthermore, as the degree of calcification, fats, and fiber content can be estimated to some extent based on the CT number, it

is an excellent means for confirming the presence of calcified lesions in the aorta and peripheral arteries. Multidetector CT (MDCT) offers superior imaging speed and spatial resolution, and by injecting a contrast medium through the peripheral veins, it enables the visualization of diseases in all the arteries and coronary arteries. It is commonly used to screen for CAD. It has excellent specificity[14-17], and organic coronary stenosis can almost be ruled out if no abnormalities are detected using this technique.

3) Magnetic Resonance Imaging/Angiography (MRI/MRA)

MRI is especially useful for detecting lesions in the brain, which include ischemic changes and cerebral infarction. MRA provides an excellent means for visualizing stenosis and obstructive lesions in the intracranial arteries, carotid arteries, aorta, renal arteries and other blood vessels. Nowadays, non-contrast enhanced MRA is sometimes used in place of angiography. The properties of the plaques can also be assessed using MRI plaque imaging.

4) Catheterization

To date, angiography using a catheter remains as one of the main methods for diagnosing arterial stenosis despite being an invasive examination. Stenotic portions are assessed on the basis of the percentage of stenosis, which is calculated using the luminal diameter of normal-appearing portions and stenotic portions. However, limitations such as eccentric plaques and compensatory remodeling hinder the accurate determination of plaque volume. Meanwhile, intravascular ultrasound (IVUS), optical coherence tomography (OCT) and the vascular endoscope are some other methods that provide an excellent assessment of the plaque volume as well as the properties of the plaques.

2. Vascular Function Tests[18]

1) Ankle–Brachial Index (ABI) and Toe–Brachial Index (TBI)

ABI is the ratio of the blood pressure (BP) in the brachial artery to the BP at the ankle joint. This ratio is an indicator of narrowing of the central major arteries from the ankle joint or the presence of obstructive lesions and the degree of compensation by collateral circulation. Methods of measurement include the Doppler technique and the oscilloscope. The Korotkoff sounds should be verified when measuring the BP in the extremities using a sphygmomanometer and a stethoscope. On the other hand, the oscillometric method is employed when performing automated

measurement using an automated sphygmomanometer or specialized equipment. Although the correlation between both methods is generally good, the precision of the oscillometric method is low when used in cases of critical limb ischemia. If the ABI is ≤ 0.9, then the presence of obstructive lesions in the lower extremities should be suspected[19, 20]. TBI is the ratio of the BP in the brachial artery to the blood pressure at the toes. Measuring both the ABI and TBI allows us to gauge the peripheral artery obstructive lesions distal than ankle joints. The reference TBI value is ≥ 0.7, and the presence of obstructive lesions in the arteries of the lower extremities should be suspected if the resulting value is ≤ 0.6. It is necessary to note that diabetes patients and patients undergoing dialysis are prone to calcification in the walls of arteries below the knee, and hence, there are cases in which the ABI cannot be accurately measured.

2) Brachial-Ankle Pulse-Wave Velocity (baPWV)

The pulse-wave velocity (PWV) produced by cardiac output reflects the stiffness of arteries[21]. It can be easily determined by measuring the pulse waves in the extremities using a specialized device. However, it is necessary to note that the PWV is an indicator of arterial stiffness and does not necessarily reflect atherosclerosis. The PWV is the speed at which the aortic vibration (i.e., pulse wave) generated by the beating of the heart is transmitted to the peripheral artery. It is proportionate to the stiffness and thickness of the arterial walls. The carotid-femoral PWV (cfPWV) and baPWV are the two forms of PWV measurement. baPWV is currently being used in clinical practice in Japan. For baPWV, influences during BP measurement must be taken note of.

Aging[22], hypertension[23], diabetes[24], and pulse rate[22] are CVD risk factors that have been reported to cause increased baPWV, and they show a good correlation with the Framingham Risk Score. A baPWV of 1,400 cm/sec corresponds to the moderate risk level in the Framingham Risk Score.

3) Stiffness Parameter β and Cardio-ankle Vascular Index (CAVI)

Stiffness parameter β is an index that represents the localized intrinsic stiffness of the arterial walls. Arterial elasticity is hardly affected by BP, and stiffness parameter β has been designed as an index of arterial elasticity that is corrected using BP during measurement. It is calculated using the formula ln (Ps/Pd)/[(Ds-Dd)/Dd], with BP and changes in carotid artery caliber as the variables[25]. Additionally, it has been reported that stiffness parameter β is correlated with

carotid atherosclerosis[26, 27].

The CAVI is an index that represents the elasticity of the entire artery, from its aortic root to the ankle, and it is derived by applying the concept of the stiffness parameter β to the long arteries. A feature of CAVI is its nondependence on BP during measurement[28]. The CAVI increases with age[28], and patients with cerebral infarction, CVD[29], chronic kidney disease (CKD), and vasculitis have high CAVI values. It is also increased in patients who suffer from hypertension, diabetes, metabolic syndromes, sleep apnea syndrome (SAS), smoking, stress caused by disasters, etc., but at the same time, it has been reported that the CAVI improves with treatment of these contributing factors[25]. Prospective surveys on cardiovascular events have revealed that a high CAVI value is associated with a high frequency of cardiovascular events[30].

In addition to these, the central BP is also an index that reflects vascular function.

4) Vascular Endothelial Function

Reactive hyperemia following a 5-minute avascularization in the forearm and certain drugs such as acetylcholine cause a vascular endothelium-dependent increase in blood flow, and vascular endothelial function is assessed by measuring the resulting increase in arterial diameter and blood flow. The first method of assessment is strain-gauge plethysmography, which measures the changes in circumference of the extremities as the arterial pulse is produced. The second method is flow-mediated dilatation (FMD), in which the changes in diameter of arteries in the upper arm are measured by ultrasonography. FMD is a test that assesses the extent of brachial artery dilation caused by reactive hyperemia after 5 minutes of forearm ischemia. The formula used for calculation is FMD (%) = (diameter of the most dilated blood vessel - resting blood vessel diameter)/resting blood vessel diameter × 100. The normal FMD value is ≥ 6-7%, and a malfunction in the endothelial cells results in poor production of nitric oxide (NO), which in turn lowers the amount of FMD. FMD starts decreasing from early stages of arteriosclerosis[31, 32], and it is therefore useful for the initial assessment of ASCVD.

3. Predicting the Risk for ASCVD by Assessing Arterial Walls

It has been reported that IMT/plaque of carotid artery, ABI, baPWV, CAVI, FMD, and such are independent predictive factors of future risk for ASCVD. However, reports of other countries have revealed that adding the result of IMT measurement does not increase the ability of risk prediction by the Framingham Risk Score[33]. Although there are reports on the significance of noninvasive arterial wall assessment in Japan[34], there is still a lack of sufficient evidence. Recent reports by Japan have shown that[35] when data from a meta-analysis that integrated personal-level data of 14,673 Japanese was used, the addition of baPWV to the classic risk factors increased the ability to predict the risk for CVD. These reports have particularly demonstrated the usefulness of baPWV in risk prediction for low-risk groups. In addition, it is suggested that a baPWV >1,800 cm/s is a risk that is equivalent to the high-risk conditions[18, 21]. However, baPWV that reflects a high risk may possibly be different in the target group, and further accumulation of data would be advantageous. To indicate the abnormal findings of these indices except ABI in the risk categories in this set of guidelines, which will lead to stricter management, more evidence needs to be built.

Chapter 3. Comprehensive Risk Assessment

1. Risk Factor Assessment
1) Dyslipidemia

CQ1. Is LDL-C a predictor of the ASCVD incidence and mortality in the Japanese people?

- **Elevated LDL-C predicts the CAD incidence and mortality in the future. Among the types of stroke, LDL-C has been shown to be positively related to cerebral infarction and negatively related to hemorrhagic stroke, but in regard to the Japanese, the evidence cannot be considered adequate. (Evidence level: E-1b)**

Many epidemiological studies have been conducted in Europe and America, including the Framingham Study in the US. Similar to the results of these studies, the increase in hazard ratio for the CAD incidence and mortality following an elevation in LDL-C has been validated in cohort studies involving the Japanese[36-40]. It was shown in the Circulatory Risk in Communities Study (CIRCS) that in comparison with the LDL-C <80 mg/dL group, the risk was increased by 1.4 times in the 80-99 mg/dL group, 1.7 times in the 100-119 mg/dL group, 2.2 times in the 120-139 mg/dL group, and 2.8 times in the ≥ 140 mg/dL group[37]. The results have therefore made it clear that the risk of CAD incidence also increases by two times or more in the Japanese if the LDL-C level is ≥ 140 mg/dL. As for deaths from CAD, gender differences were observed in regard to risk, and a significant increase was seen only in men[38].

An elevated LDL-C level also increased the risk for cerebral thrombosis (except lacunar infarction) among the subtypes of ischemic stroke[36]. However, on the contrary, it has been reported that there was a negative relationship between hemorrhagic stroke (primarily intracerebral hemorrhage) and a decrease in hazard ratio in the groups with high LDL-C levels[40].

Interventions for hypercholesterolemia, including lifestyle modifications, have been clearly shown to significantly suppress CAD events according to the Western studies. Large-scale clinical studies conducted in Japan have also reported similar results[41-44], in which it was evident that the occurrence of CAD in the Japanese subjects decreased as a result of treating the hyper-LDL cholesterolemia. Furthermore, it has not been observed in these studies that decreasing the LDL-C level adds to the risk for intracerebral hemorrhage.

Overlapping risk factors also increase the incidence and mortality rates of CAD in the Japanese[45, 46]. It has been shown that even with the same degree of hypertension, the addition of hyper-LDL cholesterolemia contributes to an increased risk for cardiovascular diseases[47].

Considering all the points mentioned above, in this set of guidelines, we have set LDL-C ≥ 140 mg/dL as the screening reference value for the Japanese. Furthermore, we have set a range of 120-139 mg/dL as the borderline level for which the effects of overlapping risk factors should be carefully assessed.

CQ2. Is total cholesterol (TC) a predictor of the ASCVD incidence and mortality in the Japanese people?

- **Elevated TC predicts the CAD incidence and mortality in the future. Regarding stroke, it has been shown that TC is positively related to cerebral infarction and negatively related to hemorrhagic stroke, a result that many studies have in common. TC therefore predicts the occurrence of and death from stroke. (Evidence level: E-1a)**

Similar to the above mention about LDL-C, a number of cohort studies conducted in Japan have reported an increase in the incidence and mortality rates of CAD following an elevation in TC level[48-54]. A 24-year follow-up in NIPPON DATA80 showed that the hazard ratio for CAD death was 1.55 times higher in the TC ≥ 220 mg/dL group than in the TC <220 mg/dL group, and the population attributable fraction (PAF) was 18.2%[54]. When the TC level was ≥ 240 mg/dL, even though the hazard ratio further increased to 1.79 times, the PAF dropped to 11.9%. The association between TC and the incidence/mortality rate of CAD is almost linear, but a statistically significant increase in risk with TC levels around 220 mg/dL has been observed in many studies. Although a relationship between TC and risk of CAD death was seen in both the men and women, some reports have stated that this relation is attenuated in elderly individuals who are ≥ 65 years old[55].

Regarding stroke, the association between TC and hazard ratio differed because of cerebral infarction and hemorrhagic stroke (primarily intracerebral hemorrhage). For hemorrhagic strokes, in contrast with the increase in risk of occurrence at low TC levels[55-57], an increased risk because of high TC levels was observed in ischemic stroke, as with in CAD[58, 59].

The synergy between BP and TC in regard to CAD death was demonstrated in the EPOCH-JAPAN study[60]. When a systolic BP of ≥ 160 mmHg overlaps with TC levels of ≥ 220 mg/dL, the adjusted hazard ratio for CAD death increased to 4.4 times that of the group with BPs <120 mmHg and TC levels <180 mg/dL. On the other hand, there was a smaller number of deaths caused by intracerebral hemorrhage in the group with TC levels of ≥ 220 mg/dL even when the BP readings were within the normal range.

CQ3. Is non-HDL-C a predictor of the ASCVD incidence and mortality in the Japanese people?

- **Elevation of non-HDL-C predicts the CAD incidence and mortality in the future. But at the same time, there are reports stating that an association does not exist in regard to stroke.** **(Evidence level: E-1b)**

As non-HDL-C includes all arteriosclerosis-causing lipoproteins, such as remnant lipoproteins, there are views that claim its relatively superior ability in predicting the CAD incidence in comparison with LDL-C[61, 62]. The association between non-HDL-C and CAD has been reported in the results of many epidemiological surveys conducted in Japan[51, 63-70]. As with LDL-C, non-HDL-C was similarly associated with the occurrence of myocardial infarction (MI), and they both had the same ability to predict MI[64]. On the other hand, non-HDL-C surpasses TC in the ability to predict the occurrence of MI[51]. On the basis of analyses performed using data obtained from men, or both men and women, there have been reports stating that the risk of and death from CAD and MI increase when the non-HDL-C levels are approximately ≥ 140 mg/dL[67, 71, 72]. In all of these studies, the risk of onset and risk of death were evidently increased when non-HDL-C levels were ≥ 170-180 mg/dL or more, but there was no fixed trend observed in the women[51, 64, 71, 73].

Meanwhile, studies concerning the association between non-HDL-C and stroke have reported varying results. There are reports saying that the association is unclear[51, 67], and there are also those that revealed an increase in risk when non-HDL-C levels were low[70]. In reports of studies that reviewed the effect of hypertriglyceridemia on the ability of non-HDL-C to predict MI[65], an obvious increase in risk for MI was seen in the presence of hypertriglyceridemia (TG ≥ 150 mg/dL) and non-HDL-C levels of ≥ 190 mg/dL. Similar to the US, the non-HDL-C levels of Japanese individuals with dyslipidemia was shown to be + 30 mg/dL that of LDL-C[74, 75].

On the basis of the results above, we concluded that non-HDL-C is possibly a useful indicator for predicting the risk of CAD incidence and mortality. Therefore, in this set of guidelines, the screening reference value for non-HDL-C has been set at ≥ 170 mg/dL. Furthermore, we have set a range of 150-169 mg/dL as the borderline level for which the effects of overlapping risk factors should be carefully assessed.

CQ4. Is HDL-C a predictor of the ASCVD incidence and mortality in the Japanese people?

- **A decrease in HDL-C level predicts the CAD and ischemic stroke incidence and mortality in the future. (Evidence level: E-1b)**

A low HDL-C level is a risk for developing CAD and ischemic stroke. On the contrary, the risk decreases when HDL-C levels are high[39, 53, 76-79]. A 9.6-year observational period in NIPPON DATA90 showed that HDL-C was significantly inversely correlated with all deaths as well as stroke-related deaths[80]. It has been revealed in regional and occupational cohort studies that the risk for CAD increases when HDL-C levels are < 40 mg/dL[46, 53, 78, 79]. Likewise, in the J-LIT study that involved a cohort of simvastatin users, the relative risk was 1.3 times higher in the < 40 mg/dL group than in the 40-49 mg/dL group in primary prevention[81]. In addition, the relative risk was higher at 1.6 times in secondary prevention[82]. Studies conducted in 23 countries in Asia and Oceania, including Japan, have shown that a decreased HDL-C level alone also becomes a risk factor for CAD when both the LDL-C and TG levels are within the normal range, and this is especially so in Asia[83]. However, there have also been reports from large-scale cohort studies involving only the Japanese that low levels of HDL-C by itself does not constitute a risk for CAD[84].

Considering the above findings, we have defined a HDL-C level of < 40 mg/dL in these guidelines as the screening reference value for hypo-HDL cholesterolemia. Women generally have a higher HDL-C level than men[46, 80, 85]. However, there is still insufficient evidence on the association between the discrepancy in HDL-C levels because of gender differences and CAD in each gender[78]. Therefore, in these guidelines, we have set the reference value for women to be the same as men.

CQ5. Is triglyceride (TG) a predictor of the ASCVD incidence and mortality in the Japanese people?

- **An increase in TG level, whether fasting or nonfasting, predicts the CAD and ischemic stroke incidence and mortality in the future. (Evidence level: E-1b)**

There have been numerous reports on the association between a high TG level and the risk for CAD not just in Europe and the US[86], but also in Asia, Oceania[87] and even in Japan[46, 78, 88-91]. Despite a normal range of HDL-C, the association between TG and CAD was still observed in several of these studies[86-89]. Subsequent to the Framingham Study, hypertriglyceridemia is currently defined as a TG level of ≥ 150 mg/dL (fasting) in the US[92]. Although TG is traditionally tested with blood collected in a fasting state, some reports have stated that its ability to predict the risk for cardiovascular events is higher using blood collected in a nonfasting state[91]. It has been shown in epidemiological surveys in Japan that the occurrence of CAD increases when fasting TG levels of are ≥ 150 mg/dL[46, 90]. These surveys have also shown that a nonfasting TG level of ≥ 165 mg/dL adds to the risk for MI, exercise-induced angina, sudden death[88] or ischemic CVD[91]. Furthermore, there have been many reports on hypertriglyceridemia being a risk factor for ischemic stroke, though the association is weaker than that with CAD[46, 65, 87, 93-95].

Considering the above findings, hypertriglyceridemia has been defined as a TG level of ≥ 150 mg/dL in these guidelines. However, hypertriglyceridemia often comes with other important implications, such as an increase in the amount of remnant lipoproteins or small dense LDL and the co-existence of hypo-HDL cholesterolemia. It could also be a finding of metabolic syndrome, and hence, other factors accompanying an elevated TG level should also be thoroughly considered.

Diagnostic Criteria for Dyslipidemia

As mentioned in CQ1 to CQ5, the positive correlation between a higher incidence rate of CAD and high levels of LDL-C, TC, non-HDL-C and TG, or low levels of HDL-C, has been shown not just in epidemiological surveys conducted in Europe and the US but also in Japan. Among the different types of stroke, the association with cerebral infarction has been found to be almost similar to that with CAD. However, for hemorrhagic stroke (primarily intracerebral hemor-

rhage), the incidence and mortality rates are instead higher at low LDL-C and TC levels. At present, the absolute risk of CAD (incidence and mortality rate) in Japan is very much lower than that in the Western countries[96]. However, there have been reports and such revealing that the LDL-C and TC levels of the Japanese have been on the rise because of recent westernization of lifestyle habits. As a result of this change, the TC levels of the Japanese have already reached the levels in the US, or even higher[97]. These reports have also pointed out the increasing incidence rate of CAD in some regions in Japan[98, 99], and this is why the management of dyslipidemia is of importance. In these guidelines, we have therefore established the diagnostic criteria for dyslipidemia with a focus on preventing the development of CAD. The diagnostic criteria are shown in **Table 1**.

The sequence of diagnosis is to first measure the TC, TG and HDL-C levels in a fasting state in the morning and subsequently calculating the LDL-C level using the Friedewald formula (LDL-C = TC − HDL-C − TG/5). However, measurement using the direct method is also allowed. Even though problems with the accuracy of the direct method have been pointed out[100], there have recently been the discontinuation of sales and production, improvement and revision of standard pricing of reagents that were found to be mediocre over time. As a result of the improved performance of reagents, the validity of LDL-C measurement within daily clinical practice has been substantiated[101]. However, most of the studies providing evidence relating to the treatment of hyper-LDL cholesterolemia have used the Friedewald formula to determine LDL-C levels. It should be noted that the diagnostic criteria, treatment targets and such are based on the Friedewald formula. Non-HDL-C or the direct method of LDL-C measurement is used when the patient is in a nonfasting state or when the TG level is ≥ 400 mg/dL. However, the accuracy of the direct method and the non-HDL-C calculation cannot be guaranteed when the TG level is ≥ 1000 mg/dL[101] and ≥ 600 mg/dL, respectively. Other methods of assessment should be considered in such cases.

2) Smoking

[Statement]
- **Smoking is a risk factor for CAD, stroke, abdominal aortic aneurysm and peripheral artery disease (PAD). (Evidence level: E-1a)**
- **Passive smoking is a risk factor for CAD and stroke. (Evidence level: E-1a)**

Smoking has been reported to be a risk factor for CAD and stroke in a number of sources, such as cohort studies conducted overseas and in Japan, as well as their meta-analyses. Compared to nonsmokers, smokers face a higher risk for CAD and stroke, and there is a dose-response relationship in this association[102]. In addition, there has been no data showing that low-tar, low-nicotine tobacco decreases the risk for these diseases. The risk increases even when the number of cigarettes smoked per day is less than five[102]. Reviews in Japan alone have shown that smoking has been consistently reported in many cohort studies[103-111] to be a risk factor. Compared to lifetime nonsmokers, the relative risk for developing CAD and death from it was 2.15 times higher for those who smoke ≤ 20 cigarettes a day and 3.28 times for those who smoke >20 sticks in a meta-analysis. Furthermore, the relative risk of getting stroke and stroke-related death was 1.41 times higher for those who smoke ≤ 20 cigarettes a day and 1.56 times for those who exceed 20 sticks[112]. Other than that, a meta-analysis of cohort studies in Japan have shown that for abdominal aortic aneurysm(AAA), the relative risk is 3.89 times higher for men and 4.30 times for women[113]. The dose–response relationship has also been made apparent in the analysis. The association with PAD has also been shown in cohort studies, including the Framingham Study. Even in cross-sectional studies conducted in Japan, the proportion of PAD, as determined using the ABI, was shown to be 3.7 times higher in current smokers (4.2 times for those with ≥ 45 pack-years) and 3.7 times in ex-smok-

ers. The dose–response relationship has similarly been demonstrated in these studies[114].

On the other hand, for passive smokers, it has been revealed in a meta-analysis that the relative risks for CAD and stroke are 1.31[115] and 1.25[116], respectively.

Smoking increases the risk for developing type 2 diabetes to 1.4 times[117], and the risk for metabolic syndrome increases in accordance with the number of cigarettes smoked[118]. A meta-analysis has shown that smokers have lower HDL-C levels and higher LDL-C and TG levels, and the dose-response relationship has again been observed[119]. Smoking by itself is not just a risk factor for ASCVD. It also increases the risk for diabetes, dyslipidemia and metabolic syndrome, in turn contributing to an added risk for ASCVD.

Recently, new forms of tobacco (heat-not-burn tobacco products and electronic cigarettes, etc) that differ from the conventional combustion cigarette have been in circulation. As these new forms of tobacco have only been in circulation for a short period of time, their effects on health, such as the risk for ASCVD and related death, cannot be determined at this point of time. Nonetheless, although heat-not-burn tobacco products do not contain substances that are produced by combustion, users still inhale and exhale the aerosol generated by heating the tobacco leaves and additives, including nicotine[120]. Moreover, from the fact that various carcinogens have been reported to be found in the aerosol, regardless of whether electronic cigarettes contain nicotine[121], the use of any of them has a possibility of adversely affecting health.

3) Hypertension
[Statement]
- **Blood pressures that exceed the optimal reading (i.e., systolic BP (SBP) <120 mmHg and diastolic BP (DBP) <80 mmHg) increase the risk for developing CVD, stroke, MI, CKD, etc. (Evidence level: E-1a)**

Hypertension is an important risk factor for cerebro- and CVD, such as cerebrovascular disease and CAD, as well as heart failure, CKD and many more. Hypertension at middle age also increases the risk for dementia when one reaches old age[122]. In the results of EPOCH-JAPAN, a meta-analysis of 10 domestic cohort studies (70,000 men and women in total), the hazard ratio for cerebro- and cardiovascular disease-related death increases progressively with an elevation of BP levels that exceed the optimal level (<120/80 mmHg). This association was stronger in the middle-aged adults than in the elderly[123].

The estimation by EPOCH-JAPAN showed a death rate of 50% from all forms of cerebro- and CVD, 52% from stroke and 59% from CAD. They

were all assessed to be caused by high BPs that exceed the optimum level. Among all deaths from these causes, subjects with grade-I hypertension made up the highest proportion[123]. A comparison between subjects with hypertension and those without hypertension in the lipid intervention study J-LIT showed that the relative risk for CAD in primary prevention subjects was 2.05 times higher in women and 2.15 times in men[124].

The basis for diagnosing hypertension is usually the BP reading measured at the outpatient clinic. However, it has been reported that BP measurements at home and 24-hour ambulatory BP monitoring (ABPM) can predict the incidence of cardiovascular events better than in-clinic BP measurements. In The

Japanese Society of Hypertension's Guidelines for the Management of Hypertension 2014 (JSH 2014), it has been explicitly stated that if the diagnosis made with in-clinic BP readings differs from that with home BP readings, BP-lowering effects should be determined and diagnosis should preferably be made on the basis of the BP measured at home[122]. The reference value for hypertension differs for in-clinic BP, 24-hour ABP and home BP. In-clinic BP readings of ≥ 140/90 mmHg, home BP readings of ≥ 135/85 mmHg and ABP readings of ≥ 130/80 mmHg shall be managed as hypertension[122].

4) Diabetes Mellitus (DM)
[Statement]
- **DM is a strong risk factor for ASCVD. (Evidence level: E-1a)**

DM is an important risk factor for ASCVD[125, 126]. In NIPPON-DATA80, diabetic patients showed significantly higher risk of 2.8 times for death from CAD than non-diabetic subjects[127]. The Hisayama study reported that the incidence rate of CAD and cerebral infarction in diabetic patients were both high after adjusting multiple factors, such as gender and age. In this study, the incidence rate of CAD was 5.0/1,000 person-years for diabetic patients and 1.6/1,000 person-years for subjects with normal glucose tolerance (NGT). Similarly, the incidence rate of cerebral infarction was 6.5/1,000 person-years in diabetic subjects, that significantly higher than the 1.9/1,000 person-years in subjects with NGT[128]. The CIRCS study also showed that the incidence rate of cerebral infarction for diabetic patients was higher at 1.9 times in men and 2.2 times in women as compared to non-diabetics[129]. Although the absolute risk of CAD among Japanese diabetic patients is thought to be 30-70% compared to that of diabetic Europeans and Americans[130, 131], the difference has been closing in the near future.

Silent myocardial ischemia often coexists in diabetic patients, and this may result in delayed diagnosis[132]. Features of coronary lesions in diabetic patients include (1) multiple-vessel disease, (2) highly complicated and diffuse[133, 134] and (3) multiple calcified lesions[135].

As for cerebral infarction, the JPHC study has shown that lacunar infarction, atherothrombotic infarction and thromboembolic infarction occur more often in diabetic patients than non-diabetic subjects[136].

Furthermore, prognosis of CAD in diabetic patients is worse than in non- diabetic subjects[137-139], and also have a higher risk for recurrence of cerebral infarction[140, 141]. The risk for PAD is as much as three to four times higher in diabetic patients[142], and this risk increases by 26% with every 1% increase in the HbA1c level[143].

The risk of CVD begins to increase since impaired glucose tolerance (IGT) state[144]. In the Hisayama study, the incidence rate of CAD in patients with IGT is 1.9 times higher than that of subjects with NGT, even though it was lower than the level of 2.6 times in diabetics[128]. The incidence rate of cerebral infarction increased significantly following the HbA1c level was ≥ 5.5-6.4%[145]. The JPHC study showed that the risk for CAD was 1.65 times higher in the borderline glucose tolerance group and 3.05 times higher in the diabetic group as compared to subjects with NGT, indicating the risk increases before the incidence of diabetes[146]. The two hours glucose level post glucose load was more strongly associated with the risk for CAD than the fasting level in subjects with IGT[147, 148]. These suggest that the significance of postprandial glucose level as a risk factor of atherosclerosis.

Women generally have a lower risk for CAD than men. But in diabetic patients, it has been reported that the increase in relative risk of CAD was higher in women than men, resulting in reduced gender differences[149, 150]. It has also reported that compared to male subjects with NGT male diabetic patients increased the risk of CAD by 17 times higher at ages 31-40 years, and by 2 to 3 times higher at ages 41 to 61 years, which suggests that the impact of diabetes on CAD was markedly greater in younger men compared with men in middle age[151].

Thus, prevention of ASCVD in addition to microvascular disease is quite important issue even in Japanese diabetic subjects[152].

5) Chronic Kidney Disease (CKD)
[Statement]
- **CKD is a high-risk condition for ASCVD. (Evidence level: E-1a)**

In the Evidence-based Clinical Practice Guideline for CKD 2013 published by the Japanese Society of Nephrology[153], CKD is defined as continuously having for ≥ 3 months, (1) an obvious renal damage based on abnormalities in urine, diagnostic images, blood, and pathology; the presence of proteinuria of ≥

0.15 g/gCr (albuminuria of ≥ 30 mg/gCr) is especially important, and/or (2) a glomerular filtration rate (GFR) of <60 mL/min/1.73 m². An estimated GFR (eGFR) is used for GFR. CKD is not merely a high-risk condition for end-stage kidney disease but also for ASCVD. As the risk of these composite outcomes differs greatly depending on the cause, GFR and amount of proteinuria (albuminuria), the severity of CKD is classified (CGA classification)[153, 154] using these three primary factors. It has been estimated that 13% adults in Japan have CKD[155], and screening for CKD is therefore an important element in the comprehensive risk management for ASCVD.

In the screening for CKD[156], urinary protein and urinary occult blood are assessed by a qualitative urine test, and eGFR is determined by measuring serum creatinine levels. Whenever necessary, the degree of proteinuria is further determined quantitatively using the casual spot urinary protein-to-creatinine ratio. If a patient is identified with CKD, even when he/she is in the group for primary prevention of ASCVD, stricter control of risk factors, including dyslipidemia, is recommended as a high-risk patient.

CKD may include conditions for which diagnosis by kidney biopsy is preferable so as to treat for remission, conditions requiring urgent treatment (immune suppression therapy with corticosteroids, immune suppressants, molecular-targeted agents, or in combination), and also conditions that may need specialized medical care with renal replacement therapy such as renal transplantation and dialysis. The Japanese Society of Nephrology recommends the following criteria for referral to nephrologists: (1) advanced proteinuria (urinary protein-to-creatinine ratio of ≥ 0.50 g/gCr or ≥ 2 + by dipstick test), (2) both urinary protein and urinary blood are positive (≥ 1 + by dipstick test) and (3) eGFR <45 mL/min/1.73 m²[154].

Traditional risk factors, such as BP, lipids and carbohydrate metabolism, are exacerbated in CKD. On top of that, non-traditional risk factors, such as abnormal phosphate-calcium metabolism play roles in advanced stages of CKD, and the relative contributions of certain risk factors for ASCVD are altered. According to a large-scale cohort study in Canada[157], the association between LDL-C and ASCVD is lower when eGFR is lower, and the association was no longer significant when eGFR was <15 mL/min/1.73 m². This finding is consistent with the results of randomized controlled trials revealing that the use of statin did not decrease the risk for ASCVD significantly in dialysis patients[158, 159], suggesting the importance of implementing effective measures on patients with earlier stages of CKD.

6) Aging and Gender Differences
[Statement]

- **Aging is the strongest risk factor for ASCVD, such as CAD and cerebrovascular disease. (Evidence level: E-1b)**
- **Women have a lower risk for MI and MI-related death than men, but the gender difference decreases with aging. (Evidence level: E-2)**

The risk for ASCVD, such as MI, and death from it increases as one moves up to the next age category. In terms of absolute risk, aging enhances the risk for ASCVD and death from it much more than any other risk factors[160-162].

Women have a lower risk for MI and MI-related death than men. In a survey conducted in Takashima town, Shiga Prefecture from 1999 to 2001, the age-adjusted incidence rate of acute MI (100,000 person-years) was 35.7 for women, and this was one-third the figure of 100.7 for men[163]. Furthermore, according to the vital statistics of 2014, the (approximate) rate of mortality due to ischemic heart disease in a target population of 100,000 is 49.8 for men and 36.6 for women. The mortality rates (target population of 100,000) according to age are as follows: 2.6 for men and 0.6 for women in the 30s, 11.0 for men and 2.3 for women in the 40s, 30.2 for men and 6.6 for women in the 50s, 66.5 for men and 17.3 for women in the 60s, 131.9 for men and 60.3 for women in the 70s, 334.9 for men and 209.5 for women in the 80s, 675.6 for men and 460.2 for women in the 90s, and last but not least, 787.5 for men and 549.0 for women in the ≥ 100s. The mortality rate of ischemic heart disease was lower in the women than men in all age groups. However, the mortality rate of ischemic heart disease for women starts increasing when they reach the 60s. Women in the 70s have a mortality rate that is almost the same as men in the 60s, which goes to show that the risk for ASCVD is not low for elderly women[164]. There was almost no difference between the mortality rates of cerebral infarction for men and women (target population of 100,000), which were 25.4 and 28.8, respectively. The mortality rates (target population of 100,000) according to age are: 0.2 for men and 0.1 for women in the 30s, 0.9 for men and

0.4 for women in the 40s, 3.6 for men and 1.1 for women in the 50s, 15.9 for men and 4.7 for women in the 60s, 61.9 for men and 24.9 for women in the 70s, 242.3 for men and 156.2 for women in the 80s, 662.7 for men and 605.3 for women in the 90s, and lastly, 1125.0 for men and 1182.4 for women in the ≥ 100s. Up to the 90s age group, the mortality rate of cerebral infarction was lower in women than men.

7) Family History of CAD
[Statement]

- **A family history of CAD is a risk factor for developing CAD.** **(Evidence level: E-1b)**

It has been reported in the Western countries since 1970s that a family history of CAD is a risk factor for the disease itself[165-172]. A family history of CAD, especially in first-degree close relatives (parents, children, brothers and sisters), and a family history of premature CAD (age of incidence: <55 years for men and <65 years for women) are strong risk factors for CAD.

It was reported in the Framingham Study that if at least one parent has CAD, the age-adjusted odds ratio for the risk of developing CAD is 2.6 for men and 2.3 for women. After adjusting all the variables in the multivariate analysis, the ratios were 2.0 and 1.7 for men and women, respectively[168]. The J-LIT study in Japan has shown that a family history of CAD increases the relative risk of developing CAD by three times[173]. The recent CREDO-Kyoto study has also reported that a family history of CAD contributes to the occurrence of major cardiovascular events at a young age[174].

Traditional risk factors (high LDL-C, low HDL-C, hypertension, diabetes, and smoking) are associated with genetic predisposition and are influenced by habits within the family. In other words, a family history of CAD is considered to also include genetic and environmental risk factors, a fact that is already known. There has been attention on other risk factors that should be considered, such as Lp (a), small dense LDL and homocysteine, which are all genetically regulated. However, it is assumed that unknown genetic factors play a role[170] as family history remains a strong risk factor even after adjusting all the traditional risk factors in multivariate analyses[80, 166-168, 175, 176].

Therefore, most studies relating to family history have concluded that a family history of CAD is an independent risk factor for CAD. Individuals with a family history of premature CAD (age of incidence: <55 years for men and <65 years for women) should particularly be considered to be at high risk for CAD.

8) History of CAD
[Statement]

- **A history of CAD poses a higher risk compared to primary prevention.** **(Evidence level: E-1b)**

It is evident in epidemiological studies and intervention trials conducted in the Western countries that the incidence rate of cardiovascular events is higher in patients with CAD than in primary prevention patients[177-179]. Similar results have also been reported in studies in Japan. The MEGA study, a primary prevention trial involving the use of statin[41], showed that the incidence rate of cardiovascular events for the group that underwent diet therapy was 2.1/1,000 person-years. In the J-LIT study, the incidence rate in primary prevention patients was 0.9/1,000 person-years[180] and 4.5/1,000 person-years in CAD patients[173]. In JELIS, primary prevention patients had an incidence rate of 1.6/1,000 person-years while the rate was 6.8/1,000 person-years in patients with CAD[181]. In addition, the incidence rate of cardiovascular events was ≥ 15/1,000 person-years in the JCAD[182] and CREDO-Kyoto studies[183], which are registry studies involving patients with CAD.

9) Noncardiogenic Cerebral Infarction
[Statement]

- **A history of noncardiogenic cerebral infarction is a high-risk condition for cerebrovascular disease and CAD.** **(Evidence level: E-1b)**

Patients with a history of cerebrovascular disease are known to be a high-risk group for CAD. In Japan, there has been reports revealing that the 1-year incidence rate for patients with a history of stroke is 0.40-0.45% (4.0-4.5 people/1,000 person-years)[184, 185]. Patients in Japan who have a history of stroke are considered to be at a high risk for developing CAD, especially those with noncardiogenic cerebral infarction

originating from arteriosclerotic lesions.

In addition, findings of arteriosclerosis in the carotid arteries are an independent risk factor for CVD[6, 8]. It has been reported that an increase in the intima-media thickness (IMT) of common carotid arteries is particularly a significant predictive factor in cerebral infarction and CAD[186-188]. However, it was reported in the results of a meta-analysis that both CVD and stroke were not seen to be significantly cor-

related with the progress of IMT[189].

On the other hand, it has been reported that the incidence rate of cerebrovascular disease is higher than the recurrence rate of CAD in patients with a history of CAD. Moreover, the risk of developing cerebrovascular disease is also higher than the risk of CAD in those with a history of PAD[184]. Therefore, a history of cerebrovascular disease is something that should be taken note of.

10) Peripheral Artery Disease (PAD)

i) Lower extremity PAD
[Statement]
- **PAD causes CAD and cerebrovascular disease to occur easily at high incidence rates.
  (Evidence level: E-1b)**

Although "ASO" has traditionally been used in Japan to refer to PAD, the term used in these guidelines is "PAD"[190]. It mainly refers to diseases based on stenosis and obstructive lesions in the arteries of the lower extremities due to atherosclerosis. Coldness in the lower extremities, intermittent claudication, ulcers, and necrosis are some of the symptoms observed in PAD. In Europe and America, it has been clearly demonstrated in epidemiological studies that PAD patients are more prone to developing other forms of ASCVD, such as CAD and cerebrovascular disease. Similar reports have also been surfacing in Japan recently.

In the Hisayama study, in which ordinary citizens were involved, 2,954 subjects who were ≥ 40 years old and did not suffer from CVD were followed up for an average of 7.1 years. The results showed that the risk for developing CAD was 4.13 times higher in subjects who had an ABI of ≤ 0.9 than those who had a normal ABI[191]. The CIRCS study was another study that involved ordinary citizens, in which 939 subjects who were 60-74 years old and did not suffer from CVD were followed up for an average of 9.3 years. The results have likewise showed that subjects with an ABI of ≤ 0.9 had a higher risk of 2.04 times for devel-

oping CAD than those with an ABI of ≥ 1.1, and the risk for developing cerebrovascular disease was also higher at 3.39 times[192]. The REACH Registry, a prospective cohort study, had 5,193 Japanese entered by 2004. Among them, the incidence of CVD within 1 year was studied in 603 individuals who were suffering from coexisting PAD. The resulting incidence rates were generally high - 1.25% for all deaths, 0.55% for cardiovascular death, 0.77% for nonfatal MI, and 1.56% for nonfatal stroke[184]. A prospective observational study was conducted on 557 patients with PAD by Shigematsu et al. It was observed in the study that the three-year incidence rate was 6.3% for cardiovascular death, 11.3% for heart disease, 7.0% for cerebrovascular disease and 16.9% for events in the lower extremities[193].

As mentioned above, other forms of ASCVD, such as CAD and cerebrovascular disease, easily occur in PAD patients at high incidence rates, and this has also been clearly shown in Japan. Therefore, when encountering a PAD patient, a careful full body examination is necessary to check for the presence of ASCVD.

ii) Abdominal Aortic Aneurysm (AAA)
[Statement]
- **Atherosclerotic disease often coexists in patients with AAA. (Evidence level: E-2)**

High LDL-C[194], high TC[195], hypertension[196], and smoking are the factors that contribute to the development of AAA, and this is a commonality with ASCVD. A survey conducted by Akai et al. on 374 Japanese patients with AAA showed that hypertension contributed to the increase in diameter of the aneurysms. However, the association of its increased size with a history of ASCVD or TC was ruled out[197].

Hollier et al. studied the long-term prognosis of 1,087 patients who had undergone open surgical repair for AAA. Among the causes of death, they reported that cardiovascular-related causes made up 37% and MI made up 22%[198]. However, they were unable to obtain any results showing that AAA is a risk factor of ASCVD. There are currently no papers relating to studies on the long-term prognosis of patients with

AAA in Japan. Nonetheless, in a study where preoperative coronary angiography was performed on 94 patients with AAA who were to undergo elective surgery for, 45.7% of them were found to having coexisting CAD[199]. In a separate study, ATP-loading myocardial single-photon emission computed tomography (SPECT) was performed on 788 Japanese patients, including 500 patients with AAA who had no history of CAD, 183 patients with PAD and 105 patients with both AAA and PAD. As a result, myocardial ischemia was seen in 37% the patients with AAA, 55% patients with PAD and 77% patients with both[200]. From these results, even though there are no longitudinal studies demonstrating AAA as a risk factor for ASCVD, there are some cross-sectional studies showing the association between AAA and ASCVD. Therefore, it is recommended to screen for ASCVD in patients with AAA.

iii) Atherosclerotic Renal Artery Stenosis
[Statement]
- **Atherosclerotic Renal Artery Stenosis Is a High-risk Condition for ASCVD. (Evidence Level: E-2)**

Ninety five percent of renal artery stenosis (RAS) is caused by arteriosclerosis and it coexists with other forms of ASCVD at a high rate. RAS is a progressive condition, and individuals with RAS have a tendency for worsened renal function. However, there is also an added risk for cardiovascular complications at the same time[201, 202]. There has been a report stating that upon examining the renal arteries during cardiac catheterization as a screening test, 30% patients who went through the procedure were found to be having RAS[203], and that the survival rate decreases with higher degrees of RAS[204]. However, there are currently no relevant detailed reports or reports from cross-sectional studies. Even though coronary artery lesions are found at high rates when RAS is present and RAS is an important high-risk condition in CVD, there is insufficient evidence showing that it is a direct primary risk factor for ASCVD.

11) Other Diseases to Be Considered

i) Hyperuricemia
[Statement]
- **Hyperuricemia can be regarded as a risk factor for ASCVD. (Evidence level: E2)**

The Guideline for the Management of Hyperuricemia and Gout (Second Edition) released by the Japanese Society of Gout and Nucleic Acid Metabolism was revised in 2010. In the revised guideline, it was mentioned that serum uric acid levels (1) can be regarded as an independent predictive factor for the development of hypertension, and (2) it can possibly be a predictive factor for the risk of incipient stroke and recurrence, as well as for the re-hospitalization and prognosis caused by heart failure. At the same time, it was mentioned in the guideline that conflicting reports on whether serum uric acid level is an independent risk factor for CVD have been produced[205].

According to subsequent reports, including a meta-analysis, it has been revealed that uric acid level is an independent risk factor for the development of hypertension, stroke, and coronary events[206-208]. Uric acid levels was also reported as an independent risk factor for cerebro- and cardiovascular death in EPOCH-JAPAN, in which 13 cohort studies in Japan were summarized[209].

On the other hand, there is still a lack of evidence from interventional studies on whether uric acid-lowering treatments contribute to the suppression of ASCVD and the improvement of prognosis, and this remains a question to be answered. Nonetheless, a meta-analysis of interventional studies has shown that uric acid-lowering treatment using allopurinol lowers BP[210]. In a study involving elderly patients with hypertension, the group that received allopurinol was compared to the propensity score-matched control group. The results showed that the suppressive effect on the incidence of stroke and coronary events (acute MI and ACS) was especially seen when high doses of allopurinol were administered[211].

ii) Sleep Apnea Syndrome (SAS)
[Statement]

- **Obstructive sleep apnea is an independent risk factor for ASCVD. (Evidence level: E-1b)**

Abnormal breathing pattern (occurrence of apnea and hypopnea) and ventilatory failure during sleep are two characteristics of SAS, a representative condition of sleep-disordered breathing (SDB) which presents various symptoms. SAS is divided into obstructive sleep apnea (OSA), which is based on obstruction of the respiratory tract, and central sleep apnea (CSA), which is caused by an absence of respiratory drive from the respiratory center. Among the two types of SAS, CSA is relatively less common. Although it is regarded in the field of circulatory system to be a condition that brings about heart failure, OSA is on the other hand, seen as a common disease that is closely related to lifestyle habits and is strongly associated with ASCVD. It is possible that OSA causes arteriosclerosis to progress through various mechanisms.

A meta-regression analysis has clearly shown that patients with OSA have lower endothelial function than those without OSA, in addition to increased stiffness of the blood vessels and high-sensitivity C-reactive protein level[212]. It has also been evident in a meta-analysis that OSA is an independent risk factor for intima–media thickening[213]. Many cohort studies and prospective studies involving large numbers of patients have confirmed that OSA poses a risk for developing type 2 diabetes[214]. It has also been substantiated in these studies that OSA increases the rate of new future occurrences of hypertension[215]. We can hence see from these results that OSA directly or indirectly contributes to the incidence and progression of ASCVD.

A comparison between subjects with severe OSA and the control group in prospective observational studies has revealed a significant increase in the occurrence of both fatal and nonfatal cardiovascular events in the group with severe OSA[216, 217]. Therefore, it is advisable to treat OSA as one of the risk factors for ASCVD and carry out screening accordingly. Regardless of whether an underlying heart disease is present, active screening is especially recommended for patients who are noticed to be experiencing two or more of the following: excessive daytime sleepiness or a choking sensation during sleep, asthma, repeatedly waking up from sleep, feels unrefreshed when waking up, feels tired during the day and lacks concentration[218]. Continuous positive airway pressure (CPAP) is an effective therapy for patients who are diagnosed with severe OSA. However, the effect of CPAP on primary or secondary prevention of CVD has not proven yet in recent RCTs[219, 220].

12) Other Risk Factors and Markers to Be Considered
[Statement]

- **Hyper-Lp(a)-lipoproteinemia is a risk factor for ASCVD. (Evidence level: E-1a)**
- **Measuring the level of malondialdehyde-modified LDL (MDA-LDL) is useful for prognostic prediction of the incidence of CAD in diabetic patients who have a history of CAD. (Evidence level: E-1b)**
- **Hyper-remnant-lipoproteinemia is a risk factor for ASCVD. (Evidence level: E-1b)**
- **Postprandial hyperlipidemia is a risk factor for CAD. (Evidence level: E-1b)**
- **A high small dense LDL level is a risk factor for ASCVD. (Evidence level: E-1a)**
- **A high apolipoprotein B (apo B) level is a risk factor for ASCVD. (Evidence level: E-1a)**
- **The TC/HDL-C ratio, non-HDL-C/HDL-C ratio, LDL-C/HDL-C ratio, and apo B/AI ratio are markers for ASCVD. (Evidence level: E-1a)**
- **High levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) are markers for ASCVD. (Evidence level: E-1a)**

It is necessary to take note that these factors include genuine risk factors that contribute to the progression of ASCVD, but at the same time, there may also be factors within that are very likely to be markers for ASCVD.

Risk factors or markers for ASCVD that should be considered are proposed separately from the risk factors established in the preceding sections.

i) Lp(a)

Lp(a) is an independent risk factor for CAD and stroke. When the size of apolipoprotein (a) [apo(a)] is small, the concentration of Lp(a) is high, and there is a high risk of CVD. Single-nucleotide polymorphisms have been revealed in genes that reflect this correlation[221-228]. There have been some hypotheses regarding the mechanism through which Lp(a) causes

ASCVD. One hypothesis is that apo(a) protein is highly homologous to plasminogen[222, 227], and it interferes with the actions of plasminogen, thereby promoting thrombus formation[228, 229]. It has also been suggested that apo(a) protein preferentially binds to oxidized phospholipids, which influence the risk for CAD[230, 231]; furthermore, it has been suggested that apo(a) is easily anchored to the arterial walls[232, 233]. High Lp(a) concentrations are found in patients with FH, and it is presumed that hyper-Lp (a)-lipoprotein-emia further increases the risk for CVD in patients with FH[222].

ii) MDA-LDL

MDA-LDL is a form of oxidized LDLs, which are lipoproteins produced through the oxidative modification of lipids, such as phospholipids, and apolipo-proteins when LDL is subjected to oxidative stress[234, 235]. MDA-LDL is involved in a wide range of processes of atherosclerosis, such as the damaging of endothelial cells, acceleration of monocyte penetration into the vascular walls, and formation of foam cells[235]. MDA-LDL is useful for prognostic prediction of the incidence of CAD and the recurrence of stenosis after percutaneous coronary intervention (PCI) in diabetic patients with a history of CAD[236]. In patients with stable angina who were receiving lipid-lowering treatment, the risk for cardiovascular events after treatment using a drug-eluting stent has been shown to increase by 1.14 times with every 10 U/L elevation in MDA-LDL levels[237].

iii) Remnant Lipoprotein

Remnant lipoprotein is an intermediate lipoprotein that is produced during the process in which chylomicrons and very low-density lipoproteins (VLDL) are metabolized. Remnant lipoproteins deposit themselves in the vascular intima, causing the progression of atherosclerosis[238]. Patients with MI have a high risk for cardiovascular events when the remnant lipoprotein level is high. In addition, hyper-remnant-lipoproteinemia is an independent risk factor even when LDL-C is maintained at <100 mg/dL[239, 240]. Studies have shown that the measurement of remnant lipoprotein levels is useful for risk assessment in secondary prevention for patients with ACS who have undergone coronary interventions and are taking statins. Its usefulness has also been demonstrated in the assessment of risk for ASCVD in primary and secondary prevention for patients with coexisting type 2 diabetes and CKD[241, 242]. In addition, hyper-remnant-lipoproteinemia can explain part of the residual risk of all-cause mortality in patients with CAD[243]. Some of the conditions in which the amount of remnant lipoprotein increases include familial combined hyperlipidemia, familial type III hyperlipidemia, DM, and metabolic syndrome.

iv) Postprandial Hyperlipidemia

Zilversmit et al. proposed that the increase in the postprandial levels of remnant lipoprotein after meals can cause atherosclerosis. Considerable evidence has been accumulated thereafter, and this hypothesis has therefore been established as the disease concept[238, 243-245]. Epidemiological studies in Japan have also demonstrated that a high nonfasting TG level adds to the risk of CAD. Overall, every 1 mmol/L increase in TG levels increases the relative risk of CAD by 1.34 times (men, 1.29 times; women, 1.42 times)[88]. The risk starts increasing when the nonfasting TG level reaches 115 mg/dL, and at ≥ 167 mg/dL, the risk increases by ≥ 3 times. The result remains the same even with correction using HDL-C[88]. In the sub-analysis of MRFIT, the nonfasting TG level was as useful as, or even more useful than, the fasting TG level for the risk for CAD; a nonfasting TG level of ≥ 200 mg/dL indicates a high risk[246]. The diagnostic criteria for hypertriglyceridemia in a nonfasting state have recently been gaining attention, especially in Europe and America[247, 248]. In addition, measurement of the amount of apolipoprotein B-48 in a fasting state is expected to be useful as a screening marker for postprandial hyperlipidemia[249].

v) Small Dense LDL

Among all the LDL particles, small dense LDL particles[250, 251] have a high density. The association between the levels of small dense LDL and CAD has been reported in numerous sources[251-256], and its relationship with PAD and aneurysms has also been demonstrated[257, 258]. In addition, small dense LDL is more strongly associated with the risk for CAD[259], the severity of coronary atherosclerosis[256, 260], and the incidence of ASCVD in secondary prevention[261] than is LDL-C among Japanese populations. There have been several hypotheses regarding the mechanism of small dense LDL as a strong atherogenic factor. One hypothesis is that small dense LDL is easily oxidized[262] and processed in pathways other than that of the LDL receptor[263]. Small dense LDL is also easily incorporated into the arterial wall[264], where it binds readily to the matrix[265], and this is another proposed mechanism. Small dense LDL is closely associated with hypertriglyceridemia and hypo-HDL cholesterolemia[259, 266]. In addition, its levels are increased in conditions such as type 2 DM, metabolic syndrome, and insulin resistance[259, 267].

vi) Apo B

Apo B (apo B-100) is an apolipoprotein found in atherosclerosis-causing lipoprotein particles, such as LDL and remnant lipoprotein. As each lipoprotein particle contains one apo B molecule, the apo B value is proportionate to the number of these lipoprotein particles. According to a meta-analysis of epidemiological studies, apo B is a stronger risk factor for cardiovascular events than are LDL-C and HDL-C[268, 269]. The Framingham Study has revealed that apo B improves the risk assessment for CAD more than do LDL-C and non-HDL-C[270]. A meta-analysis of studies using statins has clearly shown that compared to a reduction in LDL-C and non-HDL-C levels, a reduction in the amount of apo B has a stronger association with the decrease in the risk of CAD[271]. Another meta-analysis has demonstrated that measurement of the amount of apo B, in addition to LDL-C and non-HDL-C, improves risk prediction[272].

vii) Ratios of Lipids and Apolipoproteins

The levels of lipids, such as LDL-C and HDL-C, are commonly considered as risk factors. However, rather than the levels of these lipids and apolipoproteins, the ratio of different cholesterols and the ratio of different apolipoproteins contained in each lipoprotein are risk factors for ASCVD. These ratios are namely the TC/HDL-C ratio, non-HDL-C/HDL-C ratio, LDL-C/HDL-C ratio, and apo B/AI ratio[268, 273-275]. Nonetheless, these data are mostly the results of studies in various Western countries; therefore, the current management targets to be achieved in Japan should be the absolute values of each lipid. In Chinese diabetic patients, the TC/HDL-C, non-HDL-C/HDL-C, LDL-C/HDL-C, and apo B/AI ratios were involved in the spread of coronary lesions. The apo B/AI ratio, in particular, was strongly involved in the coronary atherosclerosis; however, the significance disappeared after adjustment for confounding factors[276]. Studies conducted in Japan have reported that the TC/HDL-C ratio is significantly associated with coronary artery calcification, even after correction for the confounding factors[277].

viii) Inflammatory Markers (C-reactive Protein and Pentraxin-3)

C-reactive protein (CRP) is an acute-phase protein that is used as an inflammatory marker. It has been already revealed that chronic inflammation of the blood vessels is an important factor for the progression of atherosclerosis. However, in recent years, high-sensitive CRP (hs-CRP) has been reported as a possible risk factor for ASCVD[278, 279]. There are reports in Japan stating that a significant association was seen between hs-CRP and stroke (especially cerebral infarction and lacunar infarction)[280]. hs-CRP has also been associated with the onset risk of MI and stroke, of which the association is particularly strong in MI[281]. Conversely, in a study on the genotype related to CRP concentration in the blood and the frequency of CAD, there was no association between the concentration of CRP and the frequency of CAD[282]. This result suggests that the concentration of CRP is probably not a cause of ASCVD but instead reflects the extent to which atherosclerosis has progressed. Pentraxin (PTX)-3 belongs to the same pentraxin family of proteins as CRP. Unlike CRP, which is found in the liver, PTX-3 is specifically expressed in the endothelial cells, smooth muscle cells, and WBCs. Recent reports have suggested that the association of CRP and PTX-3 in coronary artery plaques in pathological autopsies shows that both CRP and PTX-3 reflect unstable plaques. However, the distributions of CRP and PTX-3 in the plaques are not the same, and there is a possibility that they play different roles. There have also been reports on the PTX-3-lowering effect of statins. PTX-3 is expected to serve as a specific marker reflecting CVD in the future[283-286].

ix) Homocysteine

The elevation of homocysteine concentration in the blood has been reported to be a risk factor not just for CAD but also for stroke and PAD[287-289]. In a study involving elderly individuals who were aged ≥ 85 years and had no history of cardiovascular disease, a high homocysteine concentration in the blood increased the relative risk for MI[290]. Furthermore, analyses in the recent years have suggested that homocysteine is a stronger marker than is CRP[291]. However, therapies for lowering the concentration of homocysteine through vitamin supplementation did not result in the suppression of events[292, 293]. Furthermore, it has also been reported that there is no association between ASCVD and hereditary genetic mutations that cause an increase in homocysteine levels[294]. In a meta-analysis related to the risk for CAD at a young age, the effect of homocysteine was not seen in all subjects. However, in the group with homocysteine levels of ≥ 15 μmol/L or in Asians with a 677C→T mutation in the methylenetetrahydrofolate reductase gene, a significant increase in risk was observed[295]. The background for this finding has been suggested to be the relatively lower intake of folic acid by Asians than that by other races, and this implies a need to study hyperhomocysteinemia as an independent risk factor in Japan. The various genetic polymorphisms affecting homocysteine concentration have been evaluated in studies that involved individuals of European

descent, using genome-wide association study. The results revealed that the concentration of homocysteine did not contribute to the risk for CAD in the Caucasians[296].

x) Blood Coagulation and Fibrinolytic Factors

Fibrinogen is an independent risk factor for cardiovascular disease[297-299]. The conclusion of an integrated analysis of 52 prospective studies was that both CRP and fibrinogen are risk factors for primary cardiovascular disease[278]. By contrast, some recent reports on the association of CRP and fibrinogen with mean IMT and coronary artery calcium score in the Japanese, Japanese–American, and Caucasian populations have stated that a significant association was not seen in any of the races after adjustment for multiple variables (age, SBP, LDL-C, HDL-C, fasting glucose level, smoking, and alcohol consumption) or for age and BMI[300, 301]. PAI-1 is a fibrinolytic factor secreted by the endothelial cells, and its activity increases in the acute phase of acute MI. Sakamoto *et al.* have shown that although its activity was decreased at the time of discharge at approximately 1 month later, the levels were still higher in patients with acute MI than in the control group[302]. Reports have demonstrated that PAI-1 is associated with ASCVD and metabolic syndrome, which involves an accumulation of visceral fats and insulin resistance[303]. The risk may possibly increase further depending on the genotypes that exist for PAI-1[304, 305].

2. Disease Concept and Diagnostic Criteria for Metabolic Syndrome

[Statement]

- **Metabolic syndrome is a condition that poses a high risk for the development of cardiovascular disease (Evidence level: E-1b).**

Japanese eating habits and dietary components have clearly changed in recent years[306]. Lifestyles that include overnutrition and physical inactivity are threatening to increase the incidence of CAD and stroke. Among the conditions underlying the development of ASCVD, particular importance is ascribed to a cluster of multiple risk factors, including hyperglycemia, dyslipidemia, and elevated blood pressure, which are closely related to lifestyle. This pathologic condition used to be called "Syndrome X,"[307], "the deadly quartet"[308], "visceral fat syndrome"[309], or "insulin resistance syndrome"[310] but those terms were unified as "metabolic syndrome"[311] in 1999. Metabolic syndrome is recognized as a condition in which the risk factors of atherosclerosis cluster on the basis of obesity, particularly visceral fat accumulation, due to overnutrition and physical inactivity[312, 313]. The dysregulated secretion of adipose tissue-derived bioactive molecules (adipocytokines), which accompanies the accumulation of visceral fat tissue, is important for the development of metabolic syndrome and related cardiovascular diseases.

1) Importance of Risk Factor Accumulation

The Group of 'The Research for the Association between Host Origin and Atherosclerotic Diseases under the Preventive Measure for Work-related Diseases of the Japanese Ministry of Labour' performed a case-control study in approximately 120,000 office workers[314, 315]. The records of annual medical health checkups performed 10 years prior to the onset of CAD were reviewed. The surveys revealed that BMI, BP, fasting blood glucose, and serum lipids levels were significantly higher in cases compared with those in controls for the evaluated 10-year period, even though these abnormalities were mild or moderate. The NIPPON DATA80 epidemiological study also showed that the relative risk of death due to CAD and stroke increased with the number of combined risk factors[314-317] [**Fig. 4**: Relationship between the number of concurrent risk factors and death due to CAD and stroke (NIPPON DATA80: 1980-1994)]. These results clearly indicate the importance of a cluster of multiple risk factors in the development of CAD in Japan, even if the severity of each risk factor is mild. According to a survey of middle-aged and elderly Japanese, the frequency of having multiple risk factors were high in subjects with visceral fat accumulation[318]. The Japan Society for the Study of Obesity proposed a definition of "obesity disease" based on susceptibility to the clustering of obesity-associated risk factors[319, 320]. The fat distribution in CAD patients revealed that approximately half of the patients had excess visceral fat accumulation[321]. A 10-year follow-up study of middle-aged and elderly Japanese-American men revealed that approximately 30% of subjects developed CAD and that the accumulation of visceral fat, hypertension, and hyperglycemia were important risk factors[322].

Conditions, such as metabolic syndrome, that involve the clustering of multiple risk factors have been shown to increase the risk of cardiovascular diseases in epidemiological studies[323-326] and meta-analy-
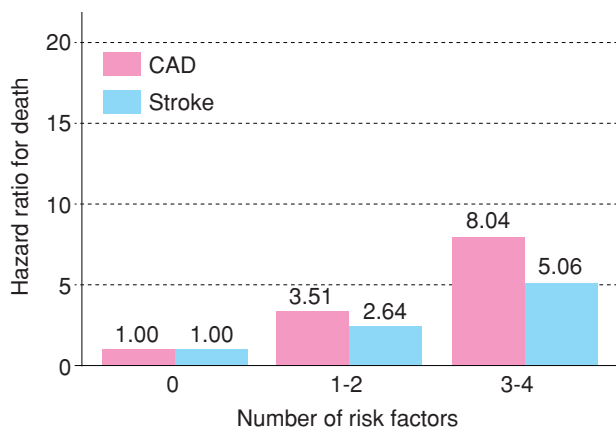
Fig. 4. Relationship between the number of concurrent risk factors and death due to CAD and stroke (NIPPON DATA80: 1980-1994)[316]

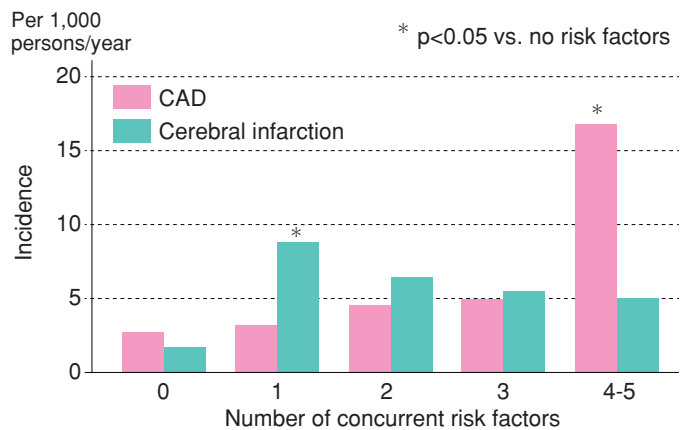Risk factors: Obesity, hypertension, hyperglycemia, hypercholesterolemia

Fig. 5. Rerationship between the number of concurrent risk factors and incidences of CAD and cerebral infarction[317]

Components of metabolic syndrome: Obesity, impaired glucose tolerance, lipidosis, hyperttention, hyperinsulinemia
After adjustment for age, 5-year (1988-1993) follow-up of 1097 men and women aged ≥ 60 years in Hisayama-cho

ses[327], as well as in CIRCS study[78], the Tanno and Sobetsu study[328] and the Hisayama study[317]. (**Fig. 5**: Relationship between the number of concurrent risk factors and incidences of CAD and cerebral infarction[317]). Concerning the secondary prevention of CAD, it was also reported that the presence of metabolic syndrome increased the incidence of subsequent cardiac events. Accordingly, metabolic syndrome is positioned as an important high risk pathologic condition for CAD[312].

2) Diagnostic Criteria for Metabolic Syndrome

The definition of metabolic syndrome in Japan, which is characterized by the accumulation of visceral fat accompanied by the concurrence of multiple risk factors including elevated blood pressure, dyslipidemia, and hyperglycemia, was established in 2005 (**Table 5**). Diagnostic Criteria for Metabolic Syndrome in Japan[312]). In the diagnostic criteria, waist circumference is used as an index of visceral fat accumulation for practical convenience, and individuals with metabolic syndrome are defined as those having visceral fat accumulation demonstrated by increased waist circumference and 2 or more risk factors[312]. The International Diabetes Federation also published similar diagnostic criteria[313]. However, European and American scientific societies issued a joint declaration later proposing that an individual with three out of the five risk factors - visceral obesity, hypertriglyceridemia, hypo-HDL cholesterolemia, high BP reading, and high glucose level - can be diagnosed as metabolic syndrome[329]. Visceral fat accumulation was not con-

Table 5. Japanese diagnostic criteria for metabolic syndrome

Visceral fat accumulation	
Waist circumference	Men ≥ 85 cm
	Women ≥ 90 cm
(The values for both men and women correspond to visceral fat ≥ 100 cm²).	
Two or more of the items mentioned below in addition to the above	
Hypertriglyceridemia and/or	≥ 150 mg/dL
Hypo-HDL cholesterolemia	< 40 mg/dL for both men and women
Systolic blood pressure and/or	≥ 130 mmHg
Diastolic blood pressure	≥ 85 nnHg
Fasting hyperglycemia	≥ 110 mg/dL

• Measurement of visceral fat by methods such as CT scanning is recommended.
• The waist circumference is measured at the umbilical level in the standing position during light breathing. If the umbilicus is displaced due to marked fat accumulation, measurement is performed at the level of the midpoint between the lower costal margin and iliac crest.
• If a diagnosis of metabolic syndrome has been made, a glucose tolerance test is recommended, but it is not essential for the diagnosis.
• If the examinee is undergoing drug treatments for hypertriglyceridemia, hypo-HDL-cholesterolemia, hypertension, and/or diabetes mellitus, each item is considered to be positive.
(Evaluation Committee on Diagnostic Criteria for Meabolic Syndrome: Internal Medicine, 2005; 94: 794-809, in Japanese)

sidered a necessary condition in this criteria.

The criteria for waist circumference in Japan were determined by the absolute visceral fat area (VFA) of 100 cm². According to a recent large-scale cross-sectional study conducted in Japan on visceral fat area and accumulated risk factors, the average number of obesity-related cardiovascular risk factors (dyslipidemia, high blood pressure, and high blood glucose) was more than 1.0 at 100 cm² for visceral fat area in both men and women[330]. It is obvious that the Japanese criteria of waist circumference is based on scientific evidence. On the other hand, Western crite-ria of waist circumferences are merely based on the value corresponding to the obesity criteria in each country.

Visceral fat accumulation is required for the diagnostic criteria in Japan, and the aim is to solve the integration of risk factors through the interventions to reduce visceral fat. Since 2008, the measurement of waist circumference has been made compulsory in specific medical examinations and occupational health examinations, with the intent to prevent diabetes and atherosclerotic cardiovascular disease based on the concept of metabolic syndrome.

Chapter 4. Comprehensive Risk Management

1. Absolute Risk of Atherosclerotic Cardiovascular Disease (ASCVD) and Lipid-Management Targets

CQ 6. Are there any assessment tool for predicting the ASCVD incidence and mortality in the Japanese people?

- **There are several assessment tool that predict the absolute risk of ASCVD in the Japanese population. Hypertension, diabetes, and smoking are regarded as predictive factor for ASCVD. In addition, total cholesterol (TC), LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) are predictive indicators in the assessment tool that predicts the coronary artery disease (CAD) incidence and/or mortality. (Evidence level: E-1b)**

Relative risk is usually used to indicate the risk of future ASCVD incidence and/or mortality. Recently, methods of assessing the actual incidence rate in individuals, otherwise referred to as absolute risk, have been developed and are being used in clinical guidelines in various countries. These include the Framingham Score[331] in the USA and the SCORE Risk Assessment Charts in Europe[332]. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines include a new pooled cohort ASCVD risk equation to assess absolute risk[333]. Not like the Framingham Score which predicts only CAD incidence, this model predicts cerebro-cardiovascular disease incidence including stroke and CAD within 10 years.

The NIPPON DATA80 Risk Chart[161] was used in the 2012 Japanese Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases to estimate absolute risk. The management target is set after categorizing the target individuals (patients) according to 10-year CAD mortality. An understanding of absolute risk is important for managing ASCVD risk factors, implementing effective preventive strategies, and establishing the priority of future treatments. We performed a systematic review to answer CQ1: "Are there any assessment tool that predict the ASCVD incidence and mortality in the Japanese?" The Japanese population in this review included adults with no history of ASCVD. It did not include individuals treated for secondary prevention or studies only consisted of patients with dyslipidemia. Nine articles published between January 01, 1990 and September 30, 2016[161, 162, 334-340] were selected for this review and are summarized in **Table 6**.

1) Establishing Absolute Risk

In this guideline revision, we reviewed the continued use of the NIPPON DATA80 risk chart for death due to CAD that had been adopted in the 2012 guidelines. The NIPPON DATA80 had various advantages, including the fact that groups were selected from all over Japan by random sampling, the chart was based on a baseline survey conducted before statins were available and its high suitability for the observation of the natural course of disease, making it very useful for the assessment of absolute risk. However, some aspects of NIPPON DATA80 are problematic such as (1) the fact that its predicted outcome is

Table 6. Tools for Predicting the Absolute Risk of ASCVD On the Basis of Cohort Studies Conducted in Japan

Name of cohort	Method of risk assessment	Period of risk assessment	Risk factors used for assessment	Outcome (event to be predicted)
(Communiy-based cohort)				
NIPPON DATA80 (CAD)[161]	Risk assessment chart	10 years	(Gender-specific tables), age, TC, smoking, SBP and random blood glucose	CAD mortality
NIPPON DATA80 (all forms of CVD)[161]	Risk assessment chart	10 years	(Gender-specific tables), age, TC, smoking, SBP and random blood glucose	all forms of CVD mortality (including stroke risk assessment chart)
Hisayama Study[334]	Scoring table	10 years	Gender, age, LDL-C, HDL-C, diabetes, SBP and smoking	MI incidence, sudden cardiac death, coronary revascularization and stroke incidence
JMS cohort (MI)[335]	Risk assessment chart	10 years	(Gender-specific tables), age, TC, SBP, smoking (for men only) and diabetes (for women only)	MI incidence
JMS cohort (stroke)[336]	Risk assessment chart	10 years	(Gender-specific tables), age, SBP, smoking and diabetes	Stroke incidence
JALS-ECC[337]	Scoring table	5 years	Gender, age, TC (or non-HDL-C), HDL-C, hypertension (grades 1 and 2), smoking and diabetes	MI incidence
Ibaraki cohort[338]	Website	5-15 years	Gender, age, body weight, SBP, HDL-C, TG, AST, blood glucose level (including status of treatment), blood withdrawal conditions, smoking and alcohol consumption	Death due to each cause (stroke, cancer, ischemic heart disease, all forms of CVD and total death)
JPHC[339]	Scoring table	10 years	Age, gender, smoking (gender-specific scoring), BMI (25-30 and ≥ 30), BP (scoring by whether the patient is taking antihypertensive drug; The Japanese Society of Hypertension's criteria are adopted in the classification) and diabetes	Stroke incidence
Suita study[162]	Scoring table	10 years	Age, gender, smoking, diabetes, BP classification (The Japanese Society of Hypertension's standards are adopted in the classification; however, grade Ⅱ hypertension and above are one category), TC or LDL-C, HDL-C and CKD	CAD incidence (MI, sudden cardiac death, coronary revascularization)
JPHC (cohort Ⅱ)[340]	Scoring table	10 years	Age (logarithmic value), gender, smoking, whether the patient is taking any antihypertensive drug, presence of diabetes, SBP (logarithmic value), HDL-C (logarithmic value), non-HDL-C (logarithmic value, only for CAD)	Incidence of CAD (MI + sudden cardiac death) or cerebral infarction

death and not CAD incidence, (2) the fact that it does not include information on LDL-C or HDL-C and (3) the fact that the baseline year is 1980, and when this baseline hazard is applied to more recent cohort populations, the estimated mortality of the high-risk group is higher than the actual measured mortality of recent populations[341].

Like the NIPPON DATA80 survey, the Ibaraki Prefectural Health Study used death as the outcome. The other seven articles selected for review used disease incidence as the outcome. Stroke was the outcome in two articles; MI in two; and CAD, combined CAD and stroke, and CAD or cerebral infarction in one article each. Hardly any cohort studies conducted in Japan have demonstrated that dyslipidemia was a risk factor for stroke[342], and hypercholesterolemia (e.g., TC or non-HDL-C) was not included as a risk factor in any of the assessment tool in which the outcome was stroke or cerebral infarction. In addition, absolute risk was assessed over 5 years in two of the reviewed articles and 10 years in the other seven. Furthermore, only two articles included both MI and coronary intervention as the outcomes, which also included both LDL-C and HDL-C as predictive indicators, i.e., important risk factors for establishing the management targets for dyslipidemia. Accordingly, we concluded that the Hisayama score[334] and the Suita score[162] include the most suitable criteria for assessment of absolute risk relevant to the primary prevention of ASCVD in Japanese adults by managing dyslipidemia. The biggest difference between these risk assessment tools is the fact that the Suita score considers only CAD (MI, PCI, coronary artery bypass, and sudden cardiac death), whereas the Hisayama score considers a combined outcome of CAD, with diagnostic criteria nearly the same as the Suita score, and stroke. In both scores, the fasting LDL-C value is calculated using the Friedewald formula. Stroke comprises a large proportion of the cases of cerebro- and cardiovascular disease in Japan. The ratio of stroke to CAD in the Hisayama study was approximately 2: 1; however, among stroke cases, the percentage of atherothrombotic cerebrovascular disease in which LDL-C was a risk factor is approximately 20%[36]. Therefore, it is difficult to determine detailed risk by LDL-C level with the Hisayama score, as it uses a combined outcome. The Suita score permits detailed risk assessment by specific dyslipidemia values because it includes five LDL-C level criteria in contrast to the Hisayama score, which includes two levels.

2) Management of Dyslipidemia Using Absolute Risk

The 2013 ACC/AHA guidelines[343] recommended avoiding setting an LDL-C control target and using statins to treat four groups of patients for whom they are considered beneficial. The JAS position on those guidelines, published as a press release in February 2014, is that having a management target is advisable in clinical practice in Japan from the viewpoint of patient adherence. Many practicing clinicians use management targets as treatment references, and our view is that their use should be continued. The 2016 European Guidelines for the Management of Dyslipidemias published in August 2016 continue to require the use of a management target[344]. We have also included management targets in the management of ASCVD with absolute risk in this revision of the guidelines.

As the threshold of each risk grade cannot be determined statistically by using the absolute risk, the criteria were based on clinical consensus and social conventions. In the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) Ⅲ guidelines of the USA, a ≥ 20% 10-year risk of incidence of fatal CAD and nonfatal MI based on the Framingham Score was considered high risk. However, this cannot be used in Japan because ASCVD types and incidence rates of ASCVD differ from those in the USA. The aforementioned 2013 ACC/AHA Guidelines, based on novel pooled risk calculations, recommend statins for anyone with a predicted 10-year incidence of cerebro- and cardiovascular disease (CAD and stroke) of ≥ 7.5%[333] which, however, is a rough indication to select the patients to for statin therapy. We have not accumulated enough evidence from clinical studies in Japan to establish a similar reference for selecting patients for statin therapy. Our society's guidelines must maintain continuity and consistency with the risk categorization used in our guidelines before. Management targets for dyslipidemia are also provided in the 2015 Comprehensive Risk Management Chart for the Prevention of Cerebrovascular and Cardiovascular Diseases jointly published by 13 academic societies, including JAS and the Japanese Society of Internal Medicine[156]. We considered these recent changes in existing recommendations when creating this set of guidelines and established risk categories and lipid-management targets.

3) CAD Risk Categories

In the 2012 version of our guidelines, the NIPPON DATA80 risk chart was the basis for categorizing absolute risk. While the chart detail allows to determine detailed individual risk, it is complex in

appearance. The guidelines published in 2007, were simple and convenient to use, but risk categorization depended on a number of risk factors other than LDL-C. Application of the 2007 guidelines results in lack of association with absolute risk because of the huge influence of age and sex. The effect of age is especially substantial. This means that the estimated absolute risk is low in young people even with multiple risk factors and high in older individuals even with few risk factors. Therefore, reference material 2 of the 2012 guidelines (http://www.j-athero.org/publications/gl2012_114.pdf) notes that the number of risk factors can be used in estimates of absolute risk if sex and age taken into account. Accordingly, we presented two types of flowchart for determining the lipid-management target; one uses an absolute risk calculation by the Suita score and the other uses the number of risk factors, consistent with the Comprehensive Risk Management Chart for the Prevention of Cerebrovascular and Cardiovascular Diseases 2015.

Fig. 1 shows the flowchart using the absolute risk derived from the Suita score. When screening for dyslipidemia, whether patients are candidates for secondary prevention is first confirmed. Next, whether these patients have a high-risk condition such as diabetes (not including impaired glucose tolerance), CKD, non-cardiogenic cerebral infarction, or PAD is evaluated. The Suita score calculation is performed in patients with none of these conditions. Diabetes and CKD are included in the original Suita score; but they are not used in calculating the score here as they would already have been treated as high-risk conditions. If the patient has a family history of premature CAD, i.e., first-degree relatives with incidence before 55 years of age for men or 65 years of age for women, or impaired glucose tolerance, it is assumed that they have a risk equivalent to smoking or low HDL-C; five points is added to the Suita score. The predictive model for CAD incidence based on the Suita score is shown in **Fig. 2**.

In terms of the probability of CAD incidence, apart from the lowest risk category (≤ 35), the minimum value of score range is shown as an integer in each risk category in the original article of the Suita score. In this guideline, ranges (smallest score-highest score) and the median of risk scores are shown in each category. For consistency with the absolute risk assessment by NIPPON DATA80 used in the 2012 guidelines, the absolute risk of CAD is classified by scores ≤ 40 as low (a 10-year probability of CAD incidence of < 2%), 41-55 as moderate (2-8%), or ≥ 56 as high (≥ 9%). Committee members have confirmed that the distribution of low risk, moderate risk, and high risk individuals in two different populations is almost identical to the distribution of categories I, II, and III calculated by the NIPPON DATA80 as in the 2012 guidelines.

On the other hand, determination of the risk for each sex and age group (i.e., age 40-59 and 60-74 years) is easily achieved with the Comprehensive Risk Management Chart for the Prevention of Cerebrovascular and Cardiovascular Diseases 2015. Using that categorization, we estimated the actual absolute risk of CAD using the Suita score (i.e., the LDL model). We made a few changes to make the evaluation easier. We adopted the Suita score age groups of 45-54 years in place of 40-59 years and 65-69 years in place of 60-74 years. Smoking, hypertension, and low HDL-C were added as risk factors. We used the median Suita hypertension scores of grade 1 and ≥ grade 2, and we increased the number of points awarded to the low HDL-C category (< 40 mg/dL) compared with the 40-59 mg/dL category. All were awarded five points. An LDL-C level of ≥ 180 mg/dL has always indicated a high risk for CAD, and may also suggest the presence of familial hypercholesterolemia (FH). Therefore, these guidelines clearly recommend drug therapy for patients with an LDL-C level ≥ 180 mg/dL regardless of the number of other risk factors. A flowchart of the recommended LDL-C management target based on the number of risk factors is shown in **Fig. 3**. The flowchart conforms to the low-risk, moderate-risk, and high-risk criteria of the simplified Comprehensive Risk Management Chart for the Prevention of Cerebrovascular and Cardiovascular Diseases 2015. However, if the estimation is performed on the basis of the Suita score, the distribution is 39-41 points for the low-risk, 42-56 points for the moderate-risk, and 49-71 points for the high-risk groups. Overlapping of groups is unavoidable, but considered acceptable in this simplified method. In addition, a family history of premature CAD, which is absent in the Suita score, and impaired glucose tolerance are considered to carry the same level of risk as the other factors included in the assessment method and are therefore also counted as risk factors. A management target that corresponds to the respective risk level, from low to high, is identified and compared with the actual lipid level. If the target has not been achieved, the aim of lowering is set.

As the risk of CAD changes with age and risk factor status, the management category should be reassessed at least once per year according to the most recent test findings. In addition, the risk scores have been basically created assuming that they apply to patients with risk factors, including dyslipidemia, that are not being treated. Two scores from the Japan Health Center Study took into account patients with

or without antihypertensive drugs for blood pressure control[339, 340]. However, no risk scores that consider whether the patient is taking any medicines for control of dyslipidemia or diabetes are available in Japan, the USA, or Europe. The currently available risk scoring tools can be used even if the patient is on medication, but the actual risks of cerebro- and cardiovascular diseases differ in patients with or without antihypertensive drug treatment. Usually patients whose blood pressure cannot be controlled by lifestyle modification are medicated and their risk of cerebro-and cardiovascular diseases are lowered by medication. However, as their blood pressure are assumed to remained high for long time before medicated, it is difficult to lower their risk to the same level of those who are not medicated. If they both have the same blood pressure, then the patient on medication is at a higher risk[345]. It should be kept in mind that the actual risk of disease in patients on medication may be higher than the risk indicated by the prediction score.

The incidence of CAD differs in the various regions and populations in Japan, and is higher in cities than in rural areas[98], and employees of large companies have an extremely low incidence rate of MI compared to the general population[346]. The NIPPON DATA80 outcome was the number of deaths in populations that were selected by stratified random sampling from all regions of Japan and should be representative of the general population. There are doubts as to whether the absolute risk assessed using the Suita score is also representative of the general population of Japan. The incidence of CAD is likely to be higher in the Suita study than in other regional cohort studies and it differs from many other regional cohort studies in the use of coronary intervention as one of outcomes. Consequently, the estimated absolute risk for CAD may be much higher than in other regional cohort studies. In Japan, the Hisayama score is the only other method in which coronary intervention is also assessed as an outcome, and coronary intervention is not used for an outcome in the scoring system of the 2013 ACC/AHA Guidelines in the USA[333].

4) Management Targets for Dyslipidemia from the Perspective of Preventing CAD

The category-specific dyslipidemia management targets are shown in Table2. For primary prevention, drug therapy should be considered after lifestyle modifications have been applied for 3-6 months and when the effects have been ascertained. However, for patients in any of the risk categories, including the low-risk category, if the LDL-C level remains at ≥ 180 mg/dL, then the addition of drug therapy and lifestyle modifications can both be considered. The validity of

an LDL-C management target has been partially confirmed by the systematic review data (see Chapter 4, CQ17). The management targets for high-risk category is ＜120 mg/dL, and for the the low-risk and moderate-risk groups are the same as in the previous guidelines, i.e., ＜160 mg/dL and ＜140 mg/dL, respectively. Achieving these management targets is challenging. The results of a meta-analysis of randomized controlled trials involving the use of statins revealed that a 20-30% decrease in LDL-C level lowers the risk for CAD by approximately 30%[347, 348]. Considering long-term effects and safety, a reduction rate of 20-30% in the LDL-C level can also be used as a target for the low-risk and moderate-risk groups. However, this management target cannot be applied to patients with FH or familial type Ⅲ hyperlipidemia. As patients with FH are difficult to treat, and their risk of CAD in the future is extremely high, it is recommended that these patients be referred to a specialist (see Chapter 5, Familial Hypercholesterolemia and Capter6, Other Types of Primary Dyslipidemias).

This set of guidelines was developed for use in adults aged ＜75 years of age. The advantages and disadvantages of lipid management in patients aged ＜40 years of age are at the discretion of the attending physician; however, if lipid management is to be carried out, then the Suita score absolute risk for 35-44 years of age group is used.

As patients with a history of CAD most likely require more aggressive treatment for secondary prevention, they are managed differently than patients in need of primary prevention. The LDL-C management target for secondary prevention should be set at a lower value than for primary prevention. Large clinical studies conducted in Western countries have shown that lowering the mean pretreatment LDL-C level decreases the risk of recurrence and total mortality of CAD and it is also effective in decreasing stroke incidence. Observational studies and clinical trials conducted in Japan found that the decrease in frequency of recurrence was proportional to the decrease in LDL-C level until it reached a level of 100 mg/dL. Consequently, by means of drug therapy together with lifestyle modification, the LDL-C management target for secondary prevention shall be at ＜100 mg/dL; however, if a level of ＜100 mg/dL is difficult to achieve, the target shall be a 50% reduction in the LDL-C level.

As in the previous guidelines, during secondary prevention, if non-cardiogenic cerebral infarction, PAD, CKD, or metabolic syndrome are also present or if the patient has multiple risk factors or is still smoking, it is advisable to make it mandatory to achieve an LDL-C level of ＜100 mg/dL considering

the higher risk. Some reports in Japan have also indicated the usefulness of controlling the LDL-C level to <70 mg/dL for a regressive effect on coronary plaques in patients complicated with ACS or diabetes mellitus. In view of the extremely high risk of CAD with FH, if the patient's condition is complicated with FH or ACS, then it would be appropriate to consider stricter lipid management with a target LDL-C level of <70 mg/dL and a non-HDL-C level of <100 mg/dL during secondary prevention. In addition, because diabetic patients who are complicated with conditions shown in Table 3b had a high risk for recurrence of CAD, their management target should be set as that of ACS or FH (see Chapter 4.4-1 'History of CAD' for details).

Although management targets for each lipid of concern in dyslipidemia have been established, the primary objective should be the achievement of the LDL-C management target. The non-HDL-C targets can be reviewed when the LDL-C target has been achieved. NCEP-ATP Ⅲ guidelines recommend a non-HDL-C target 30 mg/dL higher than that of LDL-C, similar to the guidelines in Japan[74, 75]. We thus include a non-HDL-C management target that is 30 mg/dL higher than the LDL-C target in this set of guidelines. If the TG level is ≥ 400 mg/dL, or if blood is collected after a meal, then the non-HDL-C target shall be used for the initial management of dyslipidemia instead of the LDL-C target. If non-HDL-C levels are used for screening in the general population, then it should also be noted that the difference between the non-HDL-C and LDL-C levels would be <30 mg/dL, at approximately 20 mg/dL[349, 350]. As in the previous guidelines, a TG level of <150 mg/dL and an HDL-C level of ≥ 40 mg/dL are the recommended targets for both primary and secondary prevention. Even if the LDL-C management target has been achieved, a high non-HDL-C level may be accompanied by hypertriglyceridemia, and management of this condition is important. Few available medications are effective for increasing low HDL-C, and some reports have found that CAD risk is low if a low HDL level is not accompanied by other lipid abnormalities[351]. On the basis of this evidence, the approach for managing HDL-C, should basically involve lifestyle modification after management of LDL-C, non-HDL-C and TG levels.

2. Lifestyle Modification

1) Overview of Lifestyle Modification

ASCVD is developed by various environmental factors such as excessive total energy intake and insufficient physical activity in addition to genetic predisposition. Many epidemiological studies in Japan and other countries have revealed that excessive intake of cholesterol and animal fats (saturated fatty acids) results in increased serum LDL-C levels. Excessive total energy intake and insufficient physical activity are the primary causes of metabolic syndrome, inducing the accumulation of visceral fat, abnormal glucose metabolism, elevated blood pressure and increased triglyceride levels, and decreased HDL-C levels. These lifestyle abnormalities result in ASCVD such as myocardial infarction. Therefore, the basic management to prevent ASCVD is the adoption of lifestyle changes such as smoking cessation and avoiding passive smoking, achieving and maintaining an appropriate body weight by re-evaluating total energy intake and physical activity, adhering to traditional Japanese dietary pattern with a low salt content, refraining from excessive alcohol intake, and performing aerobic exercise for at least 30 minutes per day. It is recommended that medical practitioners take improvements in patient lifestyle and ASCVD risk factors into account.

Table 7. Lifestyle Modifications for ASCVD prevention

- Stop smoking and avoid passive smoking
- Pay attention to excessive total energy intake and insufficient physical exercise, and maintain an appropriate body weight
- Refrain from the consumption of large amounts of fatty meat, animal fat, eggs, and processed foods with fructose
- Increase the intake of fish, green and yellow vegetables, seaweed, soy products, and unrefined grains
- Moderately consume fruits with low carbohydrate content
- Avoid excessive alcohol consumption
- Perform moderate- or high-intensity aerobic exercise for a target of at least 30 minutes a day

Table 8. Dietary Advice for Prevention of ASCVD

- Total energy intake (kcal/day) is generally calculated as body weight [kg, (height in meter)^2 × 22] × physical activity (25-30 for light, 30-35 for normal, and ≥ 35 for strenuous activity)
- Limit fat intake to 20-25%, saturated fatty acids intake between 4.5% ≤ and <7% of total energy intake, and cholesterol intake to <200 mg/day
- Increase the intake of n-3 polyunsaturated fatty acids
- Refrain from consuming industrial trans fatty acids
- Limit carbohydrate intake to 50-60% of total energy intake and increase dietary fiber intake
- Keep salt intake to <6 g/day
- Limit alcohol consumption to ≤ 25 g/day

2) Smoking Cessation

[Statement]

- **For primary and secondary prevention of ASCVD, one should stop smoking and avoid passive smoking. (Evidence level: 2, recommendation level: A)**

Smoking is an independent risk factor for ASCVD, and regardless a history of ASCVD, smoking cessation decreases the development and subsequent progression of ASCVD, and the risk of death due to ASCVD. The effects of smoking are not dependent on age or gender[102]. In ASCVD patients, the benefits of smoking cessation are apparent soon after quitting, and the longer the duration of abstinence from smoking, the greater is the decrease of risk[107]. As decreasing the number of cigarettes smoked or switching to low-nicotine or low-tar tobacco does not lead to a reduction in risk, cessation is a must for primary and secondary prevention of ASCVD. All smokers should be encouraged to quit regardless of age. Passive smoking also increases CAD and stroke risk[115, 116], and it is also important to advise patients to avoiding secondhand smoke exposure. A meta-analysis found that in other countries, the implementation of smoke-free legislation decreased the number of cases of ACS and stroke[352].

For all patients, the first step is to determine whether they have a history of smoking or passive smoking[156]. The rate of successful smoking cessation increases by 1.7 times if physicians advise their patients to quit smoking, compared with not doing so[353]. The "5A approach," i.e., Ask, Advise, Assess, Assist, and Arrange can be effective in such cases in a short time[354]. As with other drug dependencies,

symptoms of nicotine withdrawal appear soon after quitting, and that makes it difficult for many smokers to quit. In Japan, when both medical facilities and patients satisfy certain requirements, health insurance coverage is applied for smoking cessation treatment for 12 weeks[355]. The 2016 medical fee revision expanded coverage to qualifying minors. The use of effective drugs to treat nicotine-dependence (e.g., nicotine patches, nicotine gum, and varenicline)[356, 357] combined with counseling for psychological dependence increase the success rate of smoking cessation.

While the long-term benefits of smoking cessation are evident, a recent meta-analysis reported a 4-5 kg increase in body weight 1 year after quitting smoking, with the increase quite pronounced within the first 3 months after cessation[358]. Short-term worsening of blood glucose and lipid levels may be observed during that interval, but improvement in insulin resistance[117], increase in HDL-C[359] and reduction in oxidized LDL[360] have been reported regardless of weight gain. Although the expectation of weight gain hinders the start of smoking cessation and causes resumption of smoking, it is suggested that discontinuing smoking surpasses the disadvantages caused by weight gain and reduce the risk of CVD[361]. Patients must be made aware of the benefits of quitting smoking and given support to discontinue smoking during the process.

3) Management of Obesity and Metabolic Syndrome

[Statement]

- **For the management of obesity and metabolic syndrome, lifestyle modification is essential for the reduction of body weight and visceral fat. (Evidence level: 2, recommendation level: A)**

To achieve and maintain an ideal body weight and optimal waist circumference are important targets

for lifestyle modification. Obesity, especially excess visceral fat accumulation, is considered to be an inde-

pendent risk factor for CVD and promotes atherosclerosis directly or indirectly via dyslipidemia, impaired glucose tolerance, hypertension and the dysregulated production of adipocytokine[362-365]. Therefore, it is important to achieve lifestyle modification through dietary management and exercise.

i) Obesity Disease

Obesity disease is an obesity with complications that require medical treatment of weight loss for the improvement. The status of body weight is evaluated based on the body mass index, BMI (body weight (kg)/[height(m)]^2). In Japan, the ideal body weight is defined to be a BMI of 22, which has the lowest morbidity, and a BMI ≥ 25 is diagnosed as obesity[366]. However, the obesity is not immediately categorized as a disease. If obesity is complicated by or associated with health problems that require weight loss for the improvement, or associated with visceral fat accumulation likely accompanied by health problems, it is diagnosed as the obesity disease[367]. For screening of obesity disease in daily clinical practice, a waist circumference at the umbilical level of ≥ 85 cm for men and ≥ 90 cm for women is used as the criteria of visceral fat accumulation[368]. Patients with suspected visceral fat accumulation should be evaluated by abdominal CT, and those with a visceral fat area of ≥ 100 cm^2 at umbilical level are diagnosed as visceral obesity, which is common to metabolic syndrome. The reduction of visceral fat is expected to normalize the multiple abnormalities in plasma lipids, glucose and blood pressure caused by obesity[312].

ii) Metabolic Syndrome

Metabolic syndrome is a condition with excessive accumulation of visceral fat complicated by anomalies of hyperglycemia, dyslipidemia and elevated blood pressure, even though the criterion for obesity (BMI ≥ 25) is not met. Metabolic syndrome is significant because it is a high risk of ASCVD even if the levels of hyperglycemia, dyslipidemia and elevated blood pressure are relatively mild[323-327]. The difference between the diagnostic criteria in Japan and the joint statement by Western academic societies[329] is whether they are based on visceral fat accumulation or not. It is generally accepted that ASCVD risk is high in conditions with coincident hyperglycemia, hypertension and dyslipidemia without visceral fat accumulation, but multiple treatments are required in such patients, and weight loss is not likely to be effective for the improvement of multiple risk factors. For the management of metabolic syndrome with excess visceral fat accumulation, however, the benefits of lifestyle modification and behavioral therapy are evident.

iii) Treatments for Obesity and Metabolic Syndrome

The target body weight in the treatment of obese patients should not immediately be set as a BMI of < 25. Rapid weight loss resulting from extensive calorie restriction may lead to rapid rebound weight gain. Weight reduction by diet and exercise therapy is expected to provide relatively rapid improvement in moderate abnormalities of plasma lipids, glucose and blood pressure caused by obesity, even if the BMI is within the range of obesity[369]. Even if medications are needed to treat coexisting diabetes, dyslipidemia, and hypertension, it is necessary that both medical staffs and patients realize the risk reduction through measuring body weight and assessing waist circumference.

Accordingly, it is important to achieve ≥ 3% reduction body weight or waist circumference over 3-6 months and to review the patient's accomplishments over time[320, 323, 370].

iv) Relationship of Hyper-LDL Cholesterolemia with Metabolic Syndrome

Hyper-LDL cholesterolemia is a major risk factor for ASCVD, and its management protocol has been established. Metabolic syndrome has been proposed as a high-risk condition for ASCVD independent of hyper-LDL cholesterolemia. Therefore, the diagnostic criteria of metabolic syndrome include no criterion concerning the LDL-C level. However, subjects with metabolic syndrome sometimes have elevated plasma LDL-C levels. The combination of metabolic syndrome and hyper-LDL-cholesterolemia will further increase the risk of ASCVD, a comprehensive approach for both risk factor control are necessary in such cases.

4) Diet Therapy

CQ7: Is limiting total energy intake and maintaining an appropriate body weight effective in preventing ASCVD?

- Limiting total energy intake and maintaining an appropriate body weight is effective in improving serum lipid levels. (Evidence level: 1, recommendation level: A)
- Although there is no direct evidence showing that limiting total energy intake and maintaining an appropriate body weight suppresses ASCVD, improvement in serum lipid levels by lifestyle

modification including body weight reduction in response to diet therapy may prevent ASCVD. (Recommendation level: A)

There is no direct evidence that diet alone, by decreasing the total energy intake, suppresses ASCVD. However, lifestyle modification including body weight reduction has positive effects on ASCVD risk factors including serum lipid levels, which may in turn suppress ASCVD.

There is no clear evidence of setting total energy intake to improve serum lipid levels. Rather, the total energy intake should be optimized on the basis of an ideal body weight and the amount of daily activity. The total energy intake (kcal/day) can be calculated as ideal body weight (kg) x physical activity (25-30 min for light activity, 30-35 for normal activity, and ≥ 35 for strenuous activity)[371]. In Japan, active support of lifestyle modification resulted in a weight loss of ≥ 3% in obese individuals within 1 year, could reduce LDL-C, TG, uric acid, and blood pressure levels, improve blood glucose control, and increase HDL-C levels significantly[320, 372].

An RCT comparing an energy-restrictive diet with an energy-restrictive diet + exercise in overweight postmenopausal women found decreases in body weight and amount of body fat; decreased TG, TC, LDL-C, and the LDL-C/HDL-C ratio; and a decrease in SBP in both groups[373].

Another RCT compared the effects of lifestyle modification, including total energy intake of 1,300 kcal/day (lowered fat intake to 25% of total energy intake and saturated fat intake to 7% of total energy intake, and lowered to 100 mg/day cholesterol) and 1,000-1,500 kcal/week of physical activity for an average of 54 months in premenopausal women. Although 35% of the women had become postmenopausal during the intervention period, the increases of LDL-C, TG, and blood glucose levels in the intervention group were significantly less than in the assessment-only group. Body weight and waist circumferences in the intervention group also decreased significantly[374]. A meta-analysis of RCTs revealed that lifestyle and weight-loss intervention including diet in overweight and obese adults with type 2 diabetes resulted in a reduction of TC, LDL-C, and TG as well as an increase in HDL-C level in the subjects that achieved a weight loss of > 5% over 1 year[375].

Therefore, maintaining an appropriate body weight is effective in improving serum lipid levels, and it is possible to prevent ASCVD by improving serum lipid levels. However, in such a case as sarcopenia and malnutrition in the elderly, caution should be exercised when decreasing the total energy intake, and the appropriate ratio and intake of nutrients should be considered.

CQ8: Is limiting the percentage of energy derived from fat in the appropriate total energy intake effective in preventing ASCVD?

- **Limiting the percentage of energy derived from fat in the total appropriate energy intake is effective in improving serum lipid levels. (Evidence level: 1, recommendation level: B)**
- **Although there is no direct evidence showing that limiting the percentage of energy derived from fat in the total appropriate energy intake suppresses ASCVD, lifestyle modifications including weight loss and modified and/or decreased fat intake may prevent ASCVD. (Recommendation level: A)**

There is no direct evidence showing that reduction of the percentage of energy derived from fat decreases ASCVD. However, many trials comparing low-fat* and low-carbohydrate meals in the appropriate total energy intake have been performed to reveal these effects on weight loss as the primary outcome and on ASCVD risk factors as the second outcomes in obese subjects with BMI more than 25 kg/m².

A meta-analysis of RCTs comparing ≥ 1 year outcomes of high-fat (> 30% of total energy intake) and low-fat diets in obese subjects with BMI > 25 kg/m², found significant reductions of TC and LDL-C levels following a low-fat diets compared with high-fat diets. The TG levels were lower and the HDL-C levels were higher following a high-fat diet. The differences in TC and LDL-C levels observed in the two groups were abolished when total energy intake was restricted. A high carbohydrate intake was associated with an increase in the TG levels[376]. Another meta-analysis of RCTs compared the effects of balanced diets (fat to 25-35% of total energy intake, and carbohydrate to 45-65% of total energy intake) with low-carbohydrate

*Many studies performed in the Western countries consider a diet containing fat to ≤ 25% or to ≤ 30% of total energy intake as being a low-fat diet. Hence, the low-fat diet mentioned here refers to a dietary pattern in which the percentage of energy of fat is 30% or less of the total energy intake. It is necessary to take note that this is different from diets containing fat to 20-25% of total energy intake that are recommended in Japan and the fat-restricted diets for hyperchylomicronemia.

(<45% of total energy intake) diets under restricting total energy intake in obese subjects with BMI ≥ 26 kg/m². This analysis found no differences in body weight or ASCVD risk factors (serum lipids, blood pressure, and fasting blood glucose) at 3-6 months and 1-2 years[377]. Another meta-analysis of RCTs that compared low-fat and low-carbohydrate diets found that the 6-month weight loss was greater in participants with an extremely low-carbohydrate diet containing ≤ 20 g or <30 g/day of carbohydrates, compared with a low-fat diet with meals containing fat to ≤ 25-30% of total energy intake. However, the difference in body weight was no longer significant at 1 year. TG decreased and HDL-C increased in the low-carbohydrate diet group; TC and LDL-C were lower in the low-fat diet than in the low-carbohydrate diet group[378]. In another RCT, obese participants with BMI of 25 to 40 kg/m² were divided into four energy-restricted diet groups that had different percentages of energy of protein in total energy intake (15-25%), fat (20-40%), and carbohydrate (35-65%) for two years. There were no significant differences in the body weights and waist circumferences among four groups after 2 years, and the body weights remained decreased in subjects who were able to continue the diet therapy for 2 years in all groups. In this study, the largest decrease in LDL-C levels was observed in the low-fat diet, TG also decreased regardless of the diet, and the largest increase in HDL-C occurred in those with the low-carbohydrate diet[379]. A meta-analysis of RCTs

comparing high-protein and low-protein diets for ≥ 12 months found improved fasting insulin levels in the high-protein diet compared with the low-protein diet, but there were no differences in body weight, serum lipid levels or blood glucose levels[380].

Thus, limiting the percentage of energy derived from fat in total energy intake in a diet with appropriate total energy intake improves blood lipid levels, which in turn may help prevent ASCVD. A meta-analysis of RCTs that evaluated diet therapy in which the fat content was modified and/or decreased did not find significant effects on total mortality or mortality due to ASCVD. However, modified and/or decreased fat intake decreased CVD events by 14% in men with high or moderate risk of CVD who continued the therapy for at least 2 years[381].

No findings contradict the setting of the percentage of energy derived from fat of total energy intake at 20-25% and the percentage of energy derived from carbohydrate at 50-60%, which have been the recommendations for some time based on the appropriate total energy intake according to the current situation in Japan and various conditions. Most importantly, limiting the percentage of energy derived from fat is effective in lowering blood LDL-C levels. For managing hypertriglyceridemia and low HDL-C, it is recommended to intake a somewhat low percentage of energy derived from carbohydrate in consideration of complications such as obesity, diabetes, and hypertension.

CQ9: Is reduction of the intake of saturated fatty acids (SFA) or substituting with monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) effective in preventing ASCVD?

- **In an appropriate total energy intake, reduction of the amount of SFA or substituting with PUFA is effective in improving serum lipid levels, and in preventing CAD.**
  (Evidence level: 1+, recommendation level: A)
- **Serum lipid levels are expected to improve by substituting SFA with MUFA.**
  (Evidence level: 1, recommendation level: A)
- **Considerable reduction in SFA intake may be associated with the incidence of cerebral hemorrhage. (Evidence level: 2)**

A meta-analysis of RCTs did not find significant decreases in overall mortality or CVD mortality associated with a reduction of SFA intake for ≥ 2 years, but did find a 17% decrease in CVD events. Substitution of SFA with PUFA resulted in a 27% reduction, but the effect of substitution of SFA with MUFA was unclear[382]. Greater reduction in SFA intake reduced CVD events, and increases in PUFA and MUFA intake were protective of CVD events. Other meta-analysis of RCTs also found that consuming PUFA in

place of SFA reduced CAD events[383]. Some meta-analyses of cohort studies have reported an association of SFA intake and the incidence of CVD events, but others have denied its involvement[384-390]. The effects of substituting SFA with carbohydrate or protein is unclear[382].

Cohort studies in American women and Japanese population have shown that cerebral hemorrhage increased when the intake of animal fat and protein was low[391, 392]. The Japan Collaborative Cohort

(JACC) Study found an inverse association between SFA intake and mortality from total stroke, cerebral hemorrhage, and ischemic stroke[393]. The Japan Public Health Center (JPHC) study found inverse associations between SFA intake and cerebral hemorrhage and ischemic stroke, and positive association between SFA intake and myocardial infarction[394].

The effect of reduction in SFA intake on serum lipid levels has been investigated in RCTs, and a meta-analysis revealed an association with decreases in TC and LDL-C with no significant effects on HDL-C and TG levels[382]. Other meta-analysis have also found decreases in TC and LDL-C levels, but the effect of decreased SFA intake on HDL-C is less clear, and many reports have not found significant changes in TG levels[395-401]. NIPPON DATA90 also found that SFA intake is positively associated with TC and LDL-C levels[402], and in the INTERLIPID Study, a dietary increase in the PUFA/SFA ratio was associated with decreases of the TC and LDL-C but not the TG and HDL-C levels[403]. A meta-analysis including the above-mentioned RCTs reported that the reduction in CVD events was clearer in subgroup with greater reduction in saturated fats, and that degree of reduction in CVD events was strongly related to degree of reduction of serum TC level, and there was a modest suggestion of greater increase in PUFA and MUFA[382]. Substitution of 9.5-9.6% of total energy intake of dietary SFA with either MUFA or n-6 PUFA significantly decreased both TC and LDL-C levels in RCT among subjects with moderate risk of CVD[397].

The available evidence shows that reduction of SFA in an appropriate total energy intake or substitution of SFA with PUFA improves serum lipid levels and prevents CAD. Substitution of SFA with MUFA also helps to improve serum lipid levels. Considerable reduction in SFA intake may also be associated with increased risk of cerebral hemorrhage. The evidence is not strong enough to establish a recommended SFA intake. However, taking account of the intake at which the incidence of cerebral hemorrhage increases and the current average intake in Japan, no findings contradict the setting of SFA intake between 4.5% ≤ and <7% of total energy intake for the patients with dyslipidemia.

CQ10: Is increasing the intake of n-3 PUFA effective in preventing ASCVD?

- **Increasing the intake of n-3 PUFA is effective in decreasing the TG level.**
  (Evidence level: 1, recommendation level: A)
- **Increasing the intake of n-3 PUFA may lead to suppression of CAD.**
  (Evidence level: 2, recommendation level: A)

A meta-analysis of RCTs found that increased intake of n-3 PUFA (fish oil and α-linolenic acid) resulted in a significant reduction of vascular death (i.e., death due to MI, stroke, and sudden death), but there was no overall effect on composite CVD events or on total mortality[404]. Participants in the JPHC cohort study with a higher fish consumption had a lower incidence of nonfatal CAD[405], and CVD mortality was low in JACC Study and NIPPON DATA80 participants with high fish consumption[406, 407]. However, the effect of fish consumption on CVD was not clear in cohort studies conducted in Western countries[408-414]. A meta-analysis of cohort studies did not find a decrease in combined CVD events, but did report a reduction in overall mortality, CVD death, fatal MI and sudden death with increasing the intake of n-3 PUFA[415]. Another meta-analysis of cohort studies reported a decrease in sudden cardiac death and a trend to a decrease of fatal CAD in subjects who consumed ≥ 250 mg/day n-3 PUFA, compared with those who consumed <250 mg/day[416]. A similar analysis reported a significant reduction of CVD events in subjects with a high intake of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and EPA + DHA + docosapentaenoic acid (DPA)[415, 417]. Thus, it is expected that CAD would be decreased in populations with a diet high in fish, which contain EPA and DHA.

Meta-analyses of RCTs including both healthy participants and those with dyslipidemia have shown that increased intake of fish oil resulted in decreased TG levels[415, 418-420]. It has also been shown to decrease postprandial elevation of TG levels[421]. Adding fish meals to energy-restricted diets for obese patients with hypertension, improved blood glucose, fasting insulin level, and oral glucose tolerance test results in addition to decreasing TG level[422]. Increasing n-3 PUFA intake is thus effective in decreasing TG levels. Although meta-analysis of cohort studies have shown that there was an inverse association (not significant) between intake of α-linolenic acid and CAD in men[423] and non-significant association of α-linolenic acid with low incidence of CVD[424], the association of α-linolenic acid with ASCVD has not been confirmed by well-controlled RCTs[425].

CQ11: Is increasing the intake of n-6 PUFA effective in preventing ASCVD?

- **In an appropriate total energy intake, increasing the intake of n-6 PUFA may improve serum lipid levels.** (Evidence level: 1, recommendation level: A)
- **It is not clear whether increasing the intake of n-6 PUFA prevents ASCVD.** (Evidence level: 1)

Many meta-analysis of RCTs to analyze the effects of increasing the intake of n-6 PUFA has been reported. A significant 27% reduction of CVD events was observed in a meta-analysis of RCTs that evaluated the effects of substituting SFA with PUFA[382], and in another analysis, substitution of dietary SFA of 5% of total energy intake with n-6 PUFA resulted in a 19% reduction in CAD events[383]. However, other meta-analysis of RCTs and cohort studies did not find that increasing the intake of n-6 PUFA was associated with a reduction of CAD[426]. Other cohort study of US also found no association with CVD for n-6 PUFA[417]. After publication of these reports, a negative correlation of the concentration of linoleic acid in the blood and both overall and CAD mortality was reported in the cohort study of the elderly[427], and an analysis of cohort studies found that CAD events were 15% lower in patients with a high compared with low linoleic acid intake, and CAD mortality was 21% lower[428]. The preventive effect of an increasing the intake of n-6 PUFA on ASCVD incidence is thus unclear.

Regarding the effect on serum lipid levels, substitution of dietary SFA of 9.5-9.6% of total energy intake with n-6 PUFA significantly decreased both TC and LDL-C levels in RCT among subjects with moderate risk of CVD[397], and a diet with n-6 PUFA as 19% of the total energy intake in the form of corn oil decreased TC, LDL-C, and TG levels in patients with dyslipidemia[400]. Thus, increasing the intake of n-6 PUFA may improve serum lipid levels.

CQ12: Is increasing MUFA intake effective in preventing ASCVD?

- **In an appropriate total energy intake, increasing the intake of MUFA may improve serum lipid levels.** (Evidence level: 1, recommendation level: A)
- **It is not clear whether increasing the intake of MUFA prevents ASCVD.** (Evidence level: 1)

Evidence from RCTs indicates that substituting SFA with MUFA had no effect on overall mortality, CVD events, or the incidence of myocardial infarction, stoke, and coronary death[382]. The PREDIMED trial found that a Mediterranean diet supplemented with olive oil or nuts, decreased the incidence of CVD events compared with a controlled diet[429]. However, a meta-analysis of cohort studies reported that the association of dietary MUFA with CVD events and CVD death was inconsistent[386]. Another meta-analysis of cohort studies reported that increasing the intake of olive oil among MUFA seems to be negatively correlated with overall and CVD mortality, CVD events, and stroke incidence[430].

In patients with dyslipidemia, a diet high in MUFA was shown to decrease TC, LDL-C, and HDL-C levels compared with a diet high in SFA[431], and the substitution of SFA with MUFA has been shown to decrease TC, LDL-C, and HDL-C[432] or TC and LDL-C levels[397]. However, the addition of MUFA to the American Heart Association (AHA) STEP 1 Diet, increasing from 30.1% to 37.8% of total energy intake, resulted in no significant improvement of serum lipid levels[433]. A comparison of high-SFA (stearic acid), high-MUFA (oleic acid) and high-PUFA (linoleic acid) diets of approximately 38% of total energy intake in healthy individuals found no significant differences in serum lipid levels[434]. A meta-analysis of RCTs reported that substitution of carbohydrate with MUFA decreased TC and LDL-C levels non-significantly, and decreased TG level significantly and increased HDL-C level significantly. However, the lowering effect on LDL-C level was less pronounced than after substitution of carbohydrate with the same amount of PUFA[435]. Other RCT has reported improvements in body weight, body fat mass, and systolic and diastolic blood pressure with diets in which the MUFA >12% of total energy intake, compared with ≤ 12%, but significant effects on the serum lipid levels have not been confirmed[436]. Meta-analysis of RCT to analyze the effect of substitution of SFA with MUFA also did not have significant effect on serum lipid levels[382]. The current evidence thus shows that increasing MUFA intake may improve serum lipid levels, but that this effect may disappear with excessive intake.

CQ13. Is reducing the intake of trans fatty acids effective in preventing ASCVD?

- **Reducing the intake of trans fatty acids is effective in preventing ASCVD.
(Evidence level: 2, recommendation level: B)**

Trans fatty acids are constituents of naturally occurring foods such as beef, mutton, milk, and dairy products, and may also be industrially produced (hydrogenation) or refinement (deodorization or high-heat processing) of fat. Trans fatty acids produced by hydrogenation are contained in hard margarine, fatty spreads, and vegetable shortening, deep-fried food and confectionery made using these products. Trans fatty acids are also contained in refined vegetable oils such as salad oil.

Industrially produced trans fatty acids increase LDL-C[437-441] and lipoprotein (a) [Lp(a)] which is a lipoprotein that promotes atherosclerosis[437, 442, 443] and decrease HDL-C[439, 442, 444], compared with other fatty acids, whereas the effect on TG is inconsistent[440-442]. Cohort studies and their meta-analyses provide concordant evidence that the intake of trans fatty acids is associated with CAD[384, 438, 445-448]. No significant relationship with ischemic stroke has been observed[447]. A cross-sectional study reported high blood concentration of elaidic acid, an industrial trans fatty acid, in Japanese patients with metabolic syndrome or young Japanese patients with CAD[449]. Currently, there is no consensus on whether naturally occurring trans fatty acids should be regarded in the same way as industrially produced ones[439, 444, 445, 450, 451].

A meta-analysis of RCTs comparing the effects of vegetable oils containing industrially produced trans fatty acids with oils substituted with other fatty acids reported that TC, LDL-C, and TG levels were significantly decreased, and the HDL-C level significantly increased, when trans fatty acids were substituted with MUFA or PUFA[448]. A meta-analysis of cohort studies in the same article found that substitution of trans fatty acids with SFA, MUFA or PUFA has decreased CAD risk[448].

The average daily trans fatty acid intake of the Japanese is 0.92-0.96 g, or 0.44-0.47% of the total energy intake[452], which is lower than the <1% target recommended by the World Health Organization[453, 454]. Caution is required as intake may exceed the average value if one consumes an imbalanced diet with an excessive amount of confectionery and high-fat foods. Trans fatty acids should be cut back on to prevent CAD.

CQ14: Is restricting cholesterol intake effective in preventing ASCVD?

- **Decreasing cholesterol intake to <200 mg/day can result in a lower LDL-C level for patients with hyper-LDL cholesterolemia. (Evidence level: 1, recommendation level: A)**
- **Restricting the intake of cholesterol may prevent ASCVD in patients with hyper-LDL cholesterolemia. (Recommendation level: A)**

Among cohort studies, the Seven Countries Study and the Honolulu Heart Program reported that cholesterol intake was associated with CAD mortality in men[384, 455]. Whereas, the Framingham Study did not find any significant relationships between cholesterol intake and the prevalence of CAD or CAD-related death in men[456]. Cholesterol intake was not also significantly associated with death due to CAD in both men and women in the Strong Heart Study[457]. In the Framingham Study, TC and LDL-C levels were significantly and positively associated with SFA but not cholesterol intake[458]. However, an RCT found that a high-cholesterol diet (600 mg/day) did significantly increase LDL-C levels more than a low-cholesterol diet (200 mg/day)[459]. Cholesterol in the same dietary concentrations produced a larger increase in LDL-C levels when combined with SFAs than with PUFAs[460]. A meta-analysis of RCTs and cohort studies reported that increasing the cholesterol intake increased TC, LDL-C and HDL-C levels, and increases of LDL-C were no longer statistically significant when intervention doses exceeded 900 mg/day[461].

Restriction of energy of fat to 30% of total energy intake, energy of SFA to 10% of total energy intake, and cholesterol intake to <250 mg/day in the AHA Step 1 diet has been shown to significantly decrease TC levels[433]. Similar RCTs reported significant reductions in TC, LDL-C, and HDL-C levels with the AHA Step 1 diet with cholesterol to <300 mg/day[462, 463] or the Step 2 diet, with fat to 30% of total energy intake, SFA to 7%, and cholesterol to <75 mg/1,000 kcal/day plus lifestyle modification[464]. A diet intervention containing SFA to 8% of total

energy intake and cholesterol to <200 mg/day also decreased LDL-C levels[465]. Many RCTs studying the effects of varying types and amounts of fatty acids on serum lipid levels do take the amount of cholesterol into account by restricting cholesterol intake to 200-300 mg/day.

Cholesterol-containing meals also contain SFA, the cholesterol absorption differs greatly from person to person, and serum cholesterol levels are regulated by the synthesis in the liver. Consequently, the effects of cholesterol intake on serum lipid levels vary among individuals[466, 467], and have also been demonstrated in intervention studies[459, 468-472]. For example, although hens' eggs are high in cholesterol content, the relationship between egg consumption and serum lipid levels is variable in both healthy individuals and in patients with dyslipidemia[469-471, 473-482]. Meta-analysis of clinical studies demonstrated that TC, LDL-C, and HDL-C levels have been shown to increase with the dietary consumption of egg yolks[483]. The average daily intake of cholesterol in the Japanese ≥ 20 years of age was estimated as 340 mg in men and 290 mg in women from the 2015 National Health and Nutrition Survey. In diabetic subjects, some cohort studies and a meta-analysis of these have found that CVD, especially the incidence of or death due to CAD, was increased with a high intake of hens' eggs[484-488].

Although it is difficult to establish a limit of cholesterol intake for patients with hyper-LDL cholesterolemia, an intake of cholesterol to <200 mg/day and of SFA to <7% of total energy intake may decrease the LDL-C level, and the improvement of serum lipid levels may prevent ASCVD. Individuals who do not have serum high-LDL cholesterol levels should also refrain from excessive intake of cholesterol, because excessive intake may elevate their LDL-C levels in future.

CQ15: Can increasing the intake of vegetables be recommended for ASCVD prevention?

- **Consumption of vegetables may decrease the risk for CAD and stroke.**
  (Evidence level: 2, recommendation level: A)
- **Consumption of green and yellow vegetables may decrease stroke risk.**
  (Evidence level: 2, recommendation level: A)

Meta-analyses of cohort studies have shown that overall mortality, death due to CVD[489], and risks of CVD[490] and CAD[491, 492] decrease when vegetable intake is high. Before 2004, an association between stroke and the vegetable consumption had not been demonstrated[493, 494], but a recent study reported that stroke risk was 14% lower in a group with the highest vegetable intake than in a group with the lowest intake. The association was strongest for the intake of leafy vegetables[495]. Cruciferous, green and yellow vegetables may have preventive effects on stroke[496].

Cohort studies in Japan reported the reduced mortality risk due to CVD in men and women who consumed vegetables in large amounts[497] and in women who consumed more vegetables dishes[498]. In one study, stroke mortality rate has been shown to be low in with frequent consumption of green and yellow vegetables[499], however this was not shown in another study[500].

Very few RCTs have evaluated the effects of increased vegetable intake. Adding 350 g of Okinawan vegetables, such as bitter gourd, green papaya, and gynura bicolor, for 2 weeks had no effect on the serum lipid levels in healthy young women[501, 502].

The consumption of vegetables including green and yellow vegetables may be useful for preventing ASCVD incidence. However, as pickled vegetables habitually consumed in Japan have a significant influence on the salt intake[503, 504], the intake of a vegetable dish containing reduced-salt content should be recommended.

CQ16: Can increasing the intake of seaweed be recommended for ASCVD prevention?

- **Consumption of seaweed may be useful for preventing ASCVD.**
  (Evidence level: 2, recommendation level: B)

Japan is one of the few countries in the world in which seaweed is regularly consumed. The consumption of seaweed has been routinely recommended in energy-restricted diets in Japan as it provides little energy[505], and is rich in viscous fibers and minerals such as potassium, calcium, magnesium, iron, zinc, and iodine.

In recent years, much attention has been focused

on the health effects of the sulfated polysaccharides and carotenoids contained in seaweed.

Although, very few studies have focused on the benefits of seaweed consumption, a cohort study in Japan reported that a high frequency of seaweed consumption was associated with decreased all-cause mortality in both men and women, as well as decreased risk of death due to cerebrovascular disease in women, but no association with CAD was found[506]. No studies have investigated the association between the dietary consumption of seaweed and cardiovascular risk factors. At present, information on the effectiveness of seaweed consumption to prevent ASCVD incidence is insufficient.

Incidentally, as seaweed contains a high concentration of iodine, and some kinds of seaweed contain a high amounts of arsenic, it is necessary to avoid excessive consumption of seaweed[507].

CQ17: Can increasing the intake of fruit be recommended for ASCVD prevention?

- **Consumption of fruit may decrease the risk for CAD and stroke; moderate consumption of fruit with low sugar content is recommended.** (Evidence level: 2, recommendation level: A)

Meta-analyses of cohort studies have shown that the regular intake of fruit decreases overall and CVD mortality[489] and CAD[492, 508], stroke[493], and type 2 diabetes risk[509], and the association is especially strong with the regular intake of citrus fruits[495, 496], apples, and pears[495].

In Japan, cohort studies have revealed that as the amount or frequency of fruit consumption increases, the risk of mortality due to CVD[497] and stroke[497, 499, 500] lowers. A high frequency of citrus fruit consumption is related to a reduction in overall mortality[500], CVD mortality[500], and CVD incidence[510], and an increased amount of citrus fruit consumption is associated with a lower risk of CVD[511]. Furthermore, increased fruit intake was reported to decrease the prevalence of hypertension[512]. Some RCTs have reported the effects of consuming additional fruit with low sugar content on serum lipid parameters. The addition of grapefruit or oroblanco to the diet resulted in small decreases in the level of LDL-C and TGs[513, 514], however, the addition of kiwifruit and berries increased the levels of HDL-C[515, 516].

The meta-analysis of RCTs showed that the consumption of fruit juice could decrease diastolic blood pressure, but did not influence blood cholesterol level[517]. However, the sweetie juice supplemented diet decreased levels of LDL-C and TGs[518] and daily consumption of a high amount (750 mL) of orange juice increased TG levels by 30% and HDL-C levels by 21%[519], in an RCT study on patients with high TC levels. It should be noted that the effects of fruit consumption on ASCVD risk factors differ according to the variety and quantity of fruit.

The evidence shows that increasing the intake of citrus fruits or fruits with low sugar content reduces stroke and CAD risk, but excessive fruit consumption may lead to increased TG concentration.

CQ18: Can decreasing the intake of processed foods containing fructose be recommended for ASCVD prevention?

- **Consuming large amounts of processed foods containing fructose may increase ASCVD risk; reducing the intake of such foods is recommended.**
  (Evidence level: 3, recommendation level: B)
- **Decreasing the intake of fructose in processed food may decrease the TG concentration.**
  (Evidence level: 3, recommendation level: B)

Fruit and honey contain natural fructose. Its sweetness is stronger than that of sugar and increases when chilled. Because of its potent sweetness, fructose, sucrose which is a disaccharide containing glucose and fructose, and isomerized sugars (high-fructose corn syrup), are used as sweeteners in soft drinks, milk beverages, and ice sweets such as sherbet and gelato. Consuming large quantities of fructose in processed foods has been considered to increase CAD risk through excess energy intake, obesity, increased TG level, worsened insulin resistance, and the incidence of type 2 diabetes.

The results of cohort studies that investigated the association of sugar-sweetened beverage consumption with CVD and stroke risk are inconsistent[520, 521]. In the JPHC cohort study in Japan, soft drink was positively associated with the risk of ischemic stroke in women, but the risk tended to be lower in men[522].

A meta-analysis of RCTs that studied the effects of sugars containing fructose in healthy and obese par-

ticipants and type 2 diabetes patients reported significant increases in TG levels when 18-35% energy derived from fructose was added to the control diet. No difference was found between the control and fructose diets in isocaloric trials[523]. Another meta-analysis of RCTs on healthy and obese subjects found an association of fructose with elevated TG levels and blood pressure as well as decreased HDL-C levels, but the significance disappeared when studies that lead to the highest effect on the heterogeneity test were excluded[524]. The effects of fructose on the risk factors for ASCVD were not observed in other RCTs[525, 526].

As demonstrated above, evidence on the direct effects of a high intake of processed foods containing fructose on ASCVD is lacking, however, it is necessary to note that this would be the cause of excessive energy intake.

CQ19: Can the consumption of soy and soy products be recommended for ASCVD prevention?

• **Consuming soy and soy products is recommended because they may decrease CAD and stroke risk.** (Evidence level: 2, recommendation level: A)

Investigations of the association of ASCVD with soy consumption are limited to cohort studies in Japan, where soy and soy products are habitually consumed. The JPHC study reported that the risk of cerebral infarction and MI in women who consumed soy ≥ 5 times/week was lower by 36% and 45%, respectively, compared to the corresponding risk in women who consumed soy 0-2 times/week[527]. A study in a cohort with a very high prevalence of hypertension did not find the same association[528].

The association of soy products that are consumed as food, such as soy milk, soybeans, kinako (toasted soybean flour), tofu, fermented soybeans and cookies with ASCVD risk factors, has been evaluated in RCTs. Some reported a decrease in TC or LDL-C levels[529-541], and others have not reported such a decrease[542-553]. Differences in the subjects, type and quantity of food products, and the intervention period make it difficult to compare studies. In a Japanese RCT, decrease in TC levels was observed in premenopausal women with a diet supplemented with soy milk[554]. Some studies have reported decrease in blood pressure associated with soy consumption[555, 556], whereas others have not reported such a decrease[540, 544-546, 557]. A meta-analysis of studies evaluating consumption of isolated soy protein reported a reduction of LDL-C levels in individuals with high TC levels[558]. The consumption of soy or soy products may play a part in decreasing CAD and stroke risk.

CQ20: Can meals following the Japanese dietary pattern (The Japan Diet) be recommended for ASCVD prevention?

• **A low-salt Japanese dietary pattern with reduced fat on meat and animal fats such as beef tallow, lard, and butter and the consumption of a combination with soy, fish, vegetables, seaweed, mushrooms, fruits, and unpolished grains are recommended for ASCVD prevention.** (Recommendation level: A)

Daily meal preparation involves combining a variety of food items. It is therefore useful to evaluate the effects of meals on the incidence of diseases and their risk factors, taking into account the combination of food items consumed (dietary pattern) and not just the individual nutrients[559].

Epidemiological findings of the Seven Countries Study obtained in the 1960s and 1970s revealed that the CAD mortality rate in Japan was extremely low compared with that in Northern Europe and the USA. The notable diet in Japan was very small amounts of meat, fats and oils, and dairy products with large amounts of rice, soy, and fish[560]. Other than polished rice, barley and slightly polished rice were consumed in Japan up to the 1960s[561]. Domestic cohort studies with baseline data up to the 1990s showed a low CVD mortality rate patients with dietary pattern containing high percentages of soy, fish, vegetables, seaweed, mushrooms and fruits[562, 563]. The mortality rate due to overall and CVD were approximately 20% lower with a Japanese-style dietary pattern with salt reduction[564]. However, the CVD mortality rate was higher if the dietary pattern contained of high percentages of meat, butter, and high-fat dairy products[562-564].

As described above, the consumption of food items that constitute the Japanese dietary pattern has been reported to decrease ASCVD risk. Furthermore, a meta-analysis of cohort studies conducted in Northern Europe, the USA, and China found that the consumption of unrefined grains resulted in a lower risk

of CAD[565].

Therefore, the traditional Japanese dietary pattern in which fat on meat and animal fats such as beef tallow, lard, and butter, are avoided, and barley, millet and unpolished grains are consumed in combination with soy, fish, vegetables, seaweed, mushrooms, and fruits, is believed to contribute to preventing ASCVD[566].

The high salt content of a Japanese diet, with an average salt intake of 10.0 g/day[567] is of concern. As excessive salt intake leads to increased blood pressure and promotes atherosclerosis, a target intake of <6 g/day is thus recommended[122]. In addition, although moderate alcohol intake may have preventive effects in terms of CAD risk, it should be noted that excessive alcohol intake causes high blood pressure and hypertriglyceridemia[568].

Diet to Improve Risk Factors

Diet modification is essential for the treatment of dyslipidemia and ASCVD. Based on "the Japan diet" with a lower salt content, it is important to instruct the patients' diet in consideration of eating behavior, condition, and lifestyle. Timely evaluations of the effects are needed to modify their diet appropriately.

•Hyper-LDL Cholesterolemia and Diet

Intake of SFAs, cholesterol and trans fatty acids, which increase the LDL-C level, should be decreased with the appropriate management of total energy intake. Replace SFAs with MUFAs or PUFAs, reduce intake of SFA to <7% of energy, and cholesterol to <200 mg a day. Specifically, reduce intake of high fatty meat and/or animal fats (beef tallow, lard, butter), milk, offals, and eggs. The consumption of vegetables, including green and yellow vegetables, and soy or soy products is recommended.

•Hypertriglyceridemia and Diet

Patients should achieve and maintain a desirable body weight. Lower intake of carbohydrates, and avoide excessive consumption of alcohol. Excessive consumption of fruits and fructose-containing processed foods should be avoided as they may contribute to an increase in TG level. The intake of n-3 PUFA should also be increased. In patients with hyperchylomicronemia, the total amount of dietary fats should be redused (≤ 15% of energy); the use of medium-chain fatty acids[569, 570].

•Low HDL-C and Diet

Patients should maintain an ideal body weight or consider a total energy intake to help achieve it. The percentage of energy derived from carbohydrates should be slightly decreased, and the amount of trans fatty acids should be decreased.

•Metabolic Syndrome and Diet

The total energy intake should be optimized on the basis of the ideal body weight and the amount of daily activity. Patients should aim to decrease their body weight or waist circumference by ≥ 3% within 3-6 months[320], rapid weight loss should be avoided. The percentage of energy derived from carbohydrates should be slightly decreased while consuming enough protein to help prevent a reduction of muscle mass[320]. Preparing meals with foods with a low glycemic index and a low glycemic load lower the risk ASCVD incidence[571-574]. Concomitant exercise therapy is effective for improving obesity, serum lipid levels, and blood pressure[373, 575].

•Hypertension and Diet

Salt intake should be restricted, with positive consumption of vegetables and fruits. It should work toward sodium restriction and potassium sufficiency, which promote the urinary excretion of sodium. It is recommended to treat obesity, maintain an ideal body weight, refrain from the consumption of cholesterol and SFAs, and positively consume fish (fish oil). The excessive consumption of alcohol should be avoided as it increases blood pressure.

•Diabetes Mellitus and Diet

Improving obesity is the most important lifestyle component for controlling type 2 diabetes. Total energy intake should be adequate for individual physical activity (energy consumption), and whenever possible, it should be divided equally into three daily meals i.e., breakfast, lunch, and dinner. Food should be chewed well and consumed without rushing. Keep in mind that sugars should not be overly consumed, and should comprise <60% of the energy intake. There should not be an excess or insufficient intake of any nutrients. Patients should increase dietary fiber. Eating the vegetables first during meals suppresses the elevation of postprandial blood glucose, which can help in decreasing body weight[576]. The dietary percentages of energy from SFAs and PUFAs should be ≤ 7% and ≤ 10%, respectively.

5) Exercise Therapy

[Statement]

- **Habitual physical activity and aerobic exercise are effective for ASCVD prevention.**
  (Evidence level: 1, recommendation level: A)

Lack of physical activity is associated with increased body fat (obesity), dyslipidemia, metabolic syndrome, hypertension, diabetes/impaired glucose tolerance, vascular endothelial dysfunction, and decreased physical fitness. It is also a risk factor for ASCVD such as CAD and cerebrovascular disease[577-587]. Increased sedentary behavior, defined as "any waking behavior with an energy expenditure of 1.5 metabolic equivalents (METs) or less in a sitting or reclining posture" may be a risk factor for various health outcomes independent of physical activity[588-590].

Increasing physical activity maintains or adds to physical fitness, improves serum lipid levels, decreases blood pressure, increases insulin sensitivity and glucose tolerance, improves vascular endothelial function, and decreases thrombosis risk[591-593]. It also decreases mental stress and slows the decline in cognitive function[594, 595]. The amount of daily physical activity, leisure time physical activity and physical fitness level have been found to be negatively correlated with morality due to cerebrovascular disease and cancer, as well as all-cause mortality in studies conducted worldwide[596-606] and cohort studies in Japan[577].

Exercise therapy includes both aerobic and resistance (muscle) exercise. Aerobic exercise is effective in improving lipid metabolism[607-615]. The effects of aerobic exercise (walking, brisk walking, supervised or nonsupervised training) compared with nonexercising controls on LDL-C, TG, and HDL-C levels have been extensively studied. However, study results are difficult to compare because of differences in subjects, exercise intensity and duration, and pre-intervention lipid levels. Among 8 reports of systematic review and meta-analysis of RCTs with comparison of exercise and non-exercise control including Japanese participants and were published after 2,000, significant decreases in LDL-C and TG levels were reported in two articles, respectively. Six reported a significant increase in HDL-C levels, which was the most frequently observed effect of exercise on serum lipids[577, 607-613]. A meta-analysis of 25 RCTs that compared aerobic exercise for training periods of at least 15 minutes for ≥ 8 weeks with nonexercise control reported that exercise therapy significantly increased the HDL-C levels[612]. The increase in HDL-C was positively correlation with the duration of exercise, and exercising for ≥ 121 minutes/week significantly increased the levels. A meta-analysis of four RCTs conducted in Japan comparing the effects of low to moderate-intensity aerobic exercise for 10 weeks to 24 months with nonexercise therapy found that exercise significantly increased the HDL-C levels[577].

Table 9 shows simplified guidelines for exercise therapy. Efforts should be made to increase daily physical activity and to incorporate exercises suited to individual lifestyles. Increasing aerobic exercise is the primarily goal, and brisk walking or slow jogging are recommended. Moderate-intensity exercise (e.g., walking at normal speed) is effective and safe and can be per-

Table 9. Guidelines for Exercise Therapy

Type	Implement with an emphasis on aerobic exercises such as walking, brisk walking, swimming, aerobic dance, slow jogging, cycling, and bench-stepping
Intensity	Aim for a moderate intensity* or above
Frequency and duration	Aim to exercise for at least 30 min per day at least 3 days a week
Others	Walk or perform other, similar activities frequently and at times other than during exercise therapy and avoid a sedentary lifestyle as much as possible

*Moderate intensity means as follows:
- An exercise intensity equivalent to walking at normal speed (=walking)
- In terms of METs (a unit that expresses the intensity of exercise as the equivalent number of times the resting metabolism), it is typically 3 METs (walking) but it differs according to individual physical fitness
- The perceived exertion during exercise corresponds to 11-13 on the Borg scale, i.e., fairly light to somewhat hard)

The Borg Scale

Scale	Perceived
20	
19	Very, very hard
18	
17	Very hard
16	
15	Hard
14	
13	Somewhat hard
12	
11	Fairly light
10	
9	Very light
8	
7	Very, very light
6	

(Borg GA: Med Sci Sports Exerc. 1973; 5: 90-93)

formed for extended periods without strain. The increase in blood pressure during moderate exercise is modest, and blood lactate does not accumulate. The aim is to exercise for at least 30 minutes a day at least three times a week, daily if possible. For the elderly with a muscle wasting, aerobic exercise combined with mild resistance training is useful. Bench-stepping exercises, which can be performed indoors, are recommended[577]. In 2013, the Ministry of Health, Labor and Welfare of Japan published "Japanese official physical activity guidelines for health promotion (Active Guide)"[616] (see **Appendices 1** and **2**). To prevent lifestyle-related diseases, starting with "Plus 10," be active for an additional 10 min every day" helps to

achieve the ultimate aim of 60 minutes of activity per day for adults and 40 minutes per day for the elderly.

Note that unaccustomed exercises carry a risk of musculoskeletal disorders, and in addition to bone and joint injury, strenuous exercise may add to the risk of sudden death and MI in patients with CVD[617, 618]. This should be taken into careful consideration, and when exercise therapy is performed, underlying ASCVD and bone and joint diseases should be taken into account. It is necessary to choose exercises and physical activities that are adapted to individual physical fitness, exercise history, and the current status of physical activity.

3. Drug Therapy

1) Drug Therapy

CQ21. Can the evidence on ASCVD prevention in Western countries be applied in Japan?

- **It has been proven that the effects of LDL-C-lowering therapy using statins to decrease the relative risk of ASCVD incidence are observed regardless of race and absolute risk.**
  (Evidence level 1+, recommendation level A)

Although the absolute risk of CAD is lower in the Japanese population than in Western countries, the relative risk of LDL-C and CAD is similar. The MEGA study[41], a large-scale clinical trial conducted in Japan, confirmed the effectiveness of LDL-C-lowering therapy using statins to prevent cardiovascular events in Japanese patients with hypercholesterolemia. Epidemiology studies, however, have not found a significant correlation of serum cholesterol level and the incidence of noncardiogenic cerebral infarction[38, 57, 64, 337]. LDL-C is also a risk factor for atherothrombotic cerebral infarction[36], and the effectiveness of statins to decrease the incidence of atherothrombotic cerebral infarction was confirmed in a Japanese population by the J-STARS study[619]. The effectiveness of statins for preventing the first occurrence and recurrence of stroke in Japanese populations was confirmed in a

sub-analysis of the MEGA study[620, 621] and in the JELIS study[622].

Meta-analyses conducted by the Cholesterol Treatment Trialists' Collaboration on large-scale clinical trials using statins confirmed that a decrease in the incidence of cardiovascular events was proportionate to the decrease in LDL-C level, regardless of pretreatment LDL-C level and individual absolute risk[177-179, 348]. The HOPE-3 study was a large international study with 21 participating countries, including some in the Asian region, and it evaluated primary prevention in populations with a risk that was equivalent to high risk in Japan. It has been proven by the study that LDL-C-lowering therapy using statins exhibits suppressive effects on cardiovascular events regardless of race[623].

2) Indications for Drug Therapy

CQ22. Is an LDL-C management target of <120 mg/dL appropriate for high-risk category of primary prevention?

- **The LDL-C level for high-risk patients in primary prevention should be controlled at a target of <120 mg/dL. (Evidence level 2, recommendation level B)**

The APPROACH-J study was a prospective Japanese study that investigated the 2-year incidence rate of cardiovascular events for high-risk patients in primary prevention who had recently started statin therapy. The risk of CAD incidence plateaued at LDL-C

levels ≤ 119 mg/dL, which demonstrates the importance of maintaining an LDL-C level of <120 mg/dL[624]. The importance of the comprehensive management of overlapping complicating risk factors in addition to LDL-C, such as smoking, hypertension, and

diabetes, was affirmed in this study. Furthermore, for diabetes patients, who are a high-risk group in primary prevention, a sub-analysis of the J-LIT study results found that keeping the LDL-C level <120 mg/dL was useful for preventing CAD incidence[625]. The HOPE-3 study was a randomized comparative intervention trial of statins for primary prevention in populations with characteristics corresponding to high risk in Japan. Significant reduction of cardiovascular events was seen in the statin-treated group that maintained LDL-C levels of <120 mg/dL. The average pretreatment LDL-C level of both study groups was approximately 128 mg/dL[623]. Thus, controlling the LDL-C level at a target of <120 mg/dL for high-risk populations in primary prevention appears to be appropriate. However, despite recent efforts to increase the awareness of and familiarity with guidelines, it has been reported that the achievement of the LDL-C management target by high-risk patients with type 2 diabetes, noncardiogenic cerebral infarction, or PAD is still not adequate in Japanese clinical practice[626, 627].

CQ23. When should drug therapy be initiated for hyper-LDL cholesterolemia?

- **For high-risk patients in primary prevention, if lifestyle modification is not likely to be effective, the combined use of drug therapy should be considered as soon as possible.**
  (Evidence level 3, recommendation level A)
- **It has been proven that initiating aggressive LDL-C-lowering therapy at an early stage after disease incidence is effective for secondary prevention.**
  (Evidence level 1+, recommendation level A)

In addition to plasma LDL-C level, physicians prescribing drug therapy in primary prevention should also be aware of other patient characteristics, including smoking habits, the presence of hypertension, diabetes, CKD, a family history of premature CAD or other ASCVD, such as noncardiogenic cerebral infarction, PAD or carotid atherosclerosis. An assessment of individual risk should include this information when drug therapy is considered for patients with high absolute risk. The long-term follow-up of large clinical trials of statins that were conducted in the 1990s, such as the West of Scotland Coronary Prevention Study (WOSCOPS) and the Heart Protection Study (HPS)[628, 629] confirmed that early initiation of LDL-C-lowering therapy regardless of the plasma LDL-C level was useful for the long-term prevention of cardiovascular events and all-cause mortality in high-risk patients. No increases in new-incidence cancer or non-CVD deaths were observed, which reconfirms the safety of long-term LDL-C-lowering therapy using statins.

Lifetime cumulative LDL-C and the threshold for CAD incidence are recent concepts. Aggressive LDL-C-lowering therapy is recommended as early as possible for patients with familial hypercholesterolemia who present with hyper-LDL cholesterolemia at a young age followed by developing the premature CAD. Cardiovascular events may occur sooner than expected in patients with usual hyper-LDL cholesterolemia because of the accumulation of LDL-C that is promoted by complicating atherosclerosis risk factors. A Mendelian randomization analysis found that the risk of cardiovascular events was extremely low in patients with hypo-LDL cholesterolemia that was caused by gene mutations[630]. There is a need to consider LDL-C-lowering therapy as soon as possible for hyper-LDL cholesterolemic patients with high absolute risk. Long-term observational included in large clinical trials found that the early initiation of LDL-C-lowering therapy decreased lifetime cumulative LDL-C, which may have made it possible to decrease the occurrence of cardiovascular events.

Low-risk patients without additional risk factors, young individuals, and premenopausal women are at low absolute risk. Even if the LDL-C management target is not achieved, it is possible that the progress may be observed with lifestyle modification only. Drug therapy should be considered on the basis of the importance of the existing risks only if strict lifestyle guidance does not improve lifestyle habits and does not achieve the management target.

CQ24. Can an LDL-C management target be set for preventing occurrence of ASCVD for secondary prevention in patients with a history of CAD?

- **In secondary prevention, the LDL-C control target should be at a level of <100 mg/dL. However, if it is difficult to achieve an LDL-C level <100 mg/dL, the alternative target would be to**

decrease the level by ≥ 50%. (Evidence level 3, recommendation level A)

Clinical trials have confirmed that the effects of statins on the reduction of cardiovascular events can improved by administering statins with more potent LDL-C-lowering effects[177, 631]. However, there are no lipid intervention studies that have set an LDL-C management target. Therefore, when LDL-C-lowering therapy is given to prevent cardiovascular events, the question of whether to "treat to target" or to use a potent statin without setting a target value i.e., "fire and forget" is under debate. Currently, it is necessary to consider the results of epidemiological studies and cohort studies to choose the LDL-C management target. In a long-term Japanese observational study of secondary prevention, the incidence of cardiovascular events was significantly decreased in patients whose LDL-C levels were controlled at <100 mg/dL[632]. In the CREDO-Kyoto Registry Cohort-2, the 3-year incidence of cardiovascular events in patients treated with potent and standard statins were compared. Patients underwent analysis stratified by LDL-C management level[633]. The incidence of cardiovascular events was significantly lower with the potent statin than with the standard statin. In addition, in patients with LDL-C levels ≥ 120 mg/dL, the risk of the incidence of cardiovascular events was 1.74 times greater than in patients with LDL-C levels of 80-99 mg/dL, which was a significant difference. A significant difference in the risk of cardiovascular events was not seen when the LDL-C level was <80 mg/dL. The mean LDL-C levels that were analyzed by the strength of statin were 92 mg/dL in patients treated with potent statins and 101 mg/dL in patients with standard statins, respectively. The study outcome supports the benefits of controlling the LDL-C level at <100 mg/dL rather than basing the treatment on the strength of statin. It has been reported that the risk of cardiovascular events increased in patients with the escape phenomenon (i.e., re-elevation in LDL-C level of ≥ 10% after a reduction) following the start of statin treatment[634]. However, patients with the escape phenomenon had an LDL-C level of 106 mg/dL; whereas the comparison group had an LDL-C level of 90 mg/dL. In addition to the choosing the strength of the statin, regular blood testing to monitor the LDL-C level is recommended. A recent survey in Japan, found that 65% patients with ACS, and 55% for other secondary prevention patients, achieved an LDL-C management target of <100 mg/dL. Thus, LDL-C management with lipid-lowering therapy for secondary prevention in Japan is still not satisfactory[626]. A meta-analysis of international trials reported that the risk for ASCVD was significantly decreased in patients with an LDL-C reduction of ≥ 50%, regardless of the LDL-C level achieved[635]. To prevent ASCVD in cases where it is difficult to control the LDL-C at <100 mg/dL, lipid management with the aim of lowering pretreatment LDL-C by 50% or more is recommended[177, 631, 633, 635].

CQ25. Is risk stratification possible in secondary prevention? In addition, is it possible to set an LDL-C management target?

- **Even in secondary prevention, the risk for cardiovascular events is high if FH, ACS, DM, non-cardiogenic cerebral infarction, PAD, CKD, and metabolic syndrome are present, or if there is an overlap in the major risk factors and the presence of smoking. Stricter LDL-C management is therefore necessary. (Evidence level 3, recommendation level B)**

Even in secondary prevention, the incidence of cardiovascular events is clearly high if FH, ACS, DM, noncardiogenic cerebral infarction, PAD, CKD, and metabolic syndrome are also present, or if there is an overlap of the major risk factors or continued smoking (Table 3) (refer to Chapter 3, 1-8: History of CAD). After the results of IMPROVE-IT[636] and clinical trials using PCSK9 inhibitors[637-639] conducted in recent years, the clinical significance of maintaining the LDL-C level at <70 mg/dL is garnering attention in secondary prevention complicated with high-risk conditions[640].

In Japan, only a few interventional studies have been conducted using cardiovascular events as the endpoint for secondary prevention. Therefore, results from interventional studies involving patients with ACS who underwent IVUS as a surrogate endpoint have instead been reported. The results of one meta-analysis revealed that the rate of change in plaque (atheroma) volume [percent atheroma volume (PAV)] correlates significantly with cardiovascular event risk[641]. The results of ESTABLISH[642], JAPAN-ACS[643], the ZEUS study[644], and PRECISE-IVUS[645] have shown that in cases stratified into a high-risk category even in secondary prevention, such as ACS or ACS complicated by DM, controlling the LDL-C at a target level of <70 mg/dL is useful for plaque regression. A meta-analysis of clinical trials that combined

primary and secondary prevention has revealed a linear relationship between the LDL-C level following statin treatment and the suppressive effects of statins on cardiovascular events. A review performed outside of Japan reported that larger suppressive effects on cardiovascular events can be achieved by maintaining the LDL-C level at <50 mg/dL[646]. We consider these findings to be supportive of the hypothesis of "lower is better." As FH puts the patient at extremely high risk for CAD, it is likely that the risk in primary prevention is equivalent to that in secondary prevention.

Therefore, in secondary prevention complicated with FH or ACS, stricter LDL-C management to achieve a level <70 mg/dL can be considered appropriate. The secondary prevention for DM patients complicated with conditions described in **Table 3b**, should also be treated based on the target level of FH or ACS, as they are considered to be at high risk of recurrence of CAD. In cases where the target cannot be achieved with monotherapy using statins, the combined use of medications such as ezetimibe should be considered.

CQ26. If the LDL-C management target has been achieved, should lipid management be carried out using the non-HDL-C level as an indicator?

•**If the TG level is high even when the LDL-C management target has been achieved, lipid management should be carried out using the non-HDL-C level as the target.**
(Evidence level 3, recommendation level B)

Undoubtedly, the LDL-C level is the most important target in lipid management. However, in managing dyslipidemia expressed by hypertriglyceridemia, the non-HDL-C level is more useful than the LDL-C level. This has been reported in a number of studies[177-179, 623, 624, 626, 627, 647]. The standard non-HDL-C level is defined as a value 30 mg/dL higher than LDL-C in NCEP-ATP Ⅲ. Studies from Japan have shown similar findings[74, 75]. Even when the LDL-C management target has been achieved, if hypertriglyceridemia is present, the non-HDL-C level should be the secondary target for lipid management aimed at preventing ASCVD. However, if the patient's TG level is ≥ 400 mg/dL or if blood sample is postprandial period, then the non-HDL-C level should be used initially instead of the LDL-C level. We hope that additional evidence will be gathered from interventional studies using the non-HDL-C level as a marker.

Q1. Is therapeutic intervention for hypertriglyceridemia effective in suppressing the incidence of ASCVD?

•**There is insufficient evidence regarding the preventive effect of drug therapy for hypertriglyceridemia upon the incidence of ASCVD. However, keeping in mind that patients with a marked increase in fasting triglyceride levels face the risk of acute pancreatitis, it is important that we consider the concurrent administration of fibrates or other drugs with dietary advice, such as limiting the amount of fat intake and abstinence from alcohol. (Recommendation level: B)**

As yet, no RCT has reported an effect on the incidence of ASCVD after conducting drug therapy targeted only at patients with hypertriglyceridemia. However, there are reports of RCTs using TG-lowering nicotinic acid derivatives and fibrates on patients with dyslipidemia, and some have shown a preventive effect on the incidence of ASCVD. The first of such RCTs is the Helsinki Heart Study, a large clinical study involving patients with hypertriglyceridemia[648]. In this study, gemfibrozil significantly suppressed the incidence of CAD by 34% in middle-aged men in primary prevention; these men had non-HDL-C levels of 200 mg/dL or higher. Subsequent to the Helsinki Heart Study, there were the FIELD[649] and ACCORD[650] studies, both conducted with fenofibrate. With respect to primary endpoints of these studies, although the effectiveness of fenofibrate was not demonstrated, a meta-analysis in primary prevention using fibrates revealed that deaths from cerebrovascular and cardiovascular diseases, non-fatal myocardial infarction, and non-fatal stroke significantly decreased by 16%[651]. These deaths were also reported to significantly decrease by 12% in secondary prevention[652]. Meanwhile, the co-administration of a nicotinic acid derivative (niacin) and statin to increase HDL-C levels did not have a suppressive effect on cardiovascular events in the AIM-HIGH[653] and HPS2-THRIVE[654] studies.

Therefore, we cannot confirm that drugs for hypertriglyceridemia, such as fibrates and nicotinic acid derivatives, have a preventive effect on ASCVD. Nonetheless, TGs have been demonstrated to be cor-

related with acute pancreatitis[655]. In addition, we should consider the risk of acute pancreatitis in patients with markedly increased fasting TG levels (500 mg/dL or higher) and consider the concurrent administration of fibrates or other drugs with dietary advice.

3) Characteristics and Criteria for Selecting the Various Drugs

Q2. Have the indications, efficacy, and safety been established for drugs used to treat dyslipidemia?

- **The indications, efficacy, and safety of statins, ezetimibe, the anion-exchange resins, probucol, fibrates, n3-PUFAs, and nicotinic acid derivatives for treating dyslipidemia have been established. Although the indications and efficacy of PCSK9 inhibitors have been established, the safety of long-term administration has not been validated.**

Table 4 shows the classification of drugs used to treat dyslipidemia according to efficacy. These are drugs for which the effects have been ascertained through double-blind studies completed in Japan. There is a need to select safe and effective medications based on understanding of the characteristics of various drugs, while taking into account any complicating diseases, drug interactions, etc. The characteristics of various drugs used to treat dyslipidemia are described below.

i) HMG-CoA Reductase Inhibitors (Statins): Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, Pitavastatin, and Rosuvastatin

Statins are indicated for cases of dyslipidemia with a high LDL-C level. They are currently one of the most effective medications for lowering the LDL-C level and have been so because their effects on FH were shown[656]. Statins competitively inhibit HMG-CoA reductase, which is a rate-limiting enzyme of cholesterol synthesis, in turn suppressing cholesterol biosynthesis[657]. The subsequent activation of SREBP2 promotes LDL receptor synthesis and results in a reduction in the blood LDL-C level[658]. The range of the LDL-C-lowering effect is 20%-50%. Although a reduction in cholesterol biosynthesis in the liver also results in a decrease in the TG level through simultaneous suppression of very low-density lipoprotein (VLDL) synthesis and secretion[659], the decrease ranges from approximately 10%-20%. Myopathy-like symptoms, such as hepatic disorders, an increased creatine kinase (CK) level, and muscular weakness, have been reported as adverse reactions to statins. Rhabdomyolysis, characterized by an increased myoglobin level in the blood and urine, has also been reported, though this complication is very rare. Rhabdomyolysis risk increases with the combined use of statins with fibrates, nicotinic acid derivatives, cyclosporine, or erythromycin, etc. Immune-mediated necrotizing myopathy, characterized by muscle fiber necrosis with-

out infiltration of inflammatory cells on histological examination and the positivity for anti-HMG-CoA reductase antibodies on serological examination, has also been reported even in Japan[660, 661]. The symptoms which are characterized by muscle weakness predominantly in proximal muscle and marked muscle pain with an increased CK level, persist even after stopping administration of oral statins, and there have been cases in which symptoms progress rapidly. Administration of oral statins should therefore be stopped immediately if myopathy-like symptoms appear and the patient's condition should be monitored closely.

Moreover, there have been reports on suspected teratogenicity in pregnant patients who incidentally took statins during early pregnancy[662]; therefore, at present, it appears that statins must not be used in women who are pregnant, possibly pregnant, trying to conceive, or lactating. Pitavastatin (1-2 mg) has been approved for pediatric FH in patients aged ≥ 10 years.

ii) Intestinal Cholesterol Transporter Inhibitor (Cholesterol Absorption Inhibitor): Ezetimibe

Ezetimibe inhibits a small intestine cholesterol transporter (NPC1L1) that exists in the small intestinal mucosa and controls the absorption of cholesterol derived from diet and bile in the small intestine, thereby exerting a blood cholesterol-lowering effect[663]. Unlike resins, this drug is absorbed into the body. After passing through the intestinal circulatory system, approximately 78% of it is excreted in the feces. Because this drug selectively inhibits cholesterol absorption, it does not affect the absorption of fat-soluble vitamins, such as vitamins A and D. The usual oral dose (10 mg/day) decreases the LDL-C level by approximately 18%. Similar to resins, it enhances cholesterol synthesis in the liver. Therefore, the combined use of ezetimibe with statins is ideal and provides a synergistic effect: combination therapy with 10 mg of ezetimibe and a statin at the usual dose decreases the LDL-C level by approximately 35-50%[664-666], which

is equivalent to the effects achieved using a maximum statin dose alone. A meta-analysis of large-scale clinical trials involving combination therapy with ezetimibe and statins in patients with high-risk conditions such as FH, ACS, and PAD, confirmed the safety of combination therapy and cardiovascular event suppression resulting from its LDL-C-lowering effects[667]. It also increased the HDL-C level by 8-9% while decreasing the TG level by 20-30%. Although gastrointestinal symptoms were found to be common adverse reactions, there were no significant differences compared to a placebo. Similar to statins, myopathy-like symptoms such as an increased CK level and muscle weakness, have been reported. These effects are rare, and there are no reports indicating that the combined use with statins intensifies adverse reactions. It has recently been reported that vitamin K absorption in the intestines is mediated by NPC1L1; therefore, it is necessary to note that the action of ezetimibe combination therapy in patients who take oral warfarin may be intensified[668].

iii) Anion-Exchange Resins (Resins): Colestimide and Cholestyramine

Resins are indicated for dyslipidemia with a high LDL-C level (type IIa). Although the first-line drugs of choice for hyper-LDL cholesterolemia are statins, resins may be the first-line drugs for patients who cannot tolerate statins because of adverse reactions, and for women who require drug therapy while pregnant or possibly pregnant. The greatest merit of resin therapy lies in combination therapy with statins.

Cholestyramine is the first medication that was proven through large-scale clinical trials to have suppressive effects on CAD incidence[669, 670]. Resin adsorbs bile acids in the intestines and inhibits intestinal circulation of bile acid via reabsorption, thereby promoting catabolism from cholesterol to bile acids. It is believed that this catabolism leads to decreased sterol pools in the body and an enhanced synthesis of LDL receptors in the liver, resulting in a decreased LDL-C level in the blood[671]. However, HMG-CoA reductase activity in the liver may simultaneously increase, enhancing cholesterol biosynthesis. Combining these drugs with statins, which are HMG-CoA reductase inhibitors, is therefore extremely logical. In contrast, bile acids act as ligands for the nuclear receptor FXR and are involved in regulating TG metabolism by controlling SREBP1c expression and enhancing lipoprotein lipase (LPL) activity. Resin administration results in a decreased LDL-C level, as well as VLDL synthesis and an increased blood TG level because of bile acid absorption. Adverse drug reactions primarily include gastrointestinal symptoms, such as constipation and abdominal bloating; however, no serious adverse reactions have been observed so far because these drugs are nonabsorbable. It has been pointed out that resins adsorb concomitant drugs, such as statins, digitalis, warfarin, thiazide diuretics, and thyroid gland preparations. Therefore, when these medications are concomitantly used, instructions to take them at intervals must be provided. Furthermore, as they may also inhibit the absorption of fat-soluble vitamins (A, D, E, and K) and folic acid, vitamin supplementation should be considered during long-term resin administration.

iv) Probucol

Probucol is indicated for dyslipidemia with a high LDL-C level (type IIa). This drug is characterized by its ability to cause xanthoma regression. In addition to decreasing the LDL-C level, this drug also decreases the HDL-C level.

LDL-C level reduction resulting from probucol is 15-25%. The mechanism underlying this decrease is thought to involve enhanced LDL catabolism, particularly the promotion of cholesterol excretion into bile. On the other hand, the mechanism underlying the decrease in the HDL-C level is thought to involve the suppression of ABCA1, a membrane protein essential for HDL production. Other possible mechanisms include enhanced activity of cholesterol ester transfer proteins (CETPs) and of SR-BI, an HDL receptor. From the viewpoint of cell biology[672, 673], immunohistology[674, 675] and other factors, it has become clear that LDL oxidation is an important aspect of the pathogenic mechanism of atherosclerosis. As probucol is made up of two butylated hydroxytoluene (BHT) antioxidants and is fat-soluble, it is taken up by lipoproteins and exerts potent antioxidant effects. Clinically, the suppressive effects on post-percutaneous transluminal coronary angioplasty (PTCA) restenosis[676, 677], carotid artery IMT progression, and cardiovascular events[678] have been reported from RCTs, albeit small-scales ones. Moreover, a cohort study has also revealed secondary-prevention effects of probucol in patients with heterozygous FH[679]. In PQRST, however, suppressive effects on atherosclerosis progression in the femoral arteries could not be achieved with probucol administration in addition to diet therapy and cholestyramine treatment[680]. In any case, because no large-scale clinical studies have been conducted, probucol use is limited to certain situations such as combination therapy with statins or in monotherapy in patients who cannot tolerate statins. Other than gastrointestinal symptoms, hepatic disorders, and rashes, adverse drug reactions include QT prolongation and torsades de pointes on electrocardiograms.

v) PCSK9 Inhibitors (Human Anti-PCSK9 Monoclonal Antibodies): Evolocumab and Alirocumab

PCSK9 inhibitors are currently indicated for FH or patients with hypercholesterolemia who have a high risk for cardiovascular events and do not benefit sufficiently from even at the maximum tolerated dose statins.

These drugs bind specifically to and inhibit the actions of the PCSK9 (proprotein convertase subtilisin/kexin type 9) protein, which is involved in the degradation of LDL receptors in the liver. In doing so, it increases the recycling of LDL receptors, thereby showing a blood LDL-C-lowering effect[681]. Although increasing the synthesis of LDL receptors, statins, which inhibit cholesterol synthesis in the liver and activate SREBP2, simultaneously increase PCSK9 synthesis. Therefore, it is reasonable to use statins in combination with PCSK9 inhibitors. Their LDL-C-lowering effect is the strongest among all the existing medications. In a phase-3 study involving subjects with a high risk for cardiovascular events including those with heterozygous FH, administrating PCSK9 inhibitor once every two weeks decreased LDL-C levels by 70-75% with combination oral statins[682, 683]. These inhibitors also decrease the Lp(a) level, on which statins do not show a lowering effect. PCSK9 inhibitors decrease TG levels by 20-25% and increases HDL-C levels by 10-15%.

As these medications are injected subcutaneously, the main adverse drug reaction reported is a reaction at the injection site, whereas others include nasopharyngitis and gastroenteritis. No reports have stated that the combined use with statins intensifies the adverse reactions in individuals with hepatic or musculoskeletal disorders. Although adverse events caused by low LDL-C levels have not been reported, the long-term efficacy and safety of PCSK9 inhibitors should be monitored carefully.

vi) MTP Inhibitor: Lomitapide

Lomitapide is currently the only microsomal triglyceride transfer protein (MTP) inhibitor approved in Europe, America, and Japan. The inhibition of MTP decreases VLDL production, which in turn causes decreased LDL-C and TG levels. Even in patients with homozygous FH (HoHF) for whom other drug therapies show no effect, lomitapide decreases the LDL-C level by approximately 50%. However, major adverse drug reactions include accumulation of fat in the liver, abdominal pain, and diarrhea. As a result of these major adverse drug reactions, its long-term safety needs to be studied further in the future. The indication for lomitapide in Japan is limited to patients with hoFH.

Four weeks following commencement of a low-fat diet and administration of lomitapide in patients with hoFH, the blood LDL-C level and apo-B level decreased by 50.9% and 55.6%, respectively (average pretreatment LDL-C level: 615 mg/dL)[684]. During lomitapide treatment, the AST and ALT levels were found to be significantly elevated, as was the liver fat content. However, these levels returned to normal in all patients 14 weeks after treatment cessation. Furthermore, a dose-dependent decrease in the LDL-C and apo-B levels was observed following lomitapide monotherapy or combination therapy with ezetimibe, in conjunction with a low-fat diet in 85 patients with high TC (average pretreatment LDL-C level: 170 mg/dL)[685]. The maximum lomitapide dose alone decreases the LDL-C level by 30% and the apo-B level by 24% from pretreatment levels. In contrast, the combination with ezetimibe showed decreases of 46% and 37%, respectively.

vii) Fibrates: Bezafibrate, Fenofibrate, Clinofibrate and Clofibrate

Fibrates are the most effective medications for hypertriglyceridemia. Fibrates are particularly effective for type III hyperlipidemia because they enhance the catabolism of remnant lipoproteins. They are also highly effective in increasing the HDL-C level.

Their primary mechanism of action is the activation of PPARα, a nuclear receptor, through binding of fibrates as ligands[686, 687]. This results in (1) enhanced β-oxidation of fatty acids and decreased TG production in the liver; (2) increased LPL production; (3) decreased Apo C-III production and enhanced LPL activity, which lead to the promotion of TG degradation and catabolism from VLDL to LDL; and (4) increased production of Apo A-I and A-II. As a result, the TG level decreases and the HDL-C level increases. Bezafibrate has a TG-lowering effect of 30-40%, a TC-lowering effect of approximately 10%, and an HDL-C-increasing effect of 35-45%. Fenofibrate is characterized by its long half-life, and exerts a uric acid-lowering effect in addition to its effect on lipids. The main adverse drug reaction is rhabdomyolysis, which is likely to occur in patients with renal dysfunction, so caution should be taken.

viii) SPPARMα: Pemafibrate

Selective peroxisome proliferator-activated receptor α modulators (SPPARMα) (pemafibrate already approved in Japan) are considered to be safer than conventional fibrates in combination with statins because they have few drug interactions with the statins currently used in Japan and are not renally

excreted.

ix) Nicotinic Acid Derivatives: Niceritrol, Nicomol, and Tocopheryl Nicotinate

Nicotinic acid derivatives are indicated for hyper-LDL cholesterolemia, hypertriglyceridemia, and dyslipidemia accompanied by increased remnant lipoproteins.

The mechanism of action of these drugs involves the suppression of hormone-sensitive lipase activation, in turn inhibiting lipolysis in peripheral fat tissue and decreasing the influx of free fatty acids into the liver. This results in lipoprotein synthesis suppression in the liver. Furthermore, nicotinic acid derivatives exert HDL-C-increasing effects by suppressing apolipoprotein A-1 catabolism. Nicotinic acid monotherapy (3.0 g/day) causes a decrease in the TG level by 26%[688]. Nicotinic acid derivatives also have Lp(a)-lowering effects[689-691]. The main adverse drug reactions include itching and facial flushing because of peripheral vasodilation. Moreover, as nicotinic acid derivative use may exacerbate insulin resistance, these drugs must be administered carefully in patients with DM.

x) N-3 Polyunsaturated Fatty Acids (PUFAs): Ethyl Icosapentate and Omega-3-Acid-Ethyl Ester

PUFAs are indicated for dyslipidemia accompanied by an increased TG level, particularly for type IIb and type IV hyperlipidemia. EPA and DHA suppress VLDL synthesis in the liver, thereby decreasing the TG level and exerting a slight HDL-C-increasing effect. The results of epidemiological studies and secondary-prevention studies have previously demonstrated that the consumption of fish oil and n-3 PUFA helps prevent cardiovascular events. The JELIS study[692] conducted in Japan found that the addition of EPA to statins showed a significant preventive effect on major cardiovascular events compared to statin monotherapy. This indicates the efficacy of EPA in preventing cardiovascular events. However, recent large-scale clinical studies involving high-risk patients with both myocardial infarction and type 2 diabetes were unable to demonstrate that n-3 PUFA administration had suppressive effect on cardiovascular events[693, 694]. In addition to their effects on lipids, EPA and DHA are expected to have antiplatelet and anti-inflammatory effects in ASCVD prevention. Other than gastrointestinal symptoms, such as diarrhea, the main adverse drug reaction is bleeding diathesis.

4) Combination Therapy

CQ27. Does combination therapy using statin and other cholesterol-lowering drugs (ezetimibe, anion-exchange resin, probucol, and PCSK9 inhibitor) prevent ASCVD incidence?

- **Combination therapy using statin and ezetimibe prevents ASCVD incidence in patients with ACS. (Evidence level 1+, recommendation level: B).**
- **Combination therapy using statin and PCSK9 inhibitor prevents ASCVD incidence in patients with a history of myocardial infarction, nonhemorrhagic stroke, or PAD. (Evidence level 1+, recommendation level: B).**

The IMPROVE-IT study[636] which enrolled ACS subjects (secondary prevention) with controlled LDL-C levels (50-100 mg/dL) under simvastatin treatment, revealed a significantly lower ASCVD incidence in the group for which ezetimibe was added on to simvastatin treatment. This study also revealed that the relationship between the reduced LDL-C value and the event inhibition rate attained with the addition of ezetimibe was similar to that observed in previous statin studies. The FOURIER study[639] was a study which enrolled high-risk subjects (patients with a history of myocardial infarction, nonhemorrhagic stroke, or PAD) with an LDL-C level of ≥ 70 mg/dL or a non-HDL-C level of ≥ 100 mg/dL under statin treatment, and examined add-on effect of PCSK9 inhibitor to the statin; this study showed that the combined use of PCSK9 inhibitors with statins suppressed ASCVD incidence. There are no large-scale RCTs which examined the effect of the combined use of statin with anion-exchange resin or probucol in preventing ASCVD.

The SHARP study[695], although the design of which does not fit into this "CQ22", showed that combination therapy using statin and ezetimibe in patients with CKD (including those for both primary prevention and secondary prevention) suppressed ASCVD incidence compared to placebo.

CQ28. For patients with dyslipidemia complicated by hypertriglyceridemia or low HDL-C, would fibrate, nicotinic acid derivative or n-3 PUFA possess beneficial effect in suppressing ASCVD incidence when used in combination with statin?

•**Combination therapy using ethyl icosapentate (EPA) preparation or fibrate with statin is effective in suppressing ASCVD incidence.** (Evidence level 2, recommendation level B).

Although no clinical studies have investigated the efficacy of combination therapy as a primary endpoint in subjects with the dyslipidemia profile assumed in this CQ, some clinical studies have investigated it in a sub-analysis.

In a sub-analysis of JELIS study[696] which enrolled subjects with hypercholesterolemia, it was shown that EPA administration added-on to statins prevented coronary event incidence for patients in primary prevention whose TG and HDL-C levels were ≥ 151 mg/dL and <40 mg/dL, respectively. The ACCORD-LIPID study, which was conducted in North America, involved type 2 diabetes subjects (primary prevention and secondary prevention). Its sub-analysis suggested that fibrate administration in addition to statins could prevent ASCVD incidence in groups with a TG level of ≥ 204 mg/dL and an HDL-C level of <34 mg/dL[697].

The AIM-HIGH study[698], which examined the effect of nicotinic acid derivative (NA) added-on to statin in the subjects with low HDL-C and hypertriglyceridemia together with ASCVD history, did not show suppressive effects of NA on ASCVD incidence. The sub-analysis of the HPS2-THRIVE study[699], which included subjects with HDL-C levels <34.8 mg/dL or TG levels ≥ 151 mg/dL and a ASCVD history, also could not show beneficial effect of NA added to statin. However, there would be some pitfalls for these two studies. Statin dose as well as the prescription rate of ezetimibe for the control group in the AIM-HIGH study was higher than the NA group. Regarding HPS2-THRIVE, the subjects were those who had already attained an average LDL-C level of 63 mg/dL, and the sample size for the sub-analysis was small (19.1% with an HDL-C level <38.4 mg/dL and 25.6% with a TG level ≥ 151 mg/dL).

5) Follow-Up of Drug Therapy

Q3. Do we need to perform blood test regularly after initiating drug therapy?

•**It is advisable to perform regular blood testing after initiating drug therapy. Test items should be chosen upon consideration of the medications administered and the patient's background.** (Recommendation level B).

Following drug therapy initiation, symptoms associated with adverse drug reactions should be monitored, and it is also advisable to perform regular blood testing two to three times within the first 6 months and once every 3-6 months thereafter. The blood test results will allow for the review of drug effects, dose adjustment, confirmation of adverse reactions and lifestyle guidance. The tests to be performed in addition to lipid tests should be selected taking the patient's background and the medications used into consideration; these tests include liver function tests (AST, ALT, and γGT), muscle enzyme tests (CK), renal function tests (BUN and Cre) and blood glucose-related tests (HbA1c and blood glucose level). Because it is usually very rare to detect serious complications in a timely manner from regular tests, there have been reports insisting that testings before drug administration and upon the appearance of symptoms are sufficient. However, regular blood testing is likely to help build a good patient–physician relationship and inhibit cardiovascular events because of better drug adherence.

Adverse reactions caused by statins (rhabdomyolysis, liver failure, etc.) are extremely rare if statins are not used in combination with fibrates and other drugs which affect statin metabolism. In a meta-analysis of 21 RCTs[700] and in another meta-analysis of 30 RCTs[701], the incidence rate of muscles-related adverse reactions with statin use was not found to be significantly different from that with a placebo. Furthermore, although the doses are much different from those in Japan, it has been suggested that a high statin dose, old age, small physical build, and female gender are risk factors for adverse reactions in Western countries[702-705]. It is also shown that adverse reaction develops often within 6 months after starting the medication[706, 707]. Post-marketing surveys in Japan have shown the same trend. We also have to keep in mind that if the liver enzyme and muscle enzyme levels are found to be elevated or abnormal, causes other than statins (such as an increase in the liver enzymes and muscle enzymes because of fatty liver and exercise, respectively) must be excluded[704]. Moreover, although

it has been suggested that the risk for diabetes increases with statin use by 9-13%, meta-analyses of large-scale RCTs suggest that incidence frequency is low (approximately one to two cases per 1,000 patients per year)[708-710]. Furthermore, it has been suggested that diabetes incidence increases in individuals already at a high risk for diabetes (e.g., the elderly, those with metabolic syndrome and impaired glucose tolerance)[708, 711]. There have been three confirmed cases of diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic syndrome in Japan for all statins; however, two of the cases were already under diabetes treatment, and the remaining case would have been slowly progressive type 1 diabetes.

Elevation in creatinine levels resulting from fibrates administration is usually mild and reversible; however, in some cases, creatinine levels may become abnormally high, thus we always need pay attention. When administering nicotinic acid derivatives (NA), an increase in the blood glucose level and the development of diabetes from metabolic syndrome should be taken into account; however, these conditions can be treated and avoided with appropriate therapy and attention. Caution should be taken when using fibrates and NA in combination with statins as this can easily bring about liver and muscle adverse effects[712].

6) Combination Therapy with Other Agents to Prevent Atherosclerosis

Q4. Does statin use in combination with drugs metabolized by CYP increase the incidence rate of adverse reactions?

- **Because many cases of rhabdomyolysis caused by the combined use of hydrophobic statins and CYP-metabolized drugs have been reported, it is advisable to pay thorough attention to the adverse reactions that appear when using these drugs concomitantly.**
  (Evidence level 4, recommendation level A).

Xenobiotic substances, such as statins, are metabolized in the liver by the cytochrome (CYP) P450 protein. Among the statins, many hydrophobic statins are CYP substrates, such as CYP3A4 and CYP2C9. Such statins are metabolized by CYP and subsequently excreted. Pravastatin is a hydrophilic statin that is barely metabolized by CYP, whereas rosuvastatin is slightly metabolized by CYP2C9.

Drugs such as antifungal agents (fluconazole, itraconazole, etc.), macrolide antibiotics (erythromycin, clarithromycin, etc.) and protease inhibitors used to treat HIV are known to be CYP substrates. Drugs used in the fields of cardiovascular medicine and metabolism, namely calcium antagonists, warfarin, nateglinide, and glimepiride, are also CYP substrates. The use of these drugs in combination with statins may cause adverse events because of the intensified effects and increased drug levels in the blood. Some macrolide antibiotics, antifungal agents, protease inhibitors, and bergamottin contained in grapefruit juice, exert an inhibitory effect on CYP, and using them in combination with statins may increase statin levels in the blood. It has also been recently shown that the combined use of statins with CYP-inducing drugs, such as rifampicin and barbiturates, may decrease the effects of statins. Statins and the main metabolic and cardiovascular drugs metabolized by CYP are shown in Table 10.

It has been reported that the AUC of the blood statin levels increases when they are used in combination with drugs that are CYP substrates[713]. However, a search for reports published between 1990 and the present did not produce any that have investigated whether the adverse reactions intensify with this drug combination. Nonetheless, many cases of rhabdomyolysis resulting from statin use in combination with CYP substrates have been reported[714]. Although it involved only a small number of patients, one report from overseas revealed that the combined use of atorvastatin and ezetimibe in patients who were undergoing anticoagulation therapy for atrial fibrillation had their doses stabilized in approximately 3 months and did

Table 10. Statins and Cardiovascular and Metabolic Drugs Metabolized by CYP

CYP	Statin(s) metabolized	Cardiovascular and metabolic drug(s) metabolized
CYP3A4	Atorvastatin Simvastatin	Calcium antagonists (diltiazem, verapamil, nifedipine, amlodipine, cilnidipine, azelnidipine, and benidipine), warfarin, and repaglinide*
CYP2C9	Fluvastatin Rosuvastatin	Angiotensin receptor blockers (ARB) (losartan, valsartan, candesartan, Irbesartan, and azilsartan), warfarin, glinides (nateglinide and mitiglinide), and glimepiride

*Repaglinide is mainly metabolized by CYP2C8, but CYP3A4 is also sometimes involved.

not experience an increase in the incidence of complications such as hemorrhage[715] These findings were demonstrated despite the need to slightly decrease anticoagulant dose in the treatment group.

In addition to CYP, hypolipidemic agents are also influenced by transporters such as the breast cancer resistance proteins, organic anion transporter protein B1 (OATP1B1), organic anion-transporting poly-peptide-C (OATP-C), and P-glycoprotein. Even for rosuvastatin, a water-soluble statin, coadministration with cyclosporine is contraindicated as concomitant use increases rosuvastatin levels in the blood. This is because transporters of hepatocytes, such as the breast cancer resistance proteins and OATP1B1, are thought to be inhibited by cyclosporine, thereby causing a decrease in drug uptake by the hepatocytes.

Q5. Is the use of compound drugs in hyperlipidemia therapy effective in improving serum lipid levels and preventing the incidence of atherosclerotic cerebrovascular and cardiovascular diseases?

•**Although the use of compound drugs has been reported to increase the adherence to medication compared to prescribing each drug separately, there are no reports of compound drugs being more effective in preventing ASCVD incidence or at changing the serum lipid levels. (Recommendation level: B).**

Many compound drugs are being used in the metabolic and cardiovascular drug categories to decrease the burden of taking medicines for the elderly and to improve adherence. In addition to those made up of multiple hypertensive agents or hypolipidemic agents, compound drugs containing hypolipidemic agents and other drugs are also available. For example, a compound drug made up of atorvastatin and amlodipine, a calcium antagonist, is being used in Japan. In other countries, compound drugs consisting of statins and DPP4 inhibitors are also being used. The use of compound drugs not only enhances patient QOL but also adherence to medication, which may lead to improved serum lipid levels and decrease CVD incidence. A report overseas found that a calcium antagonist–statin compound drug significantly improved serum lipid levels and better controlled blood pressure compared to placebo[716]. However, there are no reports of comparisons between the administration of a compound drug and the administration of the various drugs separately. In regard to CVD incidence, there are similarly no reports in which the effects of prescribing a compound drug were compared to those of drugs prescribed separately.

It has been reported that compound drugs improve patient adherence to medication compared to prescribing the drugs separately[717]. The maintenance of adherence is greatest when a single medication is added for patients who take only one drug orally[718]. Although the preventive effects on CVD have not been shown, the use of compound drugs is likely beneficial considering Japan's currently aging society, improvement of adherence, patient convenience, and healthcare economics.

7) Adherence

Q6. What are the factors that affect adherence?

•**Adherence to hypolipidemic agents is low in individuals aged <50 years, ≥ 70 years, women, and low-income earners. Adherence is high in patients who have a CVD history.**
•**It has been suggested that frequent lipid testing, low copayment, and the use of generic drugs are associated with an increase in adherence.**
•**As with other therapeutic agents, adherence decreases as the number of doses per day increases. (Evidence level: 2)**

Meta-analyses conducted overseas have demonstrated that adherence to oral statins differs according to factors, including age, gender, income, and whether other treatments are being implemented for comorbid disease. Women and low-income earners have been shown to have low adherence rates. In individuals aged <50 years or ≥ 70 years, the adherence was low, with a "U-shaped" distribution. Secondary-prevention patients who have a CAD history showed high adherence, whereas primary-prevention patients showed low adherence. There have been many reports indicating that adherence is also high in patients receiving treatment for hypertension or diabetes. The frequency of lipid testing and low cost to the patient has also been shown to be associated with good adherence[719]. In addition, there are differences in adherence between

Table 11. Adherence to Statins Reported Outside of Japan[719]

Name of Country	Sample Size	Adherence Rate	Reference
United States	19,422	1 year: 30% 2 years: 20% 3 years: 25%	728)
United Kingdom	6,262	1 year: 66% 5 years: 75% 10 years: 68%	729)
United States	4,776	6 months: 80% 1 year: 74% 2 years: 65% 3 years: 61%	730)
United States	34,501	3 months: 79% 6 month: 56% 1 years: 50% 10 years: 42%	731)

Adherence Rate: PDC [No. of prescription days/observation period × 100 (%)]

drugs. It is known that the adherence to anion-exchange resins is particularly low, whereas the adherence to fibrates, omega-3-acid-ethyl esters, and nicotinic acid derivatives is lower than that to statins[720].

Lipid level improvement and CVD prevention are not likely to occur if the patient does not actually take the drugs prescribed. The adherence to medication is high in clinical studies and trials because of strict dosing management by study coordinators, but adherence is lower in actual clinical practice (Table 11), and high discontinuation rates have been reported overseas.

Adherence is associated with the preventive effects of CVD. In a retrospective cohort study on statins conducted overseas, the 4–5-year mortality rate in the group that had a high ≥ 90%) adherence rate was 45% lower than the group with a low (<10%) adherence rate[721]. Likewise, in Japan's JELIS study, the group of secondary prevention patients who achieved an adherence rate of 80% had significantly fewer primary endpoints consisting of sudden cardiac death and fatal/nonfatal myocardial infarction compared to the group that did not[722].

To improve drug adherence, guidance on lifestyle modification, such as diet and exercise therapy, should be provided to individuals who have low adherence, namely women, young individuals, the elderly, and primary prevention patients. Moreover, medical professionals must make an effort thoroughly explain the association between dyslipidemia and CVD incidence to patients, as well as aid patient understanding of the purpose of their treatment. It is advisable for other members of the medical team, such as nurses and pharmacists, to also provide regular explanations to patients regarding the importance of taking their medicine. In a recent comparative study, the study group that met with a pharmacist regularly had a lower discontinuation rate than the group that did not[723]. Discontinuation often occurs 1-2 years after treatment initiation; however, the discontinuation rate is known to decrease after that[724]. For this reason, to prevent discontinuation, it is particularly important to repeatedly explain the need for treatment to patients in the 1-2 years after treatment initiation. Regular lipid testing has also been reported to help increase adherence[719].

It is known that the adherence to medication decreases when the number of daily doses increases[725, 726]. Therefore, when writing prescriptions, physicians should try to keep the number of doses as low as possible. In addition, the timing of medication doses (e.g. before or after meals) should not be confusing for the patient. The use of compound drugs has been known to increase adherence compared to prescribing drugs separately[717]; hence, the use of compound drugs should be considered for patients who require multiple drugs. A low copayment for the drugs is also associated with adherence. A cohort study conducted in the United States compared patients who were prescribed name-brand statins to those prescribed generic statins. It was found that patients who were prescribed generic statins not only had better adherence rates than those who were prescribed name-brand statins but also fewer composite endpoints such as hospitalization because of ACS and stroke, and all-cause mortality[727].

4. Managing Major High-Risk Conditions

1) History of CAD

[Statement]

- **Even in secondary prevention, the risk for cardiovascular events is high if FH, ACS, DM, non-cardiogenic cerebral infarction, PAD, CKD, and metabolic syndrome are present, or if there is an overlap in the major risk factors and the presence of smoking. (Evidence level: Ep-Ib)**

In secondary prevention in patients with a history of CAD, the LDL-C control target should be at a level of <100 mg/dL. As the risk of ASCVD incidence is high in patients with FH or ACS, stricter LDL-C management to achieve a level <70 mg/dL should be considered . The secondary prevention for DM patients complicated with conditions described in **Table 3b**, should also be treated based on the target level of FH or ACS, as they are considered to be at high risk of recurrence of CAD.

i) Familial Hypercholesterolemia (FH)

It has been reported that the cumulative LDL-C (total LDL-C from the time of birth) plays a role in cardiovascular incidence[732]. In addition, observational studies have reported that LDL-C-lowering therapy using statins decreases cardiovascular event risk[733], and delays the age of incidence of these events[734]. From an ethical viewpoint, it is difficult to conduct randomized comparative studies involving secondary prevention patients with FH. However, based on the findings that patients with early-incidence CAD have are more likely to have FH[735, 736], and that FH patients have a higher risk of CAD recurrence than non-FH patients[737], it is recommended that the LDL-C level be controlled at a stricter level (as much as possible to LDL-C <70 mg/dL) in FH patients[738].

ii) Acute Coronary Syndrome (ACS)

Patients who have experienced ACS have a higher risk of recurrence for cardiovascular events than patients with stable CAD. The OACIS-LIPID study in Japan investigated the effect of early administration of statins on suppressing cardiovascular events in patients with acute myocardial infarction[739]. The study showed an incidence rate of 40/1,000 person-years for all-cause mortality and nonfatal myocardial infarction in the group that underwent lipid-lowering therapy using drugs other than statins. However, at 30/1,000 person-years, the incidence rate of cardiovascular events was also remarkably high in the group that received statins. In the PACIFIC study[740], which was a multicenter observational registry study on ACS, the incidence rate of fatal and nonfatal myocardial infarction was high, at 35/1,000 person-years, despite approximately 80% subjects being administered statins.

Meanwhile, it has been reported that providing LDL-C-lowering therapy at an early stage following ACS incidence is effective in suppressing cardiovascular events[741], and that stricter LDL-C-lowering therapy suppresses cardiovascular events significantly more than conventional LDL-C-lowering therapy[742]. Regarding the LDL-C management target, the IMPROVE-IT[636] study revealed that lowering the LDL-C level to 53.6 mg/dL using statin–ezetimibe combination therapy suppressed cardiovascular events by 6.4% more than the group that had their LDL-C level controlled at 69.5 mg/dL with statins only. In meta-analyses of RCTs in which statins were administered within 14 days after ACS, cardiovascular events shown to be significantly suppressed after ≥ 2 years[743]. However, these preventive effects were not able to be proven in a shorter observational period of 4 months[744].

The effectiveness of early LDL-C-lowering therapy for patients with ACS has been studied in Japan by observing the coronary plaques using intravascular ultrasound (IVUS). In the ESTABLISH study[642], strict LDL-C-lowering therapy was administered early after ACS. The therapy decreased the average LDL-C level to 70 mg/dL after 6 months, which resulted in a 13.1% decrease in plaque volume. Moreover, it was reported that the change in plaque volume showed a significant positive correlation with the post-treatment LDL-C level and the rate of decrease in the LDL-C level. Additional cases were added and follow-up surveys (completed an average of 4.2 years later) were conducted in the same study. The results of the follow-up surveys revealed that starting a strict LDL-C-lowering therapy at an early stage significantly suppressed cardiovascular events[745]. In JAPAN-ACS[643], it was similarly demonstrated that the early initiation of a strict LDL-C-lowering therapy using statins for patients with ACS suppresses plaque progression. However, no significant relationship was demonstrated between the rate of decrease in the LDL-C levels, or in the post-treatment LDL-C level and the rate of plaque regression. It was reported in the recent PRECISE-IVUS study that decreasing the LDL-C level to <70 mg/dL using a combination of statin and ezetimibe resulted in a marked plaque volume regres-

sion in patients with ACS, compared to those who were treated with statins only[645]. In recent years, the development of vascular imaging techniques other than IVUS has made it possible to assess the characteristics of plaques, and the association of these characteristics with clinical events is also being studied[746-748].

iii) Diabetes Mellitus (DM)

For patients with a myocardial infarction history, it has been reported that the risk of recurrence of cardiovascular events increases with the presence of diabetes[137, 749-751]. Epidemiological studies in Japan involving subjects with CAD have also revealed that diabetic patients have a high risk for all-cause mortality and cardiovascular events[138, 182, 752]. Likewise, in the analysis of the J-LIT study on patients with CAD, it was shown that the presence of diabetes causes the relative risk for cardiovascular events to increase by approximately 2.5-fold[173].

According to a meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration, the effects of LDL-C-lowering therapy using statins on cardiovascular event are equal regardless of whether the patient had diabetes[751]. In the sub-analysis of the TNT study, which involved subjects with CAD complicated with diabetes, treatment using a high statin dose significantly suppressed cardiovascular and cerebrovascular events by 25% and 31%, respectively, compared to treatment using the usual statin dose[753].

A meta-analysis of clinical studies using IVUS, which has been implemented overseas, reported that diabetes was an independent risk factor in cases where the coronary plaques were found to be progressing, regardless of whether their LDL-C levels had been decreased to ≥ 70 mg/dL with treatment[754]. It has been demonstrated that coronary plaque volume progression, the incidence rate of cardiovascular events, and the post-treatment LDL-C level show a significant positive correlation with one another. This suggests the importance of a stricter LDL-C-lowering therapy if CAD is complicated with diabetes. The sub-analysis of JAPAN-ACS[755], a study conducted in Japan involving patients with ACS, showed that the presence of diabetes posed a strong negative risk on plaque regression. Even if the LDL-C level is controlled to the same extent as that of nondiabetic patients, the rate of plaque regression in diabetic patients is markedly low. However, this study also reported that significant plaque-regressing effects can be achieved if the LDL-C level is controlled at <75 mg/dL[756]. Furthermore, the ZEUS study, despite being small-scale, reported that strict LDL-C-lowering therapy using statins and ezetimibe in combination is useful for regressing plaques

in CAD complicated with diabetes[644].

iv) Noncardiogenic Cerebral Infarction

ASCVD that occurs with atherosclerosis as an underlying basis, such as CAD, cerebrovascular diseases, and PAD, are mutually high-risk conditions for vascular complications. It was demonstrated in the REACH registry, a registry study on patients with ASCVD or overlapping risks factors for ASCVD, that approximately 16% registered cases are complicated with two or more ASCVD[757]. A comparison between the database of the Texas Heart Association in the United States and CREDO-Kyoto study, a registry study that involved subjects who had undergone coronary revascularization in Japan, showed a significantly higher rate of complication with cerebrovascular diseases in Japan (16.4% vs. 5.0%). However, it was confirmed that the complication of cerebrovascular disease is a high-risk condition for cardiovascular event in both Japan and the United States[752].

Results of secondary prevention studies on CAD conducted in western countries, such as 4S, LIPID, and CARE, have revealed a high risk for the recurrence of cerebrovascular and cardiovascular events in patients with CAD who have a cerebrovascular disease history. However, it has been reported that LDL-C-lowering therapy using statins suppresses the risk for recurrence of both cerebrovascular and cardiovascular events[758-760].

v) Peripheral Arterial Disease (PAD)

In the comparison between the aforementioned database of the Texas Heart Association in the US and CREDO-Kyoto study in Japan, it was confirmed that PAD is a high-risk condition for cardiovascular event in both Japan and the US[752], though the complication rate of PAD was significantly higher in the US.

Patients with PAD who have a CAD history are at extremely high risk for total mortality and fatal cardiovascular events[761-767]. There are no reports of lipid intervention studies involving subjects with PAD complicated by CAD. However, in the sub-analysis of IDEAL, a study that involved subjects with myocardial infarction complicated with PAD, it was reported that an LDL-C-lowering therapy using a high statin dose significantly suppressed cardiovascular events compared to a moderate statin dose[767]. It was also confirmed that the therapy prevented the new incidence of PAD by 30% in cases that were not already complicated with PAD.

A meta-analysis of clinical studies in which coronary plaque progression was analyzed by IVUS showed that the inhibition of the progression and plaque regression is observed when the LDL-C level is

controlled at <70 mg/dL, regardless of the presence or absence of PAD. Thus, strict LDL-C lowering therapy in patients with PAD expect to suppress CAD events because plaque regression has been shown to be associated with fewer cardiovascular events[768].

vi) Chronic Kidney Disease (CKD)

Stratified analyses of the eGFR have been performed in long-term observational studies involving subjects with ACS and on post-PCI patients. The results of these studies have found that, compared to patients with normal renal function, the risk for cardiovascular events, including cerebrovascular disease, cardiac death, and total mortality increases by 2-3-fold in those with CKD even when the CKD is mild. It has been reported that the risk increases in association with the severity of the disease[740, 769, 770]. In addition, according to the observational CREDO-Kyoto study, the risk for cardiovascular death is 2.9-fold higher for post-PCI patients with CKD, and the risk for total mortality increases by 2.1-fold[183]. In particular, patients aged ≥ 55 years have a 3.7-fold increased risk for cardiovascular events, including cerebrovascular diseases[174]. Furthermore, patients with CKD and a serum creatinine level ≥ 2.0 mg/dL were found to have a 7.0-fold increased risk for total mortality. This suggests that the risk for cardiovascular events increases markedly with the presence of CKD in patients who have undergone PCI[752].

For patients with CKD complicated with CAD, the preventive effects of lipid-lowering therapy on cardiovascular events have been investigated in post hoc analyses of early-stage secondary prevention studies using statins. These analyses have reported that statin use suppresses cardiovascular events in patients with mild CKD and an eGFR <75 mL/min/1.73 m^2 [771, 772]. However, suppressive effects on cerebrovascular diseases were not demonstrated. Furthermore, post hoc analyses of secondary prevention studies have shown that high-dose statin treatment decreases cardiovascular event significantly, by approximately 30%, in patients with moderate CKD compared to the usual dose[773, 774]. In CREDO-Kyoto PCI/CABG Registry Cohort-2, a secondary-prevention cohort study on CAD in Japan, patients with mild CKD and an eGFR of 30-60 mL/min/1.73 m^2 who took oral statins had a significantly lower incidence rate of major cardiovascular events. The incidence rate of cerebrovascular disease was also significantly lower in patients who were taking oral statins[775]. However, similar effects were not seen in patients with severe CKD whose eGFRs were <30 mL/min/1.73 m^2 or in patients undergoing hemodialysis.

vii) Metabolic Syndrome and an Overlap of Major Risk Factors

The results of a meta-analysis of 87 clinical studies have shown that the presence of metabolic syndrome results in an added risk for total mortality, coronary events, and cerebrovascular events for patients with CAD[327].

A sub-analysis was performed with just those complicated by metabolic syndrome among all the subjects with CAD in the TNT study, and it was shown that an overlap of the major risk factors poses a risk for cardiovascular events. The incidence rate of cardiovascular events is particularly high in cases where three or more major risk factors are present. However, it has been shown that cardiovascular event is significantly suppressed by 29% with high-dose statin therapy compared to a usual-dose statin therapy[776].

JCAD observational study in Japan also revealed that if three or more major risk factors are present, the risk for cardiovascular events is 1.3-fold higher compared to having two or fewer risk factors[182]. In a study where patients who underwent PCI were followed up with for a long period, the relative risk for cardiovascular events in those with metabolic syndrome was 2.1-fold higher[777]. However, statin administration resulted in a significant decrease in total mortality by 44% and in coronary death by 47%[778].

viii) Smoking

In patients with CAD who continue to smoke, the risk of recurrence of cardiovascular events is higher than that observed in nonsmokers. The total mortality, cardiac death, and sudden cardiac death risks are also significantly higher[779-783]. In the REACH Registry, a registry study on patients with ASCVD, CAD, cerebrovascular diseases, and PAD or overlapping risks factors for ASCVD, the incidence rate of cardiovascular events in patients who continued to smoke was approximately 1.3-fold higher than that observed in lifelong nonsmokers[784]. In the OACIS study, even after adjusting for age, gender, DM, hypertension, dyslipidemia, and therapeutic agents, the risk for total mortality in post-myocardial infarction patients who continued smoking was 2.3-fold higher than in lifelong nonsmokers. In contrast, the total mortality risk in patients who quitted smoking after myocardial infarction incidence decreased to the same level as the nonsmokers. Compared to those who continued smoking, the total mortality risk of patients who quitted smoking decreased significantly by 61%[785]. Many epidemiological studies have reported that regardless of age and gender, the risk of recurrence of cardiovascular events decreases by approximately half after the

first year of smoking cessation and continue to decrease thereafter. Such studies have also reported that the risk further decreases to almost the same level as that of the lifelong nonsmokers approximately 10 years after smoking cessation[779-786].

On the basis of a composite analysis of secondary prevention studies, TNT and IDEA[787], and the post hoc analysis of the GREACE study[788], even with a strict LDL-C-lowering therapy using statins, the risk for cardiovascular events is higher in patients who continue smoking than in lifelong nonsmokers or the ex-smokers. Therefore, providing guidance on smoking cessation to patients who continue to smoke is extremely important.

2) Diabetes Mellitus (DM)
[Statement]
- **Not only hyperglycemia but also dyslipidemia and hypertension should be comprehensively controlled soon after the onset of diabetes. (Evidence level: 1, recommendation level: A)**
- **More strict control of LDL-C should be considered among diabetic subjects with FH, noncardiogenic cerebral infarction, PAD, microvascular complications (retinopathy and nephropathy), metabolic syndrome, continuation of poor glycemic control, an overlap of major risk factors of ASCVD, or smoking. (Consensus, recommendation level: A)**

i) Prevention and Treatment of ASCVD in Patients with DM

a) Risk Factors for ASCVD
It has been reported that LDL-C, HDL-C, and HbA1c levels, as well as and systolic blood pressure are risk factors for CAD, whereas hypertension, male gender, and atrial fibrillation are risk factors for cerebral infarction[789]. However, a study conducted in Japan (JDCS) has suggested that LDL-C and TG levels are risk factors for CAD, and that systolic blood pressure is a risk factor for stroke[790]. Other Japanese studies have reported that smoking, male gender, and high Lp(a)[791] are risk factors for CAD. It is important to manage these risk factors comprehensively in patients with DM to prevent ASCVD. Lifestyle intervention is especially important in diabetic subjects with metabolic syndrome. The presence of microvascular complications such as diabetic nephropathy[792, 793] or retinopathy[794] is a predictive factor for CAD.

b) Blood Glucose
Meta-analyses have clearly shown that tight blood glucose control leads to the suppression of ASCVD incidence[795, 796]. However, a longer duration of 8-15 years after strict glycemic control is necessary for the suppression of ASCVD risk[797, 798]. There is little evidence showing that tight blood glucose control with specific drug can suppress the occurrence of ASCVD events. However, recent investigations reported that the suppression of composite cardiovascular events and cardiovascular death by SGT2 inhibitors[799], and that the suppressive effects of glucagon-like peptide-1 (GLP-1) receptor agonists on ASCVD incidence[800, 801]. On the other hand, strict blood glucose control increases the risk for hypoglycemia, and hypoglycemia has been reported to be related to cardiovascular death in the Japanese[802]. Strict blood glucose control must be carefully carried out.

According to the J-EDIT study, a Japanese study that involved elderly subjects, stroke risk was 2.63-fold higher in the group with HbA1c levels ≥ 8.5% than in the group with HbA1c levels of 7.0-8.4%. On the other hand, subjects with HbA1c levels <7.0% also had a 2.35-fold higher risk. Thus, elderly patients with DM require both hyperglycemia prevention while avoiding excess strict glucose control[803].

c) Lipids
Patients with DM are often complicated with hyper-LDL cholesterolemia, hypertriglyceridemia, and low HDL-C levels. In a meta-analysis including CARDS[804], LDL-C-lowering therapy using statins greatly decreases CAD-related mortality, CVD, and cerebral infarction in diabetic patients. These effects were similar to those in nondiabetic subjects[751].

In contrast, it was reported in the FIELD study that fibrates decrease CAD events in primary prevention[805]. In the ACCORD study involving high-risk subjects with DM, the sub-analysis suggested that the risk for cardiovascular events might be significantly suppressed by adding fibrate in patients who have hypertriglyceridemia and low HDL-C after statin administration[806]. The additional administration of EPA was also reported to significantly decrease coronary events in Japanese patients who were taking statins for treating hypercholesterolemia complicated with impaired glucose metabolism[807]. Furthermore, CVD risk decreases significantly because of a decrease of LDL-C level from 94 mg/dL to 54 mg/dL when

statins and ezetimibe are used for treatment in patients with ACS. The effects were evident especially in patients with DM[808].

d) Blood Pressure

Elevated blood pressure leads to an increased risk of ASCVD in DM subjects[809]. In meta-analyses, blood pressure-lowering therapy was found to decrease risk of cerebrovascular diseases[810]. However, risk reduction of CAD has only been observed in subjects with hypertension before treatment initiation[811], which indicates that the effects are limited for CAD prevention. Angiotensin-converting enzyme inhibitors[812], angiotensin Ⅱ receptor blockers[813], and calcium channel antagonists[814] have been reported to be effective for preventing cardiovascular events in patients with DM.

e) Comprehensive Risk Management

Early comprehensive management of risk factors, such as hyperglycemia, hypertension, dyslipidemia, smoking habit, and visceral fat obesity, is important in prevention of ASCVD among diabetic subjects[815, 816]. Lifestyle modification such as diet therapy[817], increasing physical activity[818], and smoking cessation[819] are important, but there is no evidence that lifestyle modifications alone decrease the risk of ASCVD in patients with DM[820, 821]. Several studies have suggested that a comprehensive and intensive therapy for the risk factors, combined with lifestyle modification and drug therapy, has a protective effect on ASCVD. These findings have also been reported in Japan[822, 823].

The ADA has recommended that aspirin use for the primary ASCVD prevention should be considered[824] for high-risk men and women aged ≥ 50 years. However, the JPAD studies conducted in Japan did not show any protective effects of aspirin on cardiovascular events in patients with DM[825, 826].

ii) LDL-C control for ASCVD prevention

a) Lipid Management for Primary Prevention

Recently published US guidelines did not refer definitive achievement goals of plasma lipids, but recommended statin administration without monitoring of lipid levels during the course of therapy[827]. However, in the ESC/EAS guidelines, LDL-C level <100 mg/dL is recommended as the primary target for patients with type 2 DM[828]. In Japan, the use of JAS guidelines for control of plasma lipids in diabetic subjects has been recommended[829].

There are only a few studies involving Japanese patients with DM; however, a TG level <150 mg/dL and a HDL-C level ≥ 40 mg/dL are recommended as

Table 12. Diabetic Patients at Higher Risk for Developing CAD

Familial hypercholesterolemia (FH)
Noncardiogenic cerebral infarction
Peripheral arterial disease (PAD)
Microvascular complications (retinopathy, nephropathy, etc.)
Persistent poor glycemic control
Metabolic syndrome
Overlap of major risk factors
Smoking

targets regardless of the presence or absence of DM. The target for the primary prevention of CAD is < 120 mg/dL for LDL-C and <150 mg/dL for non-HDL-C. Some clinical conditions in patients with DM have been shown to have CAD risk. These conditions include the following: (1) FH; (2) noncardiogenic cerebral infarction[830], (3) PAD[830]; (4) microvascular complications (retinopathy, nephropathy, etc.)[792, 794, 831-833]; (5) persistently poor glycemic control[143, 795, 834]; (6) metabolic syndrome-related complications (visceral obesity)[835]; (7) overlap of major risk factors[836, 837]; and (8) smoking[836].

Although all primary prevention patients with DM should predict LDL-C level <120 mg/dL, patients who have any of the above listed characteristics should implement stricter management (i.e., compulsory achievement of the target value). Furthermore, diabetic patients with FH or more than one of above eight characteristics are at extremely high ASCVD risk, the targets of secondary prevention should be considered.

In the CTT study, it was reported that decreasing LDL-C level by 38.7 mg/dL using statins, cerebrovascular disease risk in DM patients is decreased by 21%. Thus, it is likely that control of LDL-C is effective for the prevention of cerebrovascular disease same as CAD prevention[838].

b) Lipid Management for Secondary Prevention

Regardless of the presence or absence of DM, LDL-C level <100 mg/dL and non-HDL-C level < 130 mg/dL are recommended. Secondary-prevention of CAD in diabetic patients shows a high rate of recurrence[137-139, 839], and it is difficult to achieve plaque regression in patients with DM even with the recommended control of LDL-C-lowering therapy[840]. In addition, DM has been reported to be the most important risk factor for CAD recurrence in the Japanese[841]. Thus, it is reasonable to set an LDL-C level of <100mg/dL as the compulsory target in secondary prevention for patients with DM[842]. As mentioned in

CQ20, among secondary prevention cases with diabetes complicated with risk factors such as noncardiogenic cerebral infarction, PAD, CKD, metabolic syndrome, overlap of major risk factors or smoking habit have a more higher risk of recurrence. Thus, it is reasonable to control of LDL-C as the same target level of FH or ACS, by achieving LDL-C level of <70 mg/dL[754, 756].

3) Cerebrovascular Disease
[Statement]
•**Statin therapy may prevent the development of cerebral infarction.**
(Evidence level: 2, recommendation level: A)

i) Frequency
Cerebrovascular disease is classified into three types (cerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage). According to the 2015 Stroke Data Bank, the cerebrovascular disease incidence in Japan is reported to be approximately 18.5% for cerebral hemorrhage, approximately 5.6% for subarachnoid hemorrhage, and 75.9% for cerebral infarction[842]. Compared to the cerebrovascular disease incidence in western countries, the cerebral hemorrhage incidence in Japan is higher whereas the cerebral infarction incidence is relatively low[843].

Cerebral infarction is further classified into three clinical types (lacunar infarction, atherothrombotic cerebral infarction, and cardiogenic cerebral embolism). In the Hisayama study, lacunar infarction accounted for approximately 50% cases of cerebral infarction, whereas the incidence rates of atherothrombotic cerebral infarction and cardiogenic cerebral embolism were just under 30% and just over 20%, respectively[844]. The J-MUSIC study published in 2,000 saw a change in the incidence rates, with a 38.8% rate for lacunar infarction, a 33.3% rate for atherothrombotic cerebral infarction, and a 21.8% rate for cardiogenic cerebral embolism[845]. The numbers were also different in the 2015 Stroke Data Bank, with an incidence rate of 31.2% for lacunar infarction, 33.2% for atherothrombotic cerebral infarction, and 27.7% for cardiogenic cerebral embolism[842]. Cerebral infarction incidence in the western Caucasian population has been reported to be approximately 30% for both lacunar infarction and atherothrombotic cerebral infarction, and approximately 40% for cardiogenic cerebral embolism[846]. It has been reported that in Japan, the number of cases of lacunar infarction is decreasing whereas the number of cases of cardiogenic cerebral embolism is increasing.

ii) Risk Factors for the Development of Cerebrovascular Disease
The results of NIPPON DATA80 indicate that the factors affecting mortality rate of cerebrovascular disease in the Japanese are age, systolic blood pressure, smoking, and hyperglycemia. Lipid levels, such as the TC level, are not recognized as risk factors[50]. Similarly, the consolidated results of 61 observational studies conducted in western countries (approximately 0.9 million subjects) found no relationship between the TC level and the mortality rate of cerebrovascular disease[847]. 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 cerebrovascular disease, and that the TC level has much less involvement than blood pressure[848].

In terms of the individual cerebrovascular diseases, studies have clearly revealed that hypertension is a risk factor for cerebral hemorrhage, and that hypertension, smoking, alcohol, and the presence of cerebral aneurysm are the major risk factors for subarachnoid hemorrhage. With respect to cerebral infarction, the major risk factors for cardiogenic cerebral embolism are hypertension and cardiac thrombi[849, 850].

A study of the risk factors for noncardiogenic cerebral infarction only revealed that in the 2015 Stroke Data Bank, the dyslipidemia incidence in patients with noncardiogenic cerebral infarction is 40-50%, a number that has been increasing in recent years[842]. However, the results of epidemiological studies conducted in Japan have indicated that there is no significant relationship between the serum cholesterol levels (TC, LDL-C, and non-HDL-C) and the incidence rate of noncardiogenic cerebral infarction[36, 38, 40, 57, 64, 78, 337]. In western countries, epidemiological studies such as MRFIT have reported that an increased TC level is associated with an increased risk for cerebral infarction[851-853]. Furthermore, the consolidated results of nine cohort studies indicated that cerebral infarction incidence is significantly decreased by 15% in patients with a decrease of 1 mmol/L (38.6 mg/dL) in the LDL-C level[854]. Similarly reported in the result from a meta-analysis of 21 large clinical trials by CTT Collaboration, stroke incidence is decreased by 15% and cerebral infarction incidence is decreased by 20% in patients with a decrease of 1 mmol/L (38.6 mg/dL) in the LDL-C level[177]. On the contrary, some reports have stated that the TC level is

either not a risk factor for cerebral infarction or has very little involvement[855, 856].

The results of the Hisayama study, which investigated cerebral infarction risk by type, demonstrated that the LDL-C level is a risk factor for atherothrombotic cerebral infarction. However, the LDL-C level is not related to the incidence of other types of cerebral infarction[36]. Furthermore, the Hisayama study reported that blood pressure has a strong effect on lacunar infarction, atherothrombotic cerebral infarction, and, in women, cardiogenic cerebral embolism[857]. Reports published in various other countries have also indicated that the major risk factor for cerebral infarction, including cardiogenic cerebral embolism, is hypertension[855]. Thus, cholesterol level is recognized to be a risk factor only for atherothrombotic cerebral infarction, whereas hypertension is considered to be the major risk factor for all types of cerebral infarction, including atherothrombotic cerebral infarction[849].

Many reports, including those from Japan, have stated that hypocholesterolemia is a risk factor for cerebral hemorrhage[40, 858]. According to a meta-analysis of cohort studies, a decrease of 1 mmol/L (38.6 mg/dL) in the cholesterol level increases the cerebral hemorrhage incidence by 19%[854]. In Japan, an LDL-C level of 80 mg/dL or less has also been reported to increase the cerebral hemorrhage incidence[40]. However, as described later, the results of a meta-analysis of prevention studies on CAD did not indicate that cholesterol-lowering therapy leads to an increased cerebral hemorrhage incidence[348].

There have been many reports, including those from Japan, stating that the lower the HDL-C level, the higher the incidence rate of cerebral infarction[46, 859-861].

Many reports have also indicated that there is no clear relationship between the TG level and cerebrovascular disease[856, 862, 863]. However, the results of a meta-analysis of epidemiological surveys conducted in the Asia-Pacific region, in which the fasting TG level was divided into four groups, reported that the group of patients with the highest TG levels had a 50% higher risk of ischemic stroke compared to the group with the lowest TG levels[87]. Furthermore, the results of cohort studies involving approximately 14,000 subjects reported that ischemic stroke incidence increases in both men and women when postprandial hypertriglyceridemia is present[864]. These results indicate that a 1-mmol/L (88.5 mg/dL) increase in the postprandial TG level increases ischemic stroke risk by 15%.

iii) Lipid-Lowering Therapy and Cerebrovascular Disease

Although it has been established that statins are important in preventing stroke incidence, there are still relatively few studies that have investigated their use for stroke recurrence prevention. Stroke is investigated as a secondary endpoint in most studies. The results of a meta-analysis of prevention studies conducted in the western counties showed that cholesterol-lowering therapy using statins significantly decreased cerebral infarction incidence by 19%. On the other hand, cerebral hemorrhage incidence did not change significantly[348]. It remains unclear as to why the statin administration decreases cerebrovascular disease in observational studies given the fact that the cholesterol level is not recognized as a risk factor for cerebrovascular disease.

There are two studies in which the recurrence of stroke was the primary endpoint: the SPARCL[865] study and the J-STARS[619] study. In SPARCL, high doses of statins were administered to subjects who had no CAD with a stroke or transient ischemic attack (TIA) history within 6 months following the incidence. The recurrence rate of stroke in these subjects was compared with that of subjects who received a placebo, and the results revealed that apart from a significant decrease in the recurrence of stroke (−16%, p=0.03), the incidence rate of CAD was also significantly lower (−35%, p=0.003). A post hoc analysis found that cerebral infarction incidence was significantly decreased (hazard ratio 0.78), but that of cerebral hemorrhage was significantly increased (hazard ratio 1.66). However, it must be noted that statin dose in this study was much higher than the upper limit approved in Japan. The J-STARS study involved Japanese subjects with ischemic stroke, excluding those with cardiogenic cerebral embolism. The results of a comparison between the pravastatin group and the non-pravastatin group revealed that the former had a significantly decreased incidence rate of atherothrombotic cerebral infarction (hazard ratio 0.33). Meanwhile, the incidence rate of intracranial hemorrhage was the same as the non-statin group (hazard ratio 1.00)[619]. In terms of secondary prevention of noncardiogenic cerebral infarction, these results suggest that statin therapy has suppressive effects on atherothrombotic cerebral infarction incidence. Moreover, in regard to the results of SPARCL, which are contrary to those of a meta-analysis[348] in which increased incidence of cerebral hemorrhage because of statin administration was not observed, it has been shown that hemorrhage incidence does not increase in the Japanese. However, regarding cerebral hemorrhage risk following cholesterol-lowering therapy, further preven-

tive studies need to be conducted.

Among the other studies conducted in Japan, the MEGA study, which involved subjects with no history of CAD or stroke, showed that statin administration tends to decrease stroke incidence, with hazard ratios of 0.66 (men) and 0.63 (women)[620]. In particular, ischemic stroke incidence in men and stroke in women who were ≥ 55 years were significantly decreased[620, 621]. The results of a sub-analysis of JELIS showed that treatment with statins and EPA in patients with a stroke history significantly suppressed the recurrence of stroke by approximately 20% compared with statin monotherapy[622].

There are also other reports suggesting that the outcome of cerebral infarction that occurs during the course of treatment with statins is satisfactory[866], and that cerebral infarction risk increases as a result of discontinuing statin treatment[867].

iv) Measures to Prevent Cerebrovascular Disease

It is vital to control blood pressure because the greatest risk for cerebrovascular disease is hypertension. Atrial fibrillation is a major risk factor for cardiogenic cerebral embolism, and cerebral aneurysm is a significant risk factor for subarachnoid hemorrhage. Therefore, it is necessary to appropriately manage these risk factors. The relevant guidelines should be referenced when managing these risk factors[868].

In western countries, based on the results of a meta-analysis, lipid-lowering therapy is recommended for the prevention of noncardiogenic cerebral infarction[847, 869]. In Japan, because the proportion of atherothrombotic cerebral infarction has been increasing, and that the MEGA study showed that statins are effective in preventing cerebral infarction, appropriate lipid management should be carried out in addition to adequate antihypertensive therapy to prevent cerebral infarction. For the prevention of noncardiogenic cerebral infarction with underlying atherosclerosis, it is advisable to implement a set of management criteria based on the criteria for the ischemic heart disease prevention.

5. Implementation of Comprehensive Risk Assessment and Management

[Statement]

- **For the prevention of cerebrovascular and cardiovascular diseases, comprehensive management of the major risk factors, such as dyslipidemia, smoking, hypertension, and DM, should be carried out as early as possible. (Recommendation level: A)**
- **Lifestyle modification, including diet therapy, exercise therapy, and smoking cessation, forms the basis of cerebrovascular and cardiovascular disease prevention. It is important to continue to provide guidance on lifestyle modification even after initiating drug therapy. (Recommendation level: A)**

Cerebrovascular and cardiovascular diseases require multiple types of risk assessment and management[870]. In view of this, 11 academic societies led by The Japanese Society of Internal Medicine, together with the Japan Medical Association and The Japanese Society of Medical Sciences, jointly published an integrated management guideline titled "Comprehensive Risk Management Chart for the Prevention of Cerebrovascular and Cardiovascular Diseases" in April 2015 (hereafter abbreviated as "comprehensive chart")[156]. As shown in **Fig. 6**, its basic concept was to decrease the risk factors (obesity, hypertension, hyperglycemia, serum lipid abnormalities, renal dysfunction, etc.) by comprehensively managing the patient's lifestyle habits. However, in cases where various risk factors overlap, other than comprehensive management including drug intervention, the comprehensive chart also emphasized that specialized drug therapy for treating the underlying causes is essential if the disease is hereditary or secondary.

In this section, we will describe the comprehensive risk assessment and their management in six steps, based on the concept of the comprehensive chart (**Fig. 7**). The main target population is primarily first-visit patients assessed as "requiring further investigation" because of the presence of risk factors for ASCVD. However, for patients who have an ASCVD history, such as CAD, and for those already receiving treatment or are being followed up for dyslipidemia, DM, or hypertension, reassessment of the risk factors and determination of the effectiveness of their case management should be carried out periodically.
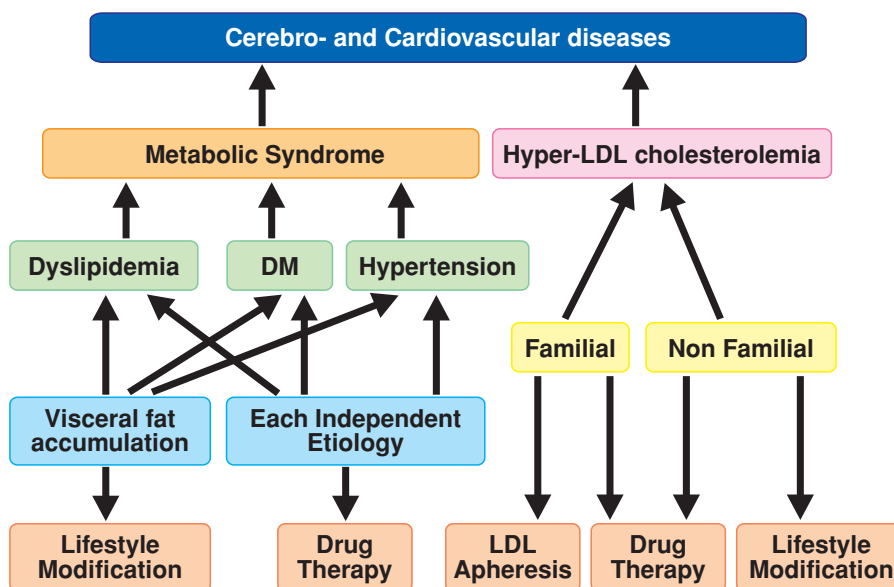
Fig. 6. Comprehensive Risks and Risk Factors for Lifestyle Habits

Joint Committee for Comprehensive Risk Management Chart for the Prevention of Cerebro- and Cardiovascular Diseases, The Journal of The Japanese Society of Internal Medicine 2015, Vol. 104, No. 4, 824-860

Fig. 7. Comprehensive risk assessment and their management in six steps

Step 1	a Screening (basic items) (**Fig. 8a**)
	b Screening (additional items) (**Fig. 8b**)
	c Determination of necessity of referral to a specialist (**Fig. 8c**)
Step 2	Diagnosis of each risk factor and additional items for assessment (**Fig. 8d**)
Step 3	Review of risk factors to be checked before initiating treatment (**Fig. 8e**)
Step 4	Set management targets for each risk factor and pathological condition (**Fig. 8f**)
Step 5	Lifestyle modification (**Fig. 8g**)
Step 6	Drug therapy (**Fig. 8h**)

[Screening]

Step 1: Screening for Cerebro- and Cardiovascular Disease Risk Assessment

- **Exhaustive screening of the major risk factors is important for the comprehensive risk management of cerebro- and cardiovascular diseases. In addition to blood biochemistry tests, careful medical history-taking and examination should be carried out.**
- **The screening consists of Step 1a (basic items), Step 1b (additional items), and Step 1c, (criteria for determining if the patient should be referred to a specialist).**
- **If possible, it is advisable to collect fasting blood for laboratory testing in Step 1a. Blood for Step 1b should generally be collected in a fasting state.**

Step 1 consists of the basic items for screening and the additional items presented in Steps 1a and 1b, as well as the criteria for determining the necessity of patient referral to a specialist in Step 1c.

Fig. 8a. Step 1a   Screening (Basic Items)

Medical interview*	Age, gender, subjective symptoms, family history, complications, medical history, medication history, lifestyle habits (smoking, passive smoking and alcohol consumption), exercise habits, and sleep and home blood pressure
Physical findings	Height, body weight, BMI (kg/m²), in-clinic blood pressure, pulse rate (regular or irregular), and chest auscultation
Basic tests (fasting blood preferred)	TC, HDL-C, non-HDL-C (TC – HDL-C), eGFR (serum creatinine), ALT, γ-GT, HbA1c**, blood glucose**, urinalysis (qualitative), and electrocardiography***

 * Specific physical examination medical interview sheet and additional interview sheets should be used.
** If either the HbA1c or blood glucose is shown to be indicative of diabetes (HbA1c ≥ 6.5%, fasting blood glucose ≥ 126 mg/dL, or random blood glucose ≥ 200 mg/dL), a re-test should be performed on a different day.
*** The patient may referral to a specialist depending on the degree of abnormality (i.e., atrial fibrillation).

Modified from Comprehensive risk management for the prevention of cerebro- cardiovascular diseases in Japan.
J Atheroscler Thromb, 2017; 24: 749-764

Fig. 8b. Step 1b   Screening (Additional Items)

Physical findings	Abdominal circumference (waist circumference), standing blood pressure (after 1-3 minutes of standing), ankle–brachial index (ABI), palpitation of extremities (arteries), and vascular murmurs at neck and abdomen
Additional tests	Blood count, fasting blood glucose*, fasting TG, LDL-C (TC – HDL-C – 0.2 × fasting TG)**, uric acid, K, chest X-ray, serum aldosterone/renin activity ratio***, urinary protein/creatinine ratio (random spot urine quantification)****

 * If either the HbA1c or blood glucose is shown to be indicative of diabetes (HbA1c ≥ 6.5%, fasting blood glucose ≥ 126 mg/dL, or random blood glucose ≥ 200 mg/dL), a re-test should be performed on a different day.
** The TC, HDL-C, and TG levels must be measured simultaneously during a fasting state, and the LDL-C level should subsequently be calculated using the Friedewald formula (TC – HDL-C – 0.2 × fasting TG) (if fasting TG < 400 mg/dL).
*** To be measured for patients with the following: hypokalemia, < 40 years of age, or blood pressure ≥ 160/100 mmHg. Patients should be referred to a specialist if the ratio is > 200 and the aldosterone concentration is 120 pg/mL.
**** Measured if the urinalysis (qualitative) shows abnormalities.

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i) Step 1a

Step 1a consists of the basic screening items. The items for the medical history-taking, physical findings, and tests necessary when assessing each patient's risk for ASCVD are shown in **Fig. 8a**. In addition to subjective symptoms, complications, medical history, lifestyle habits (smoking, passive smoking, and alcohol consumption), exercise habits, and sleep habits, which are standard items specific to a physical examination, it is recommended to check the patient's home blood pressure and family history during the medical history-taking. Age, gender, height, body weight, and BMI (kg/m²) are the recommended items to include in the physical findings, and the recommended examinations are in-clinic blood pressure, pulse rate (regular or irregular), and chest auscultation. It is preferable to collect fasting blood for the blood tests as much as possible. Other than TC, HDL-C, non-HDL-C (TC – HDL-C), eGFR (serum creatinine), ALT, γ-GT, HbA1c, and blood glucose, it is recommended to perform urinalysis (qualitative) and electrocardiography.

If atrial fibrillation is detected, the patient should be referred to a specialist depending on the degree of abnormality.

ii) Step 1b

Step 1b consists of the additional items for screening, which are to be carried out concurrently with 1a or if abnormalities are observed in 1a (**Fig. 8b**). For the physical findings, measurement of the abdominal circumference (waist circumference), standing blood pressure (after 1-3 minutes of standing), ankle–brachial index (ABI), arterial palpation in the extremities, and auscultation of vascular murmurs in the neck and abdomen should be performed. In principle, the blood count, blood glucose, TG, and LDL-C measurements should be tested using fasting blood, and in addition to a chest X-ray and uric acid test, the urinary protein/creatinine ratio should be measured if abnormalities are found in the urinalysis (qualitative). Whenever necessary, the plasma aldosterone concentration/renin activity ratio should also be

Fig. 8c. Step 1c Determination of Necessity for Referral to a Specialist

(1) If the patient is suspected of having a history of or being complicated with stroke/transient ischemic attack (TIA), coronary artery disease (CAD), arrhythmia (such as atrial fibrillation), aortic disease, or peripheral arterial disease (PAD)	
(2) Hypertension:	Suspected secondary hypertension (early incidence, acute incidence, etc.), pregnancy-induced hypertension, hypertensive emergency or urgency (untreated diastolic blood pressure ≥ 120 mmHg), blood pressure ≥ 180/110 mmHg despite treatment, or not achieving the antihypertension goal despite the combined use of three agents
(3) Diabetes Mellitus (DM):	Type 1 DM, HbA1c ≥ 8.0%, fasting blood glucose ≥ 200 mg/dL (or random blood glucose ≥ 300 mg/dL), acute complications (hyperglycemic emergency), or gestational diabetes
(4) Dyslipidemia:	LDL-C ≥ 180 mg/dL, HDL-C <30 mg/dL, fasting TG ≥ 500 mg/dL, non-HDL-C ≥ 210 mg/dL, or suspected primary hyperlipidemia or secondary dyslipidemia
(5) Chronic Kidney Disease (CKD):	Severe proteinuria (urinary protein/creatinine ratio of ≥ 0.5 g/gCR or ≥ +2 according to the litmus paper method), positivity for both urinary protein and hematuria (≥ 1+ according to the litmus paper method), eGFR <50 mL/min./1.73 m^2 (<60 for patients younger than 40 years, <40 for patients aged 70 years or older with stable renal function*)
(6) Obesity:	Severe obesity (BMI ≥ 35) or suspected secondary obesity (symptomatic obesity)

*The Japanese Society of Nephrology has eliminated the segmentation by age and revised to eGFR <45 mL/min./1.73 m^2.

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measured.

iii) Step 1c

Step 1c lists the circumstances in which referral to a specialist is likely to be necessary based on the outcome of the above-mentioned screening (**Fig. 8c**).
① If the patient is suspected of having a history of or being complicated with stroke/ TIA, CAD, arrhythmia such as atrial fibrillation, aortic disease, or PAD
② For patients with hypertension, if secondary hypertension (early incidence, acute incidence, etc.), pregnancy-induced hypertension, hypertensive emergency or urgency (untreated diastolic blood pressure ≥ 120 mmHg) is suspected, or if refractory hypertension (blood pressure ≥ 180/110 mmHg despite undergoing treatment, or not achieving the antihypertension goal with the combined use of three agents) is present
③ For patients with DM, if type 1 DM, HbA1c ≥ 8.0%, fasting blood glucose ≥ 200 mg/dL (or random blood glucose ≥ 300 mg/dL), acute complications (hyperglycemic emergency), or gestational diabetes is present
④ For patients with dyslipidemia, if LDL-C ≥ 180 mg/dL, HDL-C <30 mg/dL, TG ≥ 500 mg/dL, non-HDL-C ≥ 210 mg/dL, or if primary or secondary dyslipidemia is suspected (**Table 13**)
⑤ For patients with CKD, if advanced proteinuria (urinary protein/creatinine ratio ≥ 0.50 g/gCr or ≥ 2+ by the litmus paper method), positivity for

Table 13. Major Secondary Dyslipidemias

•Hypothyroidism
•Nephrotic syndrome
•Renal failure/uremia
•Primary biliary cirrhosis
•Obstructive jaundice
•Diabetes mellitus
•Cushing's syndrome
•Obesity
•Alcohol consumption
•Autoimmune diseases [systemic lupus erythematosus (SLE), etc.]
•Drug-induced dyslipidemia (diuretics, β-blockers, steroids, estrogen, retinoic acid, cyclosporin, etc.)
•Pregnancy

both urinary protein and urinary blood (≥ 1+ by the litmus paper method), or eGFR <50 mL/min/1.73 m^2 (<60 for those aged <40 years and <40 for those aged ≥ 70 years with stable renal function) is observed. (The Japanese Society of Nephrology has eliminated the segmentation by age and revised to eGFR <45 mL/min./1.73 m^2 in 2017[154].)
⑥ For patients with obesity, if severe obesity (BMI ≥ 35) or if secondary obesity (symptomatic obesity) is suspected

Step 2:

Step 2 consists of the diagnosis of each risk factor as well as additional assessments. It should be carried out using the five items in Table 4-15 as guidelines. Moreover, for any of the conditions, carotid ultrasonography, echocardiography, coronary computed tomography (CT), chest, and abdominal CT, magnetic resonance imaging (MRI), magnetic resonance (MR) angiography, brachial–ankle pulse wave velocity (baPVW), or cardiac–ankle vascular index (CAVI) should be performed as necessary.

i) For patients with hypertension (in-clinic blood pressure ≥ 140/90 mmHg or home blood pressure ≥ 135/85 mmHg), 24-hour blood pressure should be measured as necessary (differentiation of nocturnal hypertension and workplace hypertension).

ii) ① If DM is suspected and cannot be ruled out (HbA1c 5.6-6.4%, fasting blood glucose 100-125 mg/dL or random blood glucose 140-199 mg/dL, or a strong family history of DM or obesity), a 75-g OGTT should be performed (except when symptoms of DM are clearly present).

② If the patient is clearly diagnosed with DM, i.e., if both the HbA1c and blood glucose level are indicative of diabetes in the same blood test, the blood glucose level is indicative of diabetes and classic symptoms (thirst, polydipsia, polyuria, and weight loss) are present, diabetic retinopathy is present, or

a test done on a different day was able to reconfirm findings indicative of diabetes (the blood glucose level must at least be indicative of diabetes in either the first test or re-test[871]), funduscopy should be performed and the urine albumin/creatinine ratio (random spot urine quantification) should be assessed.

iii) For patients with dyslipidemia (LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, fasting TG ≥ 150 mg/dL, or non-HDL-C ≥ 170 mg/dL[872]), in addition to checking for the presence of arcus corneae, Achilles tendon thickening, cutaneous/tendon xanthomas and eruptive xanthomas, lipoprotein agarose gel electrophoresis or polyacrylamide gel electrophoresis should be performed to measure the apoproteins (AI, AII, B, CII, CIII, E), small dense LDL particles, Lp (a), remnant lipo-

Fig. 8d. Step 2　Diagnosis of Each Risk Factor and Additional Items for Assessment*

2A Hypertension:	In-clinic blood pressure ≥ 140/90 mmHg or home blood pressure ≥ 135/85 mmHg Measure the 24-hour blood pressure as necessary (differentiation of nocturnal hypertension and workplace hypertension)
2BDiabetes mellitus(DM): 2B-1)	DM is suspected and cannot be ruled out (either HbA1c 5.6-6.4%, fasting blood glucose 100-125 mg/dL or random blood glucose 140-199 mg/dL, or a strong family history of DM or obesity) →Perform 75-g OGTT (except if symptoms of DM are clearly present) If the patient is diagnosed with DM**
2B-2)	→Perform funduscopy and determine the urine albumin/creatinine ratio (random spot urine quantification)
2C Dyslipidemia:	LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, fasting TG ≥ 150 mg/dL, or non-HDL-C ≥ 170 mg/dL) →Check for the presence of arcus corneae, Achilles tendon thickening, cutaneous/tendon xanthomas and eruptive xanthomas, and perform lipoprotein agarose gel electrophoresis or polyacrylamide gel electrophoresis***, apoproteins (AI, AII, B, CII, CIII, E), small dense LDL particles, Lp (a), remnant lipoprotein cholesterol particles, lipoprotein lipases, hepatic lipases, and lecithin–cholesterol acyltransferases (LCAT)
2D CKD:	eGFR persistently remains at < 60 mL/min/1.73 m² or proteinuria is present for ≥ 3 months
2E Metabolic syndrome:	Abdominal circumference ≥ 85 cm (men) or ≥ 90 cm (women) and two or more of the following: serum lipid abnormalities (HDL-C < 40 mg/dL or fasting TG ≥ 150 mg/dL), high blood pressure readings (130/85 mmHg) and high blood glucose (fasting blood glucose ≥ 110 mg/dL)

* For each of these conditions, carotid ultrasonography, echocardiography, coronary CT, chest, and abdominal CT, MRI, MR angiography, baPVW, or CAVI should be performed as necessary.

** If both the HbA1c and blood glucose level in the same blood test are diabetic type, if the blood glucose level is diabetic type and classic symptoms (thirst, polydipsia, polyuria, and weight loss) are present, or if diabetic retinopathy is present. Alternately, if a test done on a different day reconfirmed findings indicating diabetes (note: the blood glucose level must at least be diabetic type in either the first test or the re-test).

*** The high-performance liquid chromatography (HPLC) method is also acceptable.

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protein cholesterol particles, lipoprotein lipases, hepatic lipases, and lecithin–cholesterol acyltransferases (LCAT).

iv) CKD is diagnosed if the patient's eGFR persistently remains at <60 mL/min/1.73 m^2 or proteinuria is present for ≥ 3 months[153].

v) The diagnosis of metabolic syndrome should be based on the diagnostic criteria by the eight academic societies for internal medicine.

Step 3:

Step 3 lists the risk factors that should be specifically taken note of for the prevention of cerebrovascular and cardiovascular diseases and before initiating treatment. These risk factors include: (1) smoking; (2) hypertension; (3) DM, including impaired glucose intolerance; (4) dyslipidemia; (5) CKD; (6) obesity, particularly visceral fat obesity; (7) aging and gender, i.e., men or postmenopausal women; and (8) family history, i.e., history or complication of cerebrovascular or cardiovascular diseases and lifestyle diseases (hypertension, DM, or dyslipidemia) in biological grandparents, biological parents, or blood siblings (especially cases of early incidence. It should always be kept in mind that strict management is necessary in cases where multiple risk factors are present (Fig. 8e).

Fig. 8e. Step 3 Risk Factors to be Reviewed before Initiating Treatment

(1) Smoking
(2) Hypertension
(3) Diabetes mellitus (including impaired glucose tolerance)
(4) Dyslipidemia
(5) CKD
(6) Obesity (especially visceral obesity)
(7) Aging and gender (men or postmenopausal women)
(8) Family history

*Always keep in mind that strict management is necessary in cases where multiple risk factors are present

Step 4:

- **The risk factors for dyslipidemia are stratified as described in Chapter 4-1.**

1) **Patients with a history of CAD are considered for secondary prevention**

2) **Among primary prevention patients, those with any of the following are considered at high risk: (1) diabetes mellitus (excluding impaired glucose tolerance); (2) chronic kidney disease (CKD); (3) noncardiogenic cerebral infarction; or (4) peripheral arterial disease.**

3) **For primary prevention patients, if additional risks are absent, they should be stratified into low-, moderate- and high-risk based on the absolute risk derived from the Suita score or the total number of additional risk factors other than LDL-C, including: (1) smoking; (2) hypertension; (3) low-HDL-C; (4) impaired glucose tolerance; or (5) family history of early onset CAD (first-degree relatives aged <55 years (men) or <65 years (women) at the time of onset).**

4) **In primary prevention, the patient is considered to be at high risk if the LDL-C level is ≥ 180 mg/dL, regardless of the number of additional risk factors present.**

- **The management targets for hypertension are $<140/90$ mmHg for patients aged <75 years (home blood pressure $<135/85$ mmHg), $<150/90$ mmHg for those aged ≥ 75 years (home blood pressure $<145/85$ mmHg), $<140/90$ mmHg if drug tolerance is noted (home blood pressure $<135/85$ mmHg), and $<130/80$ mmHg for those complicated with diabetes or proteinuria-positive CKD (home blood pressure $<125/75$ mmHg).**

- **An HbA1c reading $<6.0\%$ is recommended if the aim of diabetes management is normalization of the blood glucose level. The recommended reading for preventing complications is HbA1c $<7.0\%$. If it is difficult to intensify the treatment, the recommended HbA1c reading is $<8.0\%$.**

- **For obesity management, the aim is to reduce body weight by 3-5%.**
- **The basis of metabolic syndrome is the excessive accumulation of visceral fat. Multiple risk factors of ASCVD are present in this condition. The correction of obesity, especially visceral fat, should be considered to be a management target. Likewise, for other diseases such as hyperuricemia, keep in mind the prevention of ASCVD by deciding on the appropriate therapy and management targets that are suited to each patient.**

Fig. 8f shows the management targets suitable for each risk factor and pathological condition. As shown in the table, the management targets for hypertension and DM are in accordance the guidelines of The Japanese Society of Hypertension[122] and The Japan Diabetes Society[871], respectively. However, particularly for the elderly, the management targets should be established with the circumstances of individuals taken into consideration, such as the activities of daily living (ADL), cognitive function, and QOL.

As mentioned in Chapter 3-1, regarding the management of dyslipidemia for the young elderly aged ≥ 65 years but aged <75 years, the risk for each patient is stratified into secondary prevention, high-risk, moderate risk, or low risk[162]. For all risk categories, the management target is ≥ 40 mg/dL for HDL-C and <150 mg/dL for TG. With respect to LDL-C and non-HDL-C, the LDL-C management target for the low-risk category is <160 mg/dL (non-HDL-C <190 mg/dL). The LDL-C management target is <140 mg/dL (non-HDL-C <170 mg/dL) for the moderate-risk category and <120 mg/dL (non-HDL-C <150 mg/dL) for the high-risk category. A patient is at high risk if he/she has a history of or is complicated with DM, CKD, cerebral infarction, or PAD, regardless of age and gender. Similarly, a patient who has an LDL-C level ≥ 180 mg/dL is also considered to be at high risk regardless of the number of additional risk factors present. This section can be applied to the risk stratification for patients with secondary hyperlipidemia. Refer to "Chapter 7. The Elderly" for old old patients (≥ 75 years).

As mentioned in Chapter 3-2, the management targets for hypertension are <140/90 mmHg (home blood pressure <135/85 mmHg) for patients aged < 75 years, <150/90 mmHg for those aged ≥ 75 years (home blood pressure <145/85 mmHg), <140/90 mmHg if drug tolerance is noted (home blood pressure of <135/85 mmHg), and <130/80 mmHg for those complicated with DM or proteinuria-positive CKD (home blood pressure <125/75 mmHg).

For DM, an HbA1c reading <6.0% is the recommended management target when the aim of diabetes management is to normalize the blood glucose level. For preventing complications, the recommended goal is HbA1c <7.0%, and if it is difficult to intensify

Fig. 8f. Step 4 Setting Management Targets Suited to the Risk Factors for Each Pathological Condition*

4A Hypertension:	(1) <140/90 mmHg for patients aged <75 years (home blood pressure <135/85 mmHg) (2) <150/90 mmHg for patients aged ≥ 75 years (home blood pressure <145/85 mmHg) (Aim for <140/90 mmHg [home blood pressure <135/85 mmHg] if drug tolerance is noted) (3) <130/80 mmHg if the patient is complicated with DM or proteinuria-positive CKD (Home blood pressure <125/75 mmHg)
4B Diabetes Mellitus:	(1) A control indicator of HbA1C <6.0% when the aim is to normalize the blood glucose level (2) A control indicator of HbA1C <7.0% for preventing complications (3) A control indicator of HbA1c <8.0% if intensification of treatment is difficult
4C Dyslipidemia:	HDL-C ≥ 40 mg/dL and TG <150 mg/dL for all risk categories in addition to the following: Secondary prevention: LDL-C <100 mg/dL (non-HDL-C <130 mg/dL) Low risk: LDL-C <160 mg/dL (non-HDL-C <190 mg/dL) Moderate risk: LDL-C <140 mg/dL (non-HDL-C <170 mg/dL) High risk: LDL-C <120 mg/dL (non-HDL-C <150 mg/dL)
4D Obesity:	Improvement of hypertension, DM, and dyslipidemia by a 3-5% reduction in body weight in 3-6 months

*For elderly patients, the management targets should be set taking their individual circumstances, including their activities of daily living (ADL), cognitive function, QOL, and living conditions (such as whether they live alone and the status of care provided) into consideration.

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the treatment, the recommended goal is HbA1c < 8.0%. In lipid management, patients with DM are stratified into the high-risk category, and the management targets are LDL-C <120 mg/dL and non-HDL-C <150 mg/dL. However, for patients predicted to be at a particularly high risk for CAD, which include those who: (1) are complicated with FH; (2) are complicated with noncardiogenic cerebral infarction; (3) are complicated with PAD; (4) are complicated with microvascular complications (retinopathy, nephropathy, etc.); (5) have persistent poor glycemic control; (6) are complicated with metabolic syndrome (visceral fat obesity); (7) have multiple overlapping major risk factors, or (8) smoking, stricter management with compulsory achievement of the management targets is necessary. Overlapping conditions are considered to be particularly high-risk, and the same management targets as those for secondary prevention should therefore also be considered.

The aim of obesity management should be an improvement of hypertension, DM, and dyslipidemia by a 3-5% reduction in body weight[369, 873]. Visceral fat accumulation is considered an independent risk factor for CVD. It has been demonstrated in epidemiological studies in western countries as well as in Japan that the presence of multiple risk factors, such as metabolic syndrome, increases the risk for ASCVD (refer to Chapter 3-2, "Metabolic Syndrome"). Besides the management of each risk factor, emphasis should be placed on the reduction of visceral fat–the basis of metabolic syndrome–or in other words, the correction of obesity.

The serum uric acid level is a predictive factor for the future incidence of hypertension and is related to CKD incidence and progression[874]. An elevated serum uric acid level is believed to be associated with an increase in metabolic syndrome incidence. Therefore, therapeutic intervention should be considered for patients with a history of hypertension, DM, or CAD if the serum uric acid level is ≥ 8.0 mg/dL, even if they are asymptomatic with no gout attacks or gout stones. However, lifestyle modification should still be the basis for therapy[875].

Step 5: Lifestyle Modification

Lifestyle modification is the core of ASCVD prevention, and physicians must refrain from initiating drug therapy without further consideration of lifestyle. Nondrug therapies should be continued during the course of treatment with drugs. In other words, guidance on lifestyle modification should not be neglected. The main improvements are shown in Fig. 8g.

With reference to and as mentioned in Chapter 3-4, among all the causes of ASCVD, smoking cessation is the easiest intervention. Regardless of gender, smoking cessation should be recommended for patients of all age groups to prevent ASCVD (Standard Procedure for Smoking Cessation Therapy Version 6, 2014 by The Japanese Circulation Society, The Japan Lung Cancer Society, Japanese Cancer Society, and The Japanese Respiratory Society). The increased risk of CAD in nonsmokers because of passive smoking is also a serious issue. Smoking cessation therapy is covered by health insurance if certain conditions are met[876].

For obese patients (BMI ≥ 25), especially those with an accumulation of visceral fat resulting from metabolic syndrome, a weight loss ≥ 3% in 3-6 months should be the goal (refer to "4. Step 4" of this section). The optimization of energy and nutritional intake, and the correction of improper dietary habits and behaviors form the basis of treatment for patients with risk factors such as dyslipidemia, hypertension, DM, or obesity. High-fat meats, animal fats, and excessive alcohol consumption should be avoided while adopting a salt-reduced Japanese dietary pattern combined with an intake of fish, soy, vegetables, seaweed, mushrooms, fruits, and unrefined grains.

Exercise has been shown to result in improvements in dyslipidemia (increase in HDL-C level, etc.), decrease blood pressure, improve insulin resistance, and decrease blood glucose levels. Patients should aim to perform aerobic exercise of moderate intensity for ≥ 30 minutes a day, three times or more per week (daily if possible). Metabolic Equivalent of Task (MET) is a unit that expresses the intensity of exercise in terms of the equivalent number of times the metabolism is at rest, and moderate intensity is defined as an intensity of ≥ 3 METs. Normal walking is equivalent to 3 METs, while brisk walking is 4 METs and jogging is 7 METs; however, these values differ according to each individual's physical fitness. Patients who do not regularly exercise should be instructed to start with light and short exercises. However, patients complicated with hypertension are subjected to exercise therapy only if they have a moderate or lower blood pressure level (<180/110 mmHg) and no CVD. Exercise therapy needs to be prohibited or restricted for diabetic patients suffering from DM with extremely poor metabolic control (fasting blood glucose ≥ 250 mg/dL or

Fig. 8g. Step 5 Lifestyle modifications

Smoking cessation	Smoking cessation is a must Avoid passive smoking
Dietary management	•Consume well-balanced meals containing an appropriate amount of energy, the three major nutrients (proteins, fats, and carbohydrates), vitamins, and minerals •Avoid excessive intake of saturated fatty acids and cholesterol •Increase the intake of n-3 polyunsaturated fatty acids •Refrain from consuming trans fatty acids •Increase intake of dietary fiber •Decrease the amount salt and aim for a salt intake <6 g/day
Weight management	Measure body weight regularly. Maintain an appropriate body weight if BMI is >25 If BMI is ≥ 25, decrease energy intake to an amount less than the amount of energy used to work toward weight loss
Physical activity and exercise	Perform exercise habitually, mainly aerobic exercise of moderate intensity[*] or above (aim for ≥ 30 minutes/day)[**] At times other than during exercise therapy, walk frequently so as to avoid a sedentary lifestyle, and lead an active lifestyle
Drinking	Keep alcohol intake at an equivalent of 25 g/day[***] of ethanol

[*] Moderate intensity is defined as ≥ 3 METs. A MET is a unit that expresses the intensity of exercise in terms of the equivalent number of times the metabolism is at rest. Normal walking is equivalent to 3 METs, brisk walking is 4 METs, and jogging is 7 METs.

[**] Patients who do not exercise regularly should be instructed to start with light and short exercises.

[***] Equivalent to approximately 180ml of Japanese rice wine, one medium-sized bottle of beer, 90 mL of shōchū, one double glass of whiskey/brandy, or two glasses of wine.

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positivity for urine ketone bodies of moderate severity or higher), new occurrence of fundal hemorrhage because of proliferative retinopathy, CAD, or renal failure. If the patient is at high risk, a medical checkup should be performed beforehand and the opinion of a specialist should be sought on whether exercise therapy is possible or if there is a need for exercise restriction.

Step 6: Drug Therapy

Drug therapy (Fig. 8h) should be carefully initiated or continued depending on the individual risk and condition while continuously implementing lifestyle modification. Meanwhile, rigid drug therapy is necessary for high-risk cases. For the details on drug therapy for hypertension and DM, physicians should follow the guidelines for each disease[122, 871].

Special attention should be paid to adverse drug reactions if the patient is ≥ 75 years old or has renal dysfunction[877].

Fig. 8h. Step 6 Drug Therapy[*]

•Continue lifestyle modification and carefully initiate or continue drug therapy depending on individual risk and condition[**]
• However, rigid drug therapy is necessary for high-risk cases.

[*] Follow the respective guidelines for details on the drug therapy.

[**] Take note of adverse drug reactions if the patient is an elderly (≥ 75 years) or has renal dysfunction.

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Chapter 5. Familial Hypercholesterolemia

[Statement]

- **Familial hypercholesterolemia (FH) is a frequent autosomal hereditary disease associated with a high risk of CAD. Its early diagnosis and intensive treatment are recommended. (Evidence level: 3, Recommendation level: A)**
- **For the treatment of heterozygous FH, strict lipid management, primarily with statin therapy, is recommended. (Evidence level: 3, Recommendation level: A)**
- **For the treatment of homozygotes FH and drug therapy-resistant severe heterozygous FH, strict LDL cholesterol control by LDL apheresis is recommended. (Evidence level: 3, Recommendation level: A)**

1. Pathophysiology and Clinical Features of FH

FH is an autosomal dominant disease with 3 major features: (1) hyper-LDL-cholesterolemia, (2) premature CAD and (3) tendon and skin xanthomas. FH is dominantly inherited except for autosomal recessive hypercholesterolemia (ARH), a very rare form. FH patients have hyper-LDL-cholesterolemia from their birth, resulting in having a considerably high risk of CAD. Untreated heterozygous FH (HeFH) 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[878]. Early diagnosis and intensive treatment as well as family screening (cascade screening) will contribute to the prevention of premature death in FH patients. HeFH patients in Japan are observed in one in 200-500 of the general population, similar to those in other countries, suggesting that there are over 300,000 patients. Accordingly, FH is the most frequently encountered genetic disease in daily practice. Its diagnosis and treatment in childhood are important when progression of atherosclerosis begins.

2. Causative Genes of FH

Genetic analysis is not necessarily required for a diagnosis of FH. However, in addition to hyper-LDL-cholesterolemia, the presence of mutation in the LDL receptor or other genes involved in LDL receptor pathway gives a definitive diagnosis of FH. FH is caused by pathogenic mutations in genes of LDL receptor, apolipoprotein B-100 (Apo B-100) and PCSK9 which play an important role in LDL receptor pathway. In 60-80% of clinically diagnosed HeFH have a mutation in these causative genes. Homozygous FH (HoFH) are defined as having 2 pathogenic mutations in 2 alleles of the causative genes. ARH is an extremely rare disease, caused by mutations in LDLRAP1 which protein is involved in LDL receptor uptake.

3. Diagnosis of FH

1) Diagnostic Criteria

Diagnostic criteria are shown in **Table 14**. When diagnosing FH, it is necessary to pay great attention to family history in the patient interview. This is especially noted for young patients because they have a less chance to have Achilles tendon thickening. When serious illness develops concomitantly, including acute myocardial infarction, there may be a temporary drop in LDL-C. Therefore, palpation should be performed to examine the Achilles tendon and survey of the family history must be conducted for all the patients with acute myocardial infarction.

HoFH can be diagnosed based on clinical features: serum total cholesterol of 600 mg/dL or more, cutaneous xanthomas and ASCVD from childhood and parents' family history of heFH. Cutaneous and tendon xanthomas frequently occur in parts subjected to mechanical stimulation, such as the finger joints, elbow joints, knee joints and so on. If it is difficult to distinguish between HoFH and severe HeFH, genetic analysis is useful.

Diagnostic criteria for pediatric FH are shown in **Table 15**. As there are few physical symptoms such as xanthomas in pediatric HeFH, diagnosis has to be made on the basis of LDL-C and family history.

2) X-ray Examination of Achilles Tendon

Achilles tendon thickening is diagnosed when the greatest dimension is ≥ 9 mm. While it is also possible to use ultrasonography for evaluation, criteria have still to be standardized. (Refer to Achilles tendon radiography procedure in appendix).

3) Differential Diagnosis

Diseases that must be distinguished from FH

Table 14. Diagnostic criteria for heterozygous FH in adults (15 years of age or older)

- Hyper-LDL-cholesterolemia (an untreated LDL-C level ≥ 180 mg/dL)
- Tendon xanthomas (thickening of tendons on dorsal side of the hands, elbows, knees or Achilles tendon hypertrophy) or xanthoma tuberosum
- Family history of FH or premature CAD (within the patient's second-degree relatives)

- The diagnosis should be made after excluding secondary dyslipidemia.
- If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In case of suspected heterozygous FH, making a diagnosis using genetic testing is desirable.
- Xanthelasma is not included in xanthoma tuberosum.
- Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is ≥ 9 mm on X-ray imaging. (See Appendix)
- 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, respectively.
- If FH is diagnosed, it is preferable to also examine the patient's family members.
- These diagnostic criteria also apply to HoFH.

Table 15. Pediatric FH diagnostic criteria

- Hyper-LDL cholesterolemia: LDL-C level of ≥ 140 mg/dL when untreated
  (If total cholesterol level is ≥ 220 mg/dL, measure the LDL-C level)
- Family history of FH or premature CAD (blood relative closer than the two parents)

- Excluding secondary hyperlipidemia, if two items are satisfied, FH is diagnosed.
- During the growth phase, there are fluctuations in LDL-C; therefore, careful observation is required.
- In pediatric cases, there are few clinical symptoms such as xanthomatosis; therefore, it is important to investigate the family history for FH. Use the family survey results of those beyond the parents as a reference if necessary.
- Early CAD is defined as CAD with an onset at <55 years of age for males and <65 years of age in females, respectively
- If xanthoma is present, LDL-C is suspected to be extremely high (homozygote).

include conditions that cause secondary dyslipidemia (e.g. diabetes mellitus, hypothyroidism, nephrotic syndrome, cholestatic liver disease, drug-induced diseases (due to steroids) and a similar disease, familial combined hyperlipidemia (FCHL). FCHL can be distinguished from FH by the absence of tendon xanthomas, the presence of small dense LDL, the presence of other types of dyslipidemia (type IIa, type IIb, type IV) in patient's family and elevation of LDL-C to a lesser extent than for FH patients.

4. Treatment of Heterozygous FH

1) Management Target Levels

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 the target level in clinical practice. Therefore, it is also acceptable to aim for <50% of the pretreatment level if the management target for LDL-C is not achieved.

In HeFH patients for secondary prevention, the LDL-C management target level is set at <70 mg/dL because they can be considered to be at even higher risk.

However, there is no clear evidence for the validity of these numerical targets because clinical studies on FH without lipid-lowering therapy are ethically not permissible. 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.

2) Lifestyle Modification

Lifestyle modification should also be performed in FH patients as described in Chapter 4-2 Lifestyle Modification. However, due to the high risk of CAD, screening for CAD before administering exercise therapy is essential. CAD should be evaluated using patient interviews to determine the presence or absence of effort angina, and exercise electrocardiogra-
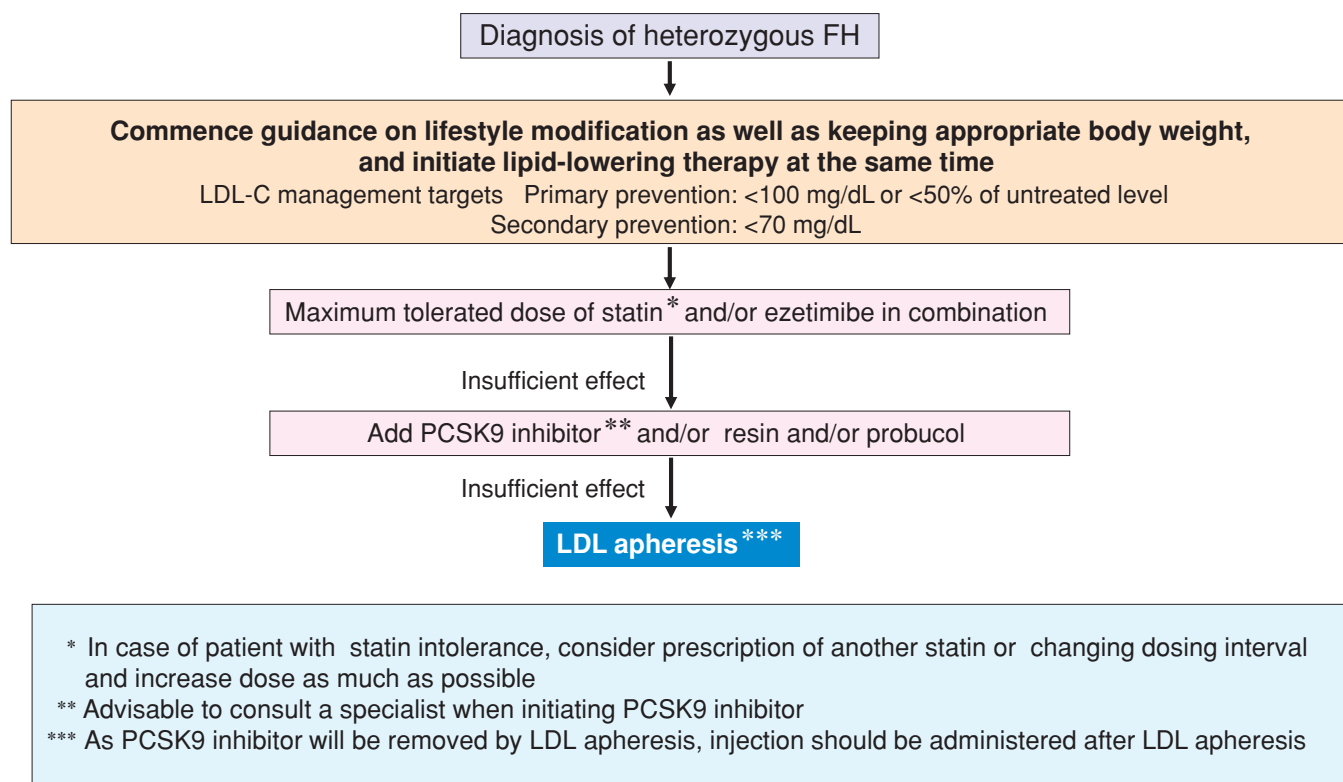
Diagnosis of heterozygous FH

↓

Commence guidance on lifestyle modification as well as keeping appropriate body weight, and initiate lipid-lowering therapy at the same time
LDL-C management targets   Primary prevention: <100 mg/dL or <50% of untreated level
Secondary prevention: <70 mg/dL

↓

Maximum tolerated dose of statin* and/or ezetimibe in combination

Insufficient effect ↓

Add PCSK9 inhibitor** and/or resin and/or probucol

Insufficient effect ↓

LDL apheresis*

* In case of patient with statin intolerance, consider prescription of another statin or changing dosing interval and increase dose as much as possible
** Advisable to consult a specialist when initiating PCSK9 inhibitor
*** As PCSK9 inhibitor will be removed by LDL apheresis, injection should be administered after LDL apheresis

Fig. 9. Treatment flow chart for adult (15 years or over) heterozygous FH

phy and echocardiography should be performed. If the existence of CAD is suspected, administering treatment for CAD before initiating exercise therapy is thus preferred. Smoking cessation and obesity management are also important.

3) Drug Therapy

In many HeFH patients, adequate lipid management is not achieved through lifestyle habit interventions alone, so drug therapy is usually combined with them. Statins are the first-line drugs for FH treatment. A retrospective analysis of 329 HeFH patients conducted in Japan revealed that statin use delayed the incidence of CAD[734]. When sufficient efficacy is not obtained with the initial statin dose, increase the dosage to the maximum tolerated dose and co-administer with ezetimibe. If efficacy is still not adequate, PCSK9 inhibitors, resins and probucol are used (**Fig. 9**). When the attending physician determines that the risk is particularly high, such as in secondary prevention patients and those with underlying diabetes, LDL-C should be lowered as early as possible.

A retrospective study suggested that probucol delayed recurrence of CAD in HeFH. In addition, it has been reported that the addition of the PCSK9 inhibitor evolocumab (Rutherford-II study[879]) or ali-

rocumab (Odyssey FHI and FHII studies[880]) in HeFH patients already being treated with statin (and ezetimibe) the further lowering of LDL-C (approx 60%) and Lp(a) was achieved relatively safely. However, it remains unclear whether such combination therapies are more effective in suppressing cardiovascular events in FH patients as compared to statin alone.

4) Application of LDL Apheresis Therapy

In HeFH patients, LDL apheresis therapy should be considered if the total cholesterol (TC) level does not decrease to 250 mg/dL or below following lifestyle habit improvement and intensive drug therapy in the presence of CAD, LDL apheresis is indicated, and it is desirable to consult a specialist.

5. Treatment of Homozygous FH

1) Target Levels for Management

In HoFH, it is essential to start intensive therapy including lowering LDL-C as early as possible. LDL-C target levels for management in HoFH are <100 mg/dL in primary prevention patients and <70 mg/dL in secondary prevention patients but in many cases they are difficult to achieve.
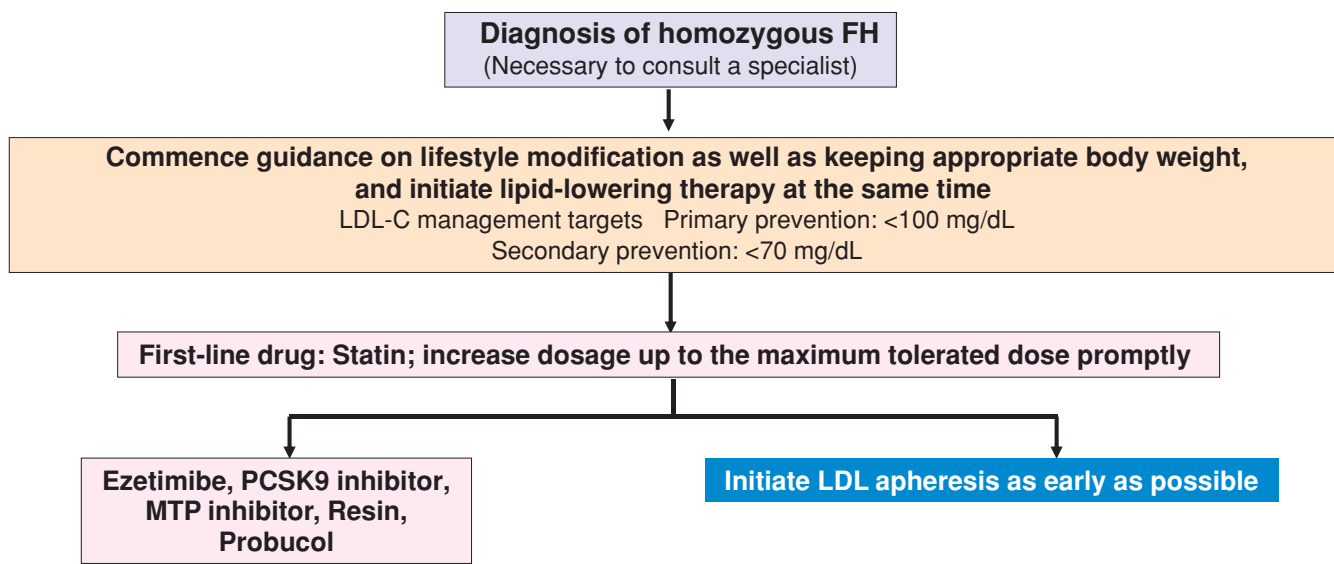
Diagnosis of homozygous FH
(Necessary to consult a specialist)

Commence guidance on lifestyle modification as well as keeping appropriate body weight, and initiate lipid-lowering therapy at the same time
LDL-C management targets   Primary prevention: <100 mg/dL
Secondary prevention: <70 mg/dL

First-line drug: Statin; increase dosage up to the maximum tolerated dose promptly

Ezetimibe, PCSK9 inhibitor, MTP inhibitor, Resin, Probucol

Initiate LDL apheresis as early as possible

Fig. 10. Treatment flow chart for adult (15 years or over) homozygous FH

2) Lifestyle Modification

Similar to that recommended for patients with HeFH, lifestyle modification, including diet therapy, exercise therapy, smoking cessation and obesity management, provides the basis for treatment in patients with HoFH, although intensive LDL-C-lowering treatment is necessary at an earlier age because patients with HoFH have an extremely high risk for the development and progression of CAD. It is necessary to assess CAD, valvular disease (aortic valve stenosis and supravalvular aortic stenosis in particular) and aortic aneurysm, and make a careful judgment based on the findings before giving any guidance on exercise therapy because progression of atherosclerosis is remarkable in HoFH patients.

3) Drug Therapy

In HoFH, in order to prevent the incidence and progression of CAD, intensive lipid-lowering therapy should be initiated as early as possible at an early age (**Fig. 10**). The major mechanisms of action of statins, bile acid adsorbing resins and PCSK9 inhibitors are to enhance expression (activation) of LDL receptors. For the defective type, in which only a small amount of LDL receptor activity remains, slight efficacy is observed but in the negative type in which LDL receptor activity is completely absent, no LDL-C lowering effect is observed[881, 882]. A retrospective study found that the administration of statin and other drugs was effective in reducing mortality rates in HoFH[883]. It has been reported that MTP inhibitors, which were developed for HoFH patients, lowered LDL-C by approximately 50%[693, 884]. However, as the frequencies of the adverse events of fatty liver and diarrhea are high, it is essential to control the fat and alcohol intake strictly. Probucol reportedly exerts a certain LDL-C lowering effect on HoFH and may cause the regression or disappearance of xanthoma in the skin or Achilles tendon[885]. Nevertheless, for LDL-C control, LDL apheresis therapy once every 1-2 weeks is still required in many cases. When patients are resistant to all of the above treatments or show intolerance, liver transplantation may be considered.

4) LDL Apheresis in HoFH

In patients with HoFH, 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 CAD, 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 on bed and extracorporeal circulation can be performed; however, it is recommended that the treatment be initiated as early as possible.

5) Pregnancy and Delivery of Patients with HoFH

It is important to permit patients with HoFH 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 athero-
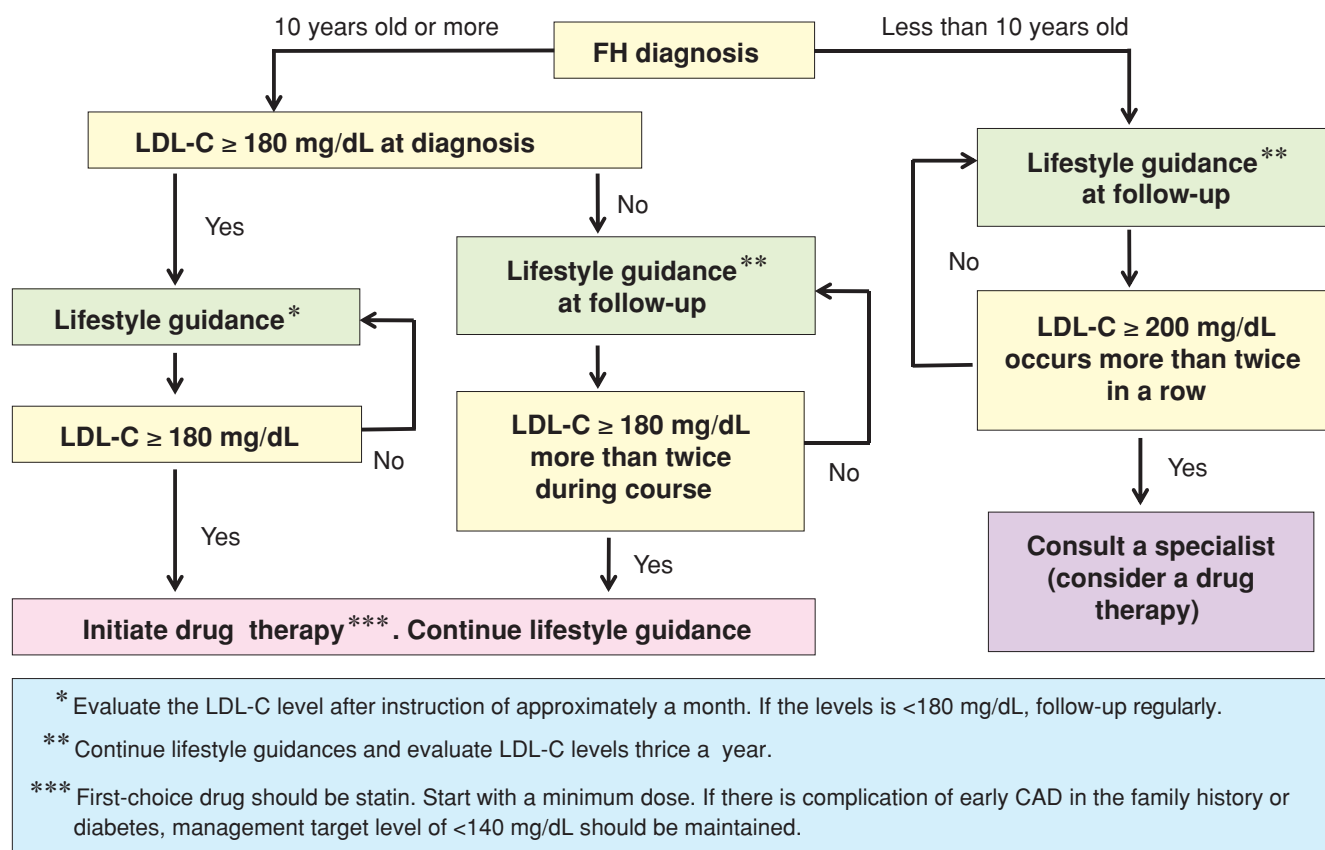
Fig. 11. Algorithm for treatment of pediatric FH heterozygote

sclerosis. 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.

6) HoFH Designated as an Intractable Disease

HoFH has been designated as an intractable disease in the Specified Disease Treatment Research Program since 2009. The criteria for designation are as follows: patients with HoFH 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.

6. Treatment of Pediatric HeFH

When HeFH is diagnosed, patients should be provided with guidance regarding lifestyle modification such as diet and exercise as quickly as possible in order to reduce the risk for atherosclerosis by means of LDL-C lowering. **Fig. 11** shows a treatment flow chart for pediatric HeFH[886]. For both boy and girl patients from the age of ≥ 10 years, pharmacotherapy needs to be considered if the LDL-C level is persistently above 180 mg/dL. Statins are the first line drugs starting from the minimal dose. In Japan, pitavastatin has been indicated for pediatric FH patients of ≥ 10 years since June 2015. The target LDL-C level should ideally be <140 mg/dL. When there is a family history of premature CAD or diabetes is also present, ensure that the LDL-C level is kept below 140 mg/dL. While it will be difficult to achieve targets in serious cases, efforts should be made to achieve a level as close to the target as possible through combination drug therapy. Guidance on lifestyle modification including diet should be continued even after commencing drug therapy.

Chapter 6. Other Types of Primary Dyslipidemias

1. Primary Hyperlipidemias other than Familial Hypercholesterolemia

Besides FH, there are various types of primary hyperlipidemias which are caused by a mutation of single-gene and highly heritable. Classification of these diseases have been proposed based on their pathogenesis and/or and genetic abnormalities (**Table 16**). 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 ASCVD. On the other hand, familial type Ⅲ hyperlipoproteinemia and FCHL are frequently associated with CVD; therefore, early diagnosis and initiation of treatment is important. It is recommended to refer the patients with these disorders to specialists. The clinically important diseases are described in depth below.

2. FCHL

1) Causes

FCHL was initially proposed as hyperlipidemia with mixed phenotypes associated with high prevalence of myocardial infarction[887]. The patients with FCHL typically manifest type Ⅱb (or combined) hyperlipidemia reflecting the variously combined effects of genetic and acquired factors (e.g., lifestyle habits). The phenotype may change to type Ⅱa or Ⅳ hyperlipidemia in response to changes in diet or age. The first degree relatives of affected patients are commonly associated with type Ⅱa, Ⅱb or Ⅳ hyperlipidemia. FCHL, which was previously believed to be an autosomal dominant monogenic disorder, is now considered to be an oligogenic disease complicated with other multiple environmental factors[888]. Genetic analyses have linked various genes to FCHL: LPL, USF-1, apoproteins B, C-Ⅱ, A-Ⅰ/C-Ⅲ/A-Ⅳ gene cluster, LDLR, and PCSK9. Besides the genetic factors, environmental factors such as over-nutrition, obesity, and lack of physical activity are believed to contribute to the manifestation of FCHL. Moreover, the prevalence of this disease is as high as 1% of the general population, and was reported to be 0.4% of the general population of children in Japan[889].

2) Clinical Symptoms

In patients with FCHL, the increase in the serum 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 incidence of CAD in patients with FCHL is high, although not as high as that in patients with FH[890, 891]. In Japanese patients with FCHL, myocardial infarctions are commonly observed in men ≥ 35 years of age and women ≥ 55 years of age. FCHL was reported to be found in 32% of patients ≤ 65 years of age with myocardial infarctions in Japan[892].

3) Laboratory Findings and Diagnosis

In patients with FCHL, the severity of hypercholesterolemia and hypertriglyceridemia is mild to moderate. FCHL is associated with an increase in the amount of apolipoprotein B and shift of the size of LDL to small (appearance of small dense LDL). 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 17**). FCHL is diagnosed if apolipoprotein B100/LDL-C ratio is > 1.0 or presence of small dense LDL is confirmed using lipoprotein polyacrylamide gel disc electrophoresis (PAG). A survey of familial history is optional for this diagnosis.

4) Treatment

Patients with FCHL should be treated according to a treatment guideline 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 ASCVD, such as CAD, is a prognostic factor.

3. Familial Type III Hyperlipidemia

1) Causes

Familial type Ⅲ hyperlipidemia, a hereditary type of hyperlipidemia also called broad β disease, is characterized by increased plasma levels of remnant lipoproteins, such as intermediate-density lipoprotein (IDL), chylomicron remnants and β-VLDL[893, 894]. Three isoforms are present for apoE, which is necessary for the hepatic uptake of remnant lipoproteins: wild-type E3 and isoforms E2 and E4. Familial type Ⅲ hyperlipidemia is caused by genetic abnormalities

Table 16. Categories of primary dyslipidemias

Primary hyperlipidemia	Primary hyperchylomicronemia	Familial lipoprotein lipase deficiency GPIHBP1 deficiency LMF1 deficiency Apoprotein A-V deficiency Apoprotein C-II deficiency Primary type V hyperlipidemia Others

	Primary hypercholesterolemia	Familial hypercholesterolemia
		[LDL receptor deficiency or abnormality, PCSK9 abnormality, familial apoB100 abnormality, LDLRAP1 abnormality (autosomal recessive hypercholesterolemia), and others]
		    Homozygous FH
		    Heterozygous FH
		Polygenic hypercholesterolemia
		Familial combined hyperlipidemia

	Familial type III hyperlipidemia	Apoprotein E abnormality Apoprotein E deficiency
	Primary hypertriglyceridemia	Familial type IV hyperlipidemia
	Primary high HDL cholesterolemia	CETP deficiency HL deficiency Others
Primary hypolipidemia	Abetalipoproteinemia (MTP abnormality)	
	Familial low betalipoproteinemia (ApoB or PCSK9 abnormality)	
	Familial low HDL lipoproteinemia	Tangier disease Familial LCAT deficiency and fish eye disease Apoprotein A-I deficiency Apoprotein A-I abnormality Others
Other dyslipidemias	Sitosterolemia and cerebrotendinous xanthomatosis	

in apoE. Patients with familial type III hyperlipidemia typically have *APOE2/E2* genotype. Other mutations of *APOE* gene, such as *APOE1*, abnormal *APOE3* and *APOE* deficiency are also known as the predisposing factor. In Western countries, the incidence of familial type III hyperlipidemia is estimated to be approximately 0.4% and 0.2% for adult men and women, respectively[895]. The incidence of E2/E2 is estimated to be approximately 0.2% in Japan; however, only a small portion of the patients with E2/E2 develop familial type III hyperlipidemia, with an incidence of 0.01-0.02% in a general population.

Abnormalities in apoE impairs the hepatic uptake of chylomicron remnants and IDL, leading to the accumulation of these lipoproteins in the blood. However, in many cases, remarkable hyperlipidemia does not develop despite the presence of apo E2/E2, other environmental conditions such as DM, obesity or hypothyroidism are necessary to develop hyperlipidemia.

2) Clinical Symptoms

Patients with familial type III hyperlipidemia are characterized by the high incidence of typical xanthoma such as xanthoma striatum palmare and/or xanthoma tuberosum, and premature ASCVD [e.g., CAD, carotid atherosclerosis, renal arteriosclerosis or PAD] and may develop renovascular hypertension or intermittent claudication due to PAD. In Western countries, the risk of CAD is increased by five- to eight-fold[896]. The incidence of complications of CAD is also high in Japan[897].

Table 17. Diagnostic criteria of FCHL

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 diabetes mellitus, should be excluded.
(4) One or more of the first-degree relatives have phenotype IIb, IIa or IV hyperlipidemia 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)

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 18**). This disease can be screened by a positive broad β pattern on lipoprotein polyacrylamide gel disc electrophoresis in patients with increases in both TC and TG and apoE/TC ratios of >0.05. Other indicators, such as apoE/B >0.20 and apoE/CIII >1.0[898], TC/apoB >6.2 and TG/apoB <10[899], RLP-C/TG>0.1[895], non-HDL-C/apoB >3[900], and apoB48/TG > 0.11[901], have also been proposed. LDL-C levels are low on lipoprotein analysis using ultracentrifugation or HPLC. Ultracentrifugation can be used to confirm a significant increase of cholesterol in IDL fraction (1.006<d<1.019) and high cholesterol/TG ratio (≥ 0.42) in the VLDL fractions (d<1.006). Finally, isoelectric focusing, Western Blotting, or genetic analysis can be used to demonstrate an apoE isoform abnormality.

4) Treatment

Dietary fat restriction is essential. Patients with familial type III hyperlipidemia respond relatively well to lifestyle modification including dietary and exercise therapy; thus, early diagnosis and treatment are extremely important. Treatment of associating comorbidities, such as DM, obesity or hypothyroidism 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. The prognosis is favorable as long as diagnosis is appropriately made and treatment is initiated early. Periodic examinations is essential to prevent the development of CAD, carotid atherosclerosis and PAD. Consultations with specialists are also recommended.

4. Other primary dyslipidemias

Primary hyperchylomicronemia (e.g., familial LPL deficiency and apoC-II deficiency) exhibits severe hypertriglyceridemia due to marked hyperchylomicronemia. In a typical case, primary hyperchylomicronemia manifests as type I hyperlipidemia; however, some patients may also exhibit type V hyperlipidemia. Primary hyperchylomicronemia often causes acute pancreatitis; therefore, a strict fat restriction is required (≤ 15–20 g/day). In hypertriglyceridemia accompanying ApoA-V gene abnormalities, it is necessary to prevent ASCVD. The following rare primary lipoprotein disorders have been listed as intractable diseases in 2015: sitosterolemia that are frequently associated with early-onset CAD, cerebrotendinous xanthomatosis, and Tangier disease were recently listed as Detailed diagnostic and treatment guidelines can be found at the Japan Intractable Diseases Information Center website under "Metabolic diseases" (www.nanbyou.or.jp/entry/504#04). PROLIPID (PROspective registry study of primary hyperLIPIDemia) study, which aims to investigate the prognostic outcome of three diseases of primary hyperlipidemia (Homozygous and heterozygous FH, hyperchylomicronemia and familial type III hyperlipidemia), is currently underway since 2015.

Table 18. Diagnostic criteria of familial type Ⅲ hyperlipidemia

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 hyperlipidemia 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)

Chapter 7.　Elderly

[Statement]

- **As is the case for nonelderly adults, hyper-LDL cholesterolemia is an important risk factor of CAD among the elderly persons 65-74 years of age. (Evidence level: E-1a)**
- **Statin therapy for hyper-LDL cholesterolemia in the elderly persons may be effective for the secondary prevention of CAD as is the case for nonelderly adults.
  (Evidence level: 1+, recommendation level: A)**
- **Statin therapy for hyper-LDL cholesterolemia in the elderly persons 65-74 years of age may be effective for the primary prevention of CAD and non-cardiogenic cerebral infarction.
  (Evidence level: 1+, recommendation level: A)**
- **The effects of lipid lowering therapy for hyper-LDL cholesterolemia in the primary prevention of CAD are not clear in the elderly patients ≥ 75 years of age, and should be handled for individual patients at the discretion of the attending physician. (Evidence level: 1)**

1. Relationship between Dyslipidemia and ASCVD in the Elderly

As aging is a significant risk factor of ASCVD, the risk for ASCVD is higher in elderly people than in nonelderly ones. The prognosis after the incidence of cerebrovascular disease and CAD is also poor, which increases the risk for disability. Therefore, primary and secondary preventions are extremely important. However, because aging is a stronger risk factor than other risk factors associated with ASCVD, the weighting of other risk factors such as dyslipidemia become relatively less. Nevertheless, these risk factors should also be managed accordingly.

Epidemiological studies in Western countries have revealed that hyper-LDL cholesterolemia is also a risk factor for CAD among the elderly (primarily in the young elderly: 65-74 years of age) as well as in nonelderly adults[902-907]. Although, many of the studies in the elderly aged ≥ 75 years reported that there was no relationship between the LDL-C level and the risk of CAD[908-910], a meta-analysis of 10 cohort studies in Japan (65,594 subjects, aged 70-89 years, EPOCH-JAPAN) reported that in men, total cholesterol ≥ 240mg/dL correlated with significantly increased death from CAD. No significant relationship was found in women. There was no significant relationship for stroke mortality in either sex[55]. Fur-

thermore, according to the NIPPON DATA 90 cohort data relating to the relationship between non-HDL-C and ASCVD, a significant relationship was found between non-HDL-C and CAD in elderly subjects aged ≥ 65 years, but no significant relationship was found between non-HDL-C and cerebral infarction or stroke[911]. A meta-analysis of 61 prospective studies including approximately 900 thousand adult men and women in Europe and North America, confirmed the deaths of 55,000 subjects from cardiovascular events during the reported observation periods, such as CAD and cerebrovascular disease. Of these, a significant correlation was found between total serum cholesterol at the beginning of the observation period and death from CAD in the elderly (aged 70-89 years), although a relationship with stroke was not identified[912]. In a further meta-analysis of 29 cohort studies in the Asia-Pacific region, a significant positive correlation was found between total cholesterol and death from CAD in not only individuals <60 years but also in the 60-74 year group and ≥ 75 year group; however, no relationship was identified between stroke and lipid levels[913]. As such, some independent cohort studies did not find a positive correlation between serum lipid levels and ASCVD in the elderly aged ≥ 65 years, but meta-analyses have reported positive correlations between CAD and total cholesterol, non-HDL-C and LDL-C. However, even meta-analyses have revealed no correlation between stroke and these lipid levels.

In the Japan Cholesterol and Diabetes Mellitus Study, an observational study including elderly Japanese people with diabetes, a significant relationship was found between CAD and HDL-C as well as the LDL-C/HDL-C ratio, and between cerebrovascular disease and HDL-C in the elderly aged ≥ 75 years; however, no relationship was found between LDL-C and non-HDL-C and either of these diseases[914].

There is almost no clinical evidence related to the elderly aged ≥ 85 years, a cohort which is expected to become larger in the future. This is because such subjects are unlikely to participate in longitudinal studies. However, the Cardiovascular Health Study has shown that in the elderly aged ≥ 85 years, LDL-C was not a risk factor for cardiovascular events[915]. It appears that aging itself has a greater impact on the prognosis of this elderly age group.

2. The Efficacy of LDL-C Lowering Therapy for Preventing ASCVD in the Elderly

1) Preventive Effects of Statins on ASCVD

PROSPER, a large clinical study involving only elderly subjects, revealed that statin therapy was able to prevent CAD[916]. In this study, 3.2 years of statin administration on patients aged 70-82 years, including secondary prevention patients, lowered the primary endpoint (CAD death + nonfatal myocardial infarction + fatal and nonfatal stroke) by 15%, clearly demonstrating that intervention with statins could also be applied to the elderly. The reduction of CAD risk was more pronounced in men than in women as well as in secondary prevention patients than primary prevention, although no significant difference was observed in the interaction analysis.

Several meta-analyses by Cholesterol Treatment Trialists have been published, and showed the following: in the >65 years group, the relative risk of statin therapy on major coronary artery events was 0.81 (95% confidence interval [CI]: 0.76-0.88) (2005)[917], the relative risk on a major vascular event of statin and high-dose statin groups in subjects aged 66-75 years was 0.78 (95% CI: 0.74-0.83) relative to the control group or a low-dose statin group, and 0.84 (95% CI: 0.73-0.97) in the group >75 years (2010). Both meta-analyses demonstrated that statin therapy showed increased effects than the control group, and that high-dose statins had greater effects than a low-dose statin group in preventing an event[918].

A meta-analysis of 51,351 elderly subjects aged ≥ 60 years, including primary and secondary prevention patients, who received intervention with statins showed that statin therapy decreased total mortality by 15% (95% CI: 7-22%), death from CAD by 23% (95% CI: 15-29%), fatal and nonfatal myocardial infarction by 26% (95% CI: 22-30%), and fatal and nonfatal stroke by 24% (95% CI: 10-35%) compared to the placebo. However, the relative risk of cancer onset with statin therapy was 1.06 (95% CI: 0.95-1.18) relative to the placebo, and the difference was not statistically significant. There was no significant difference between statins and the placebo in terms of adverse events, such as a ≥ 3-fold increase of AST and ALT, ≥ 10-fold increase of CK or termination of the trial. However, muscle pain and gastrointestinal symptoms occurred significantly more often in the statin group. Moreover, new-onset diabetes was significantly higher in the statin group among those ≥ 65 years[919]. A meta-analysis of CAD mortality risk in a secondary prevention intervention trial, including elderly subjects aged ≥ 65 years, showed that the effects of secondary prevention on the elderly are far greater than that would be predicted from the outcomes in younger individuals[920]. As such, the secondary prevention effects of statin in the elderly with CAD history are evident and are recommended. The recently published J-STARS is a research study investigating

the efficacy of 10 mg pravastatin on patients with ischemic stroke aged 45-80 years. Although no significant difference was found in terms of the primary endpoint, statins decreased the incidence of atherothrombotic cerebral infarction by 67%[921]. Considering the mean patient age of 66 years in this study, approximately half of the subjects were presumed to be elderly, and considering that the effects of statin therapy were observed regardless of age group, these results suggest that statins are capable of preventing the recurrence of atherothrombotic cerebral infarction in the elderly.

Meanwhile, the MEGA Study on primary prevention in the elderly showed that the concurrent risk of CAD and cerebral infarction decreased significantly in individuals aged ≥ 65 years [hazard ratio: 0.60 (0.39-0.93)], which was related to the efficacy of statin treatment in the elderly with high LDL-C[922]. Another meta-analysis, involving only primary prevention studies, also indicated that statin administration lowered the risk of all-cause mortality, major cardiovascular events and major cerebrovascular events[923]. Another meta-analysis of primary prevention including 24,674 elderly patients (mean age: 73 years, 43% women) confirmed that statins decreased myocardial infarction and stroke by approximately 40% and 25%, respectively[924]. The efficacy of statin treatment has thus been established, at least for primary prevention in younger elderly patients. Consequently, pharmaceutical therapy can be recommended on the basis of the risk factors present. However, there is still a lack of strong evidence for primary prevention in the elderly aged ≥ 75 years. As there is no method of risk assessment for elderly patients aged ≥ 75 years, as indicated in Chapter 2, treatment should be given, or dismissed, at the discretion of the attending physician. In addition, as geriatric syndrome complications, such as frailty and sarcopenia, are common in elderly aged ≥ 75 years, it is important to confirm whether patients in this particular group have adequate protein intake when dietary counseling is provided.

2) The Effects of Statins in Dementia Prevention

A selection of observational and interventional studies has attempted to investigate the effects of statin treatment on dementia prevention. However, many of these reports relate to subanalysis and secondary endpoints, and studies that set cognitive function as the primary endpoint involved sample sizes that were too small. An observational study suggested that statin treatment improves cognitive function[925], many research results do not support these effects[926, 927]. A meta-analysis of interventional trials of four statins on patients with Alzheimer's disease patients in a recent

Cochrane review, however, failed to demonstrate that statins could improve cognitive function[928]. Therefore, we can conclude that the effects of statins in the prevention and treatment of Alzheimer's disease are not positive. Although there is no research data relating to the assessment of statin effects on vascular dementia, we do know that stroke increases dementia risk by approximately 2-fold and that statins decrease the incidence of stroke; consequently, the preventive effects of statins on vascular dementia incidence can be expected. However, there are some case reports in which statins decreased cognitive function, and must, therefore, be approached with caution.

3) Frailty, a New Risk Factor that should be Considered in the Elderly

In the elderly, frailty is another factor which can require long-term care, much like dementia. In fact, there have been recent studies reporting that the incidence of cardiovascular events increases in elderly patients with frailty, or those who show vulnerability to acute stressors, a condition that appears with age. For example, White et al. conducted a prospective follow-up study dividing non-ST-elevating ACS patients aged ≥ 65 years into three groups: frail, pre-frail, and nonfrail groups using Fried criteria and found that the frail group had significantly higher primary endpoints of cardiovascular, myocardial infarction and stroke mortality than the nonfrail group (HR: 1.76；95% CI: 1.36-2.28), and that all-cause mortality also increased significantly (HR: 1.98；95% CI: 1.47-2.68)[929]. In another study, Sergi et al. divided 1,567 nonfrail elderly patients aged 65-96 years into three groups: a group meeting 1 Fried criterion, a group meeting 2 Fried criteria and a third group that did not meet any of the criteria; these groups were followed-up for 4.4 years in relation to CAD, heart failure, stroke, PAD and cardiovascular death as the primary endpoints. Even after adjustment for the confounding factors, event incidence occurred significantly more frequently in the groups meeting 1 or 2 Fried criteria; in other words, those in the pre-frail groups, compared to the robust group[930]. This suggested that frailty, characterized by low grip strength and slower walking speed, may represent a new risk factor for cardiovascular events in the elderly, and that there may be a need to make more comprehensive assessments that include geriatric syndromes such as frailty.

Sarcopenia is a pathological condition related to frailty. Sarcopenia is characterized by decreased muscle mass associated with age, which decreases muscular strength and walking speed, and has been suggested to not only cause falls and fractures but also exert impact on cardiovascular events[931]. Because statins cause

muscle disorder as a side effect, it is concerned that long-term continuous use may be related to sarcopenia incidence. For example, Scott et al. showed that the use of statins in the community-dwelling elderly was linked to decreased leg muscle strength[932]; however, a subsequent meta-analysis by Krishnan et al. concluded that the earlier study by Scott et al. was lacking in convincing evidence[933]. Lynch et al. further reported that the use of statins in 3,422 elderly patients in rehabilitation (mean age = 81.4 years) was associated with an improvement in the activities of daily living[934]. As such, at present, there is simply not enough evidence to support the fact that statin treatment increases the risk of sarcopenia.

4) The Advantages and Disadvantages of Statin Treatment during End-of-Life Care

Sometimes doctors cannot decide whether or not a patient's medication should be continued or terminated, even during end-of-life care. Most clinical research tests the effects of pharmaceutical drugs by initiating them; however, Kutner *et al.* randomly assigned 381 patients estimated to have ≤ 1 year of life expectancy into two groups: one group for which treatment would be terminated and a second group that would continue taking the prescribed statin. These authors set death as the primary endpoint, and also studied quality of life (QOL) and financial effects. Results showed that there was no increase in deaths or cardiovascular events when statin treatment was terminated, and instead showed that QOL improved and that patients were able to save on their medical costs[935]. At the end of life, it is sometimes difficult to continue taking medication due to decreased appetite or dysphagia; hence, it is logical that being able to decrease oral medication in a safe manner will lead to an improvement in patient QOL.

Because statins in primary prevention are thought to take 3-4 years to have an effect upon the suppression of vascular events, the use of statins should only be considered in cases with at least ≥ 3 years of life expectancy.

3. Care of the Elderly

For preventing ASCVD in the elderly and maintaining QOL, it is important to manage dyslipidemia, particularly hyper-LDL cholesterolemia, which is an important risk factor. At the same time, it is important to consider the increase in secondary dyslipidemia, which occurs with complications such as hypothyroidism. There are many aspects to carefully consider in providing treatment to the elderly, such as the comorbidities other than ASCVD that may impact upon vital prognosis, latent organ disorder, atypical symptoms, decreased organ spare ability, decreased drug metabolism ability, malnutrition, frailty, polypharmacy, and due to variability in physical functions, careful considerations should be paid to treatment.

The basic treatment for dyslipidemia is dietary and exercise therapy for the elderly. Drug therapy should not be given at ease without implementing nonpharmaceutical therapies first. However, because adherence to strict diet therapies can worsen the nutritional state of the elderly, particularly in the latter-stage elderly population, and because it is difficult for many to take on the same-level of physical activity as nonelderly adults for exercise therapy, it is best to make an intervention which is adapted to each individual's capacity. Pharmaceutical therapy should be prescribed with extreme care with the understanding that elderly patients are more prone to side effects.

Chapter 8. Women

[Statement]

- **It is important to manage risk factors, such as hypertension, diabetes, and smoking regardless of menopause status. In particular, diabetes and smoking are related to an increased the coronary artery disease (CAD) risk in women than in men. (Evidence level: E-1a)**
- **The intensity of treatment for hypertension and diabetes should be personalized for each patient; however, smoking cessation is important for women across all age groups. (Evidence level: 2, recommendation level: A)**
- **In premenopausal women, lifestyle modification is the most important aspect of dyslipidemia treatment. (Evidence level: 2, recommendation level: A)**
- **Even before menopause, pharmacotherapy should be considered for high-risk women, such as**

those with familial hypercholesterolemia or CAD, and primary prevention subjects with high CAD risk. (Evidence level: 3, recommendation level: A)

- **Lifestyle modification is the fundamental aspect of treatment for dyslipidemia in postmenopausal women; however, pharmacotherapy should be considered in patients with high CAD risk. (Evidence level: 2, recommendation level: A)**

1. Current Status of ASCVD in Japanese Women

According to the gender-specific causes of death in the 2014 Population Census of Japan, mortality rates for cardiovascular disease, including heart failure, and cerebrovascular disease in women is 26.8%, which is higher than the rate of 22.3% in men and the rate of 24.4% for malignant neoplasms[936]. However, myocardial infarction incidence is lower in women than in men[937, 938] The epidemiological survey conducted in Japan between 1990 and the beginning of 2000 revealed that the age-adjusted incidence (100,000 persons/year) of myocardial infarction in women is 20-50% of that in men[98, 163, 939, 940]. Although the incidence rate of myocardial infarction increases after menopause, the rate is still lower than that in men[163]. According to the 2013 demographic statistics, mortality rate (per 100,000 persons) due to myocardial infarction in women is lower than that in men in the corresponding age groups: approximately 20% of the men's rate in the 50s, 20-30% in the 60s, and 37-48% even in their 70s[936]. In contrast, it has been reported that the mortality rate after a coronary event is higher in women than in men among both Western[941-944] and Japanese subjects[945, 946]. Aging among Japanese women is progressing and is accompanied by an increased morbidity and mortality due to myocardial infarction[163, 936]. Thus, it is important to take future measures for prevention and care even in Japanese women.

Among the Japanese, the age-adjusted incidence of cerebral infarction is higher than that of myocardial infarction. However, the incidence in women is approximately 50-70% of that in men[98, 939, 940, 947-949]. The incidence rate of cerebral infarction in women increases with age, and it reaches 60-90% of that of the men for women aged ≥ 75 years. Compared to myocardial infarction incidence, the gender difference in the rate of cerebral infarction is small[163, 948, 949]. Mortality rate due to cerebral infarction in women in 2013 (per 100,000 persons) is also lower than that in men[936]. On the other hand, cross-sectional study of acute cerebral infarction reported that the duration of hospitalization is longer for women than for men and that patient status at the onset and after discharge is poorer for women than for men[950].

Among the Japanese, cerebral infarction incidence is higher than that of myocardial infarction, and the gender differences in cerebral infarction incidence are smaller than that of myocardial infarction. Furthermore, proportion of older women continues to increase in Japan. Thus, the prevention and management of cerebral infarction among women is an important issue for the future.

2. Relationship between Risk Factors for Atherosclerosis and ASCVD in Women

1) Serum Lipids

Age-related changes in serum lipid levels are significantly different between men and women. Total cholesterol (TC) and low-density-lipoprotein cholesterol (LDL-C) levels are higher in men than in women until the fourth decade of their lives; however, because of menopause, the levels become higher in women than in men after the age ≥ 50 years[85]. High-density-lipoprotein cholesterol (HDL-C) levels are higher in women than in men among all age groups. Triglyceride (TG) levels are also higher in men than in women, but this increases with age in women, and the difference between genders diminishes after age 50 years[85]. It is likely that the changes in serum lipid levels, especially changes in LDL-C after menopause, may influence the ASCVD risk in women.

JALS-ECC[337], a longitudinal epidemiological study reported that CAD risk was significantly higher in the high-TC group than in the low-TC group after adjustment for multiple confounding factors in women. CIRCS also showed that myocardial infarction risk after adjustment of multiple factors increase 1.42 times with each increase LDL-C by 30 mg/dl[37].

EPOCH-JAPAN studied the relationship between TC levels and CAD mortality risk, and found that the risk was significantly higher in the high-TC group than in the low-TC group for women aged between 40 and 69 years[951]. The NIPPON DATA 80 also showed a significantly higher cardiovascular mortality risk among women with hypercholesterolemia group[54]. However, in the Ibaraki Prefectural Health Study, no significant correlation was found between LDL-C and CAD mortality[38]. Thus, cholesterol level is a significant risk factor for the CAD incidence

among Japanese women, and also might be a risk factor related to CAD mortality.

The JPHC Study[59] and EPOCH-JAPAN[951] examined the relationship between TC and cerebral infarction risk, and concluded that no significant correlation existed among women.

Iso *et al.* reported that elevated TG level was also a significant risk factor for the incidence of myocardial infarction and ischemic cardiovascular diseases in women[88, 93]. In addition, JALS-ECC[337] and CIRCS[63] reported that non-HDL-C is a significant risk factor for CAD incidence but not CAD mortality[66].

Thus, abnormalities in TC, LDL-C, TG, and non-HDL-C levels might be an important risk factors of CAD for Japanese women.

2) Smoking

The JPHC Study Cohort1[786] and Suita Study[108] found that the incidence rate of myocardial infarction was three to eight times higher among smokers than among nonsmokers even among women. In addition, CAD-related mortality risk was significantly higher in women smokers[952, 953]. Meta-analyses involving studies conducted in Japan have reported that the influence of smoking on CAD risk in women is greater than that in men[954]. JACSS, a multicenter collaborative research of acute coronary syndrome (ACS) in Japan, found that women who smoke had extremely higher ACS risk than men with smoking, with an odds ratio of 8.2 in women compared to that of 4.0 in men[955].

Smoking is also a significant risk factor for cerebral infarction in women[108]. Moreover, passive smoking increases cerebral hemorrhage risk but not cerebral infarction risk among Japanese women[956].

Thus, smoking should be considered as an important risk factor for CAD and cerebral infarction among Japanese women.

3) Hypertension

Epidemiological studies in Japan did not demonstrate that hypertension was a significant CAD risk factor in women[957, 958], although there was a trend for increase the CAD risk[958]. However, it has been reported that hypertension was a significant risk factor for cerebral infarction incidence among women[857, 957, 958]. NIPPON DATA 80, which studied the relationship between hypertension and cardiovascular mortality risk, reported that the association between the two was significantly stronger for in younger women aged 30-59 years than in women aged ≥ 60 years[959].

Thus, hypertension is an important risk factor for cerebral infarction among women, and it is necessary to treat hypertension from a younger age.

4) Diabetes

The JPHC[136, 146, 960], Hisayama[961], and Suita studies[962] reported that CAD and cerebral infarction risk as well as the related mortality risk were significantly higher among patients with diabetes than among those without. The NIPPON DATA 80 showed that CAD mortality risk was high among older women whose random blood glucose ≥ 200 mg/dL[161]. JACCS reported that the odds ratio for myocardial infarction incidence for female diabetics was 6.12 compared to 2.90 for male diabetics, indicating a significant increased myocardial infarction risk among women[954]. In the meta-analyses, including the research in Japan, it was reported that CAD risk and all-stroke risk were 44%[149] and 27%[150] higher, respectively for diabetic women than for diabetic men.

3. Primary and Secondary ASCVD Prevention in Women

The fundamental strategy for ASCVD prevention is lifestyle modification. The Nurses' Health Study (NHS) in US revealed that the increasing of favorable lifestyle factors (e.g., smoking cessation, increase in physical activity, maintenance of ideal body weight, restriction of alcohol consumption, and healthy eating habits) were associated with lower risk of CAD[963] and sudden cardiac deaths[964]. In addition, a collaborative analysis of NHS and Health Professionals Follow-up Study reported that the relative cerebral infarction risk among women who had all five factors described above was extremely low at 0.19, compared to women without any of favorable lifestyle factors[965]. Moreover, NHS, which included young women aged 27-44 years, showed that CAD incidence was decreased by 98% who had six factors (the above described five factors plus restricted TV-watching time) compared with women without any of these factors[966]. Thus, maintaining a healthy lifestyle from a younger age is quite important for preventing ASCVD in women.

Although effect of smoking on CAD risk is greater for women than for men[953], this effect is diminished after smoking cessation[108]. Because smoking has a negative effect on pregnancy[967] and smoking cessation decreases ASCVD risk regardless of age[107], it is extremely important for women to stop smoking from a younger age.

Few large scale trials have investigated the primary prevention of CAD using statins in women. In the MEGA Study conducted in Japan, 68% subjects were postmenopausal women aged ≤ 70 years. In this study, statins did not decrease the risk of CAD and cerebral infarction significantly in women[41]. How-

ever, in the sub-analysis among women, risk of CAD combined with cerebral infarction was significantly decreased among the women aged ≥ 55 years[620]. In JUPITER, statins were administered to 3,426 female subjects, and the risks of unstable angina and reperfusion therapy were significantly decreased compared to the placebo group. However, significant risk reduction of myocardial infarction and cerebrovascular events was not observed in women with statin therapy[968]. In addition, the risk for the primary endpoints that include these events was significantly lower among the women aged ≥ 65 years but not in women aged <65 years[620]. CTT reported that the significant risk reduction of CVD for 0.72 with each decrease in LDL-C by 38.7 mg/dL for men without history of vascular diseases. On the other hand, risk reduction was 0.85 for women, and this was not statistically significant[179].

Because effect of statins on the primary prevention of ASCVD is not evident in women, the primary treatment strategy for women is lifestyle modification. However, drug therapy should be considered for women with FH and CAD as well as for primary prevention subjects who are at high CAD risk. There is little evidence that dyslipidemia increased CAD risk in premenopausal women. Thus, lifestyle modification is fundamental for treating dyslipidemia in premenopausal women after ruling out dyslipidemia due to secondary causes. A consensus has not been reached about the teratogenic risks on a fetus by statins during pregnancy[662, 969, 970], and there is insufficient knowledge on the secretion of statins into breast milk. Thus, statin administration during pregnancy or lactation must be prohibited.

In secondary prevention, a meta-analysis of 11 studies, including 4S and CARE, reported that statins significantly decreased cardiovascular event risk to 0.82 in men and 0.81 in women[971]. The results of a CTT also showed a significant risk reduction of 0.84 for CVD with each decrease in LDL-C by 38.7 mg/dL in women with a history of vascular diseases, similar to that in men[179]. J-STARS investigated the effect of statins on the prevention of recurrent stroke in patients with cerebral infarction history. During 5-year study revealed that atherothrombotic cerebral infarction risk decreased significantly to 67%; however, risk reduction in women was not significant compared to that in men[619].

Thus, it is necessary to treat women for the secondary prevention of CAD; however, the effect of statins on preventing the recurrence of cerebral infarction is not evident in women.

Although strict glycemic control contributes to the CAD prevention in diabetics[972], it requires a lon-

ger duration to reveal a protective effect[973, 974]. In addition, its effect is small compared to the risk reduction seen for microvascular complications[834]. Because of increase in risk of hypoglycemia, strict glycemic control should be carefully considered by patients' conditions[972, 975]. The effect of diabetes on ASCVD incidence is greater for women than for men[149, 150]. Thus, it is important to initiate early comprehensive management, including risk factors other than hyperglycemia for ASCVD prevention.

Hypertension is an important risk factor for cerebral infarction in women and has been suggested to be a CAD risk factor. The number of hypertensive subjects increases with age both men and women, and the number of female patients surpasses that of males from age 60 years[976]. After menopause, LDL-C increases in women[950] and ASCVD risk increases. Thus, hypertension management becomes important in postmenopausal women. Meta-analysis reported that there was no clear difference in the risk reduction of CVD by hypertension treatment between men and women[977].

Intervention trial of hypertension among premenopausal women has not performed yet. Thus, lifestyle modification is quite important among premenopausal women after ruling out hypertension due to secondary causes. For the control of pregnancy-related and postmenopausal hypertension, the guidelines of the Japanese Society of Hypertension should be applied[122].

Hormone-replacement therapy (HRT) is effective treating postmenopausal disorders and osteoporosis prevention. Multiple clinical trials on the relationship between HRT and CVD risk have been reported. In HERS, women who had CAD were given HRT, did not reveal any risk reduction of CAD or cerebrovascular disease[978, 979]. In a study including 16,608 postmenopausal women, Women's Health Initiative (WHI) examined the effect of HRT (conjugated estrogen + medroxyprogesterone acetate) on middle-aged and older US women who suffered from disorders that disturbed their quality of life. The results of this study showed a significant increase in cerebral infarction risk (1.44)[980] and CAD (1.24) among women with HRT than among control women[981]. In this study, only women with conjugated estrogen replacement therapy showed a significant increase in cerebral infarction risk of 1.55[982]. Although, the increase in the risk of HRT-related CAD and cerebrovascular diseases are associated with age; there was no increased risk for either diseases among women aged <60 years and the risk for CAD was relatively low[982, 983].

The Japan Society of Obstetrics and Gynecology and Japan Society for Menopause and Women's

Health developed a 2012 version of HRT guidelines[984]. The guidelines prohibit the use of HRT for patients who have a history of myocardial infarction, other CAD, and stroke. They also recommend the careful consideration of HRT when patients are obese, aged ≥ 60 years, have been postmenopausal for ≥ 10 years or have a history of coronary spasms and microvascular angina, severe hypertriglyceridemia, or uncontrollable diabetes or hypertension. To date, several studies have reported the negative effect of HRT on CVD risk; however, favorable effects of estrogen on lipid metabolism and vascular function have been established, and transdermal estrogen has been reported to significantly decrease myocardial infarction risk[985]. Thus, the benefits and safety of different types and dosages of estrogen and progestin not used in WHI, and the route of administration cannot be overlooked and further research is needed[986].

Currently, CAD incidence among women is considerably lower in Japan than in Western countries[938]. A decrease in cerebrovascular disease incidence has also been observed because hypertension control[938]. On the other hand, new concerns related ASCVD risk such as westernized eating habits and decreasing of physical activity become apparent. Moreover, in a 2014 survey, 10-15% women in their 20s and 30s reported smoking[987]. Because women live longer than men, it is particularly important to introduce healthy lifestyle and control of risk factors of ASCVD from a younger age in woman.

Chapter 9. Children

[Statement]
- **Early detection and correct diagnosis of dyslipidemia are important. (Consensus, recommendation level: A)**
- **In cases of familial hypercholesterolemia, attempt to identify new patients (children) in the family (cascade screening). (Consensus, recommendation level: A)**
- **Provide patients with familial hypercholesterolemia with guidance on lifestyle habits, including diet, while considering the indication of drug therapy. (Consensus, recommendation level: A)**
- **Nonpharmacological therapy is the main treatment for primary dyslipidemia other than familial hypercholesterolemia. (Consensus, recommendation level: A)**
- **In cases of secondary dyslipidemia, adequately treat the primary disease. (Consensus, recommendation level: A)**
- **It is recommended that children establish appropriate dietary and exercise habits and maintain proper body weight. (Consensus, recommendation level: A)**

1. Early Detection of Dyslipidemia

Children do not have many opportunities to have their blood tested. If there is an opportunity to collect and test their blood, TC and TG should be tested at least once. Any abnormalities should be investigated in detail. For blood samples collected in a fasting state, LDL-C is calculated based on TC, TG, and HDL-C. For blood samples collected in a non-fasting state, LDL-C measured using the direct method and non-HDL-C should be used as a reference.

2. Criteria for Dyslipidemia in Children

Diagnostic criteria for dyslipidemia in children (i.e., elementary and junior high school students) are presented in Table 19. These values are derived from a report by Okada et al.[988] based on a nationwide survey conducted in the 1990s. TC, LDL-C, and TG are based on the 95th percentile values, and HDL-C is based on the 5th percentile value. Although some age-related differences are seen, the entire group of children is represented by a single value. Recent studies have also reported that lipid levels do not substantially differ from the previously determined levels[989]. Regarding the reference value for non-HDL-C, the 95th percentile value is reported to be approximately 140 mg/dL in junior high school boys, whereas it is approximately 150 mg/dL in elementary school boys, as well as elementary and junior high school girls[989].

Postprandial TG levels in children were studied by Kobayashi et al.[990] during screening for lifestyle-related diseases and were found to increase within 1 h

Table 19. Diagnostic Criteria for Dyslipidemia in children (elementary and junior high school students) (fasting blood samples)

Total cholesterol (TC)	≥ 220 mg/dL
LDL cholesterol (LDL-C)	≥ 140 mg/dL
Triglycerides (TG)	≥ 140 mg/dL
HDL cholesterol (HDL-C)	< 40 mg/dL

TC, LDL-C, and TG are derived from the 95th percentile values and HDL-C is derived from the 5th percentile value[988].

after eating and remained nearly constant until 3 h later, after which they decreased. The 95th percentile value for postprandial TG is approximately 200 mg/dL.

3. Primary Dyslipidemia

Primary hypercholesterolemia and primary hyperchylomicronemia are primary concerns for children. Type Ⅲ hyperlipidemia is considered to be rare in children.

1) Primary Hypercholesterolemia (Hyper-LDL-Cholesterolemia)

FH requires appropriate medical attention beginning from childhood. This is because LDL-C values become extremely high because of abnormalities in gene encoding for the LDL receptor system. Genetic testing results suggest that the incidence of FH is higher than that previously described. When a child is suspected of having FH, interviews to obtain a detailed family history and blood tests of family members (i.e., lipid tests) should be conducted to identify any newly affected children and adults in the family (e.g., cascade screening). It is recommended that proactive treatment be initiated in childhood because CAD often occur at a young age. When LDL-C is ≥ 180 mg/dL even with continuing guidance regarding lifestyle habits, it is recommended to consider drug therapy from approximately 10 years of age (See Chapter 5 "Familial Hypercholesterolemia").

For FCHL, there is no evidence indicating the necessity of proactive drug therapy during childhood.

2) Primary Hypertriglyceridemia

It is important to detect primary hyperchylomicronemia, which can cause pancreatitis, particularly LPL deficiency, in children. Many reports have documented LPL gene mutations. Other possible causes include a deficiency of apolipoprotein C-Ⅱ, which activates LPL, and mutations in apolipoprotein A-V genes.

Homozygotes have very severe hypertriglyceridemia (≥ 1,000 mg/dL). Diet therapy (fat intake restriction and the use of medium-chain fatty-acid milk for infants) is the primary form of treatment.

4. Secondary Dyslipidemia

Various causes are involved in the development of secondary dyslipidemia. Among these, obesity is frequently involved. In addition, thyroid hormones should always be tested when the cause is unclear because some patients with hypothyroidism (e.g., Hashimoto's thyroiditis) have severe hyper-LDL-cholesterolemia. Attention should also be paid to drug-induced dyslipidemia.

Obese patients require treatment to reduce the degree of obesity. Hyper-LDL-cholesterolemia accompanying diabetes is also particularly problematic in children. Diabetes itself is a major risk factor for arteriosclerosis, and blood glucose control alone seems to be insufficient for preventing ASCVD (see Chapter 4 "Comprehensive Risk Management, 4-2) Diabetes"). The International Society for Pediatric and Adolescent Diabetes guidelines[991] state lipid management targets of < 100 mg/dL for LDL-C, > 35 mg/dL for HDL-C, and < 150 mg/dL for TG. When LDL-C is above the target level, blood glucose control is intensified and diet and exercise therapies for hyperlipidemia are added. For hypo-HDL-cholesterolemia and hypertriglyceridemia, the basic approach is to improve lifestyle habits[991]. In Japan, the general consensus is that LDL-C should be maintained at least within the normal range (< 140 mg/dL)；however, no explicit criteria are currently available for drug therapy for children[992]. Therefore, it is important to take care of children's diets and continue with strict blood glucose control.

5. Maintaining Proper Body Weight with Appropriate Diet and Exercise Habits

Pathological blood vessel changes associated with arteriosclerosis have been reported to gradually occur in childhood[993, 994]. It is important to prevent such changes from occurring and progressing as much as possible. To achieve this, it is important to develop correct lifestyle habits (e.g., diet) and maintain a proper body weight from childhood. Even in children, obesity causes problems such as abnormal blood test values (e.g., adipocytokine secretion) and blood pressure[995, 996]. Thus, obesity in children is also considered to promote ASCVD similar to that in adults, and attention paid to obesity during childhood helps reduce the risk of future lifestyle-related diseases.

The 2015 Dietary Reference Intakes for Japanese[997] lists the desirable daily energy intake according to age and body size. Regarding nutritional balance, the target ratios of energy intake from fat and carbohydrates are 20-30% and 50-65%, respectively, which are same for all age groups (from 1 year to ≥ 70 years). Fat intake should be moderate because in recent years, due to the westernization of dietary habits, fat intake has increased. Therefore, it is recommended that individuals consume a well-balanced amount of fish, soybeans (products), vegetables, fruits, and seaweed, by utilizing Japanese food patterns as a main method, with no preference to a particular type of food. Care should also be taken to avoid excess salt intake.

Because BMI percentile (or standard deviation) method is inappropriate to evaluate overweight and obesity in children, because of the large variability in body height, it is better to assess the percentage of overweight (POW) based on comparison with standard body weight[998]. The POW is calculated as [(measured body weight − standard body weight)/ standard body weight] × 100 (%). In general, elementary and junior high school students are classified as obese if the calculated POW is +20% or higher (≥ 120% of the standard body weight)[998]. Like in obese adults, LDL-C and TG tend to be high in obese children, whereas HDL-C tends to be low. Even if the calculated POW is not indicative of severe obesity (≥ 50%), the child is considered to be "obesity disease", a target of treatment for reducing the severity of obesity, when he or she exhibits any obesity-related complications[996].

In obesity, the energy intake is increased and exceeds the necessary level; it should be reversed to normal levels. Obese children should increase their vegetable intake and avoid certain drinks and seasonings. The degree of obesity improves more easily during childhood because body height continues to increase. Moreover, an exercise habit should be established at the same time as dietary restrictions. In particular, adequate guidance should be given to children who are obese or not accustomed to exercise. In cases of severe obesity, energy intake may also need to be restricted.

Smoking is also an independent major risk factor for ASCVD, and smoking cessation is known to reduce the risk of developing such diseases. Because passive smoking has also been reported to increase the risk for CAD and diabetes, attention should be paid to smoking not only by the patient themselves but also by other family members.

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Appendix 1. Physical Activity Guidelines for Health Promotion 2013
[Chapter 4 2-5. Exercise Therapy]

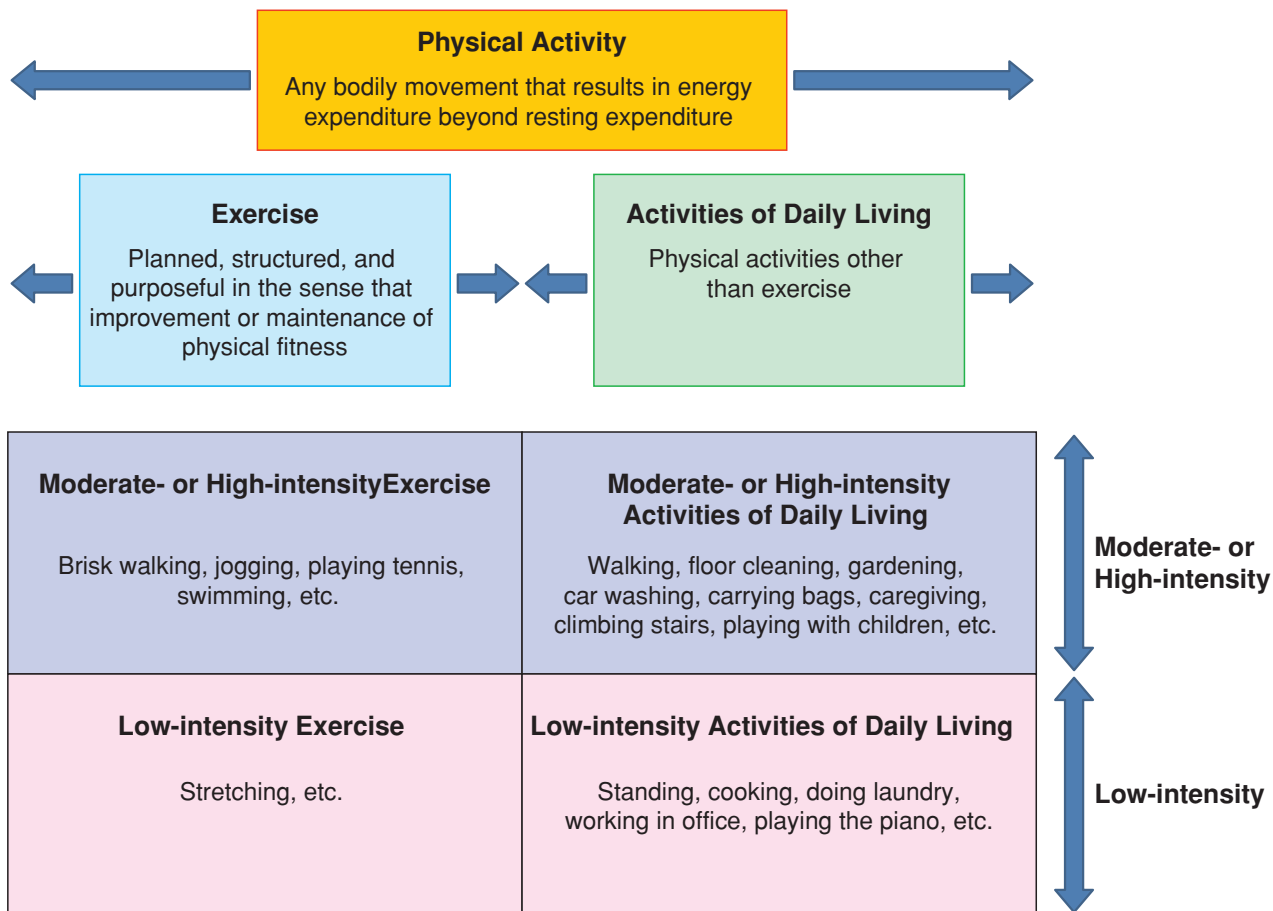| Status on blood glucose/pressure/lipids		Physical activity (activity of daily living/exercise)		Exercise		Physical fitness (physical endurance)
Health checkup results are within the reference range	≥ 65 years	Physical activity of any intensity for 40 min/day (10 METs·hour/week)	Increase even if slightly more than the current activity level (e.g., additional 10 min of walking)	-	Try to establish exercise habits (≥ 30 min for ≥ 2 days/week)	-
	18–64 years	Physical activity of ≥ 3 METs intensity[3] for 60 min/day (23 METs·hour/week)		Exercise of ≥ 3 METs intensity for 60 min/ week (4 METs·hour/week)		Can continue exercise of intensity specified for sex/age range for approximately 3 min
	< 18 years	-		-		-
Any of the blood glucose/pressure/lipids levels are at the recommended health guidance levels		Help the subject to assess his or her own physical condition before and during exercise; then, provide proactive exercise instructions as a part of health guidance if the subject is not visiting a medical institution and is confirmed to not have any risk according to "Screening sheet for physical activity risks."				
Those with multiple risks or requiring immediate medical consultation		Patients with lifestyle-related diseases should consult their primary physicians before commencing active exercise because safety considerations are particularly important.				

Adapted/modified from: Ministry of Health, Labour and Welfare "Japanese official physical activity guidelines for health promotion 2013 (outline)"

[Commentary]
1. "Japanese official physical activity guidelines for health promotion 2013" is the successor of "Exercise Guidelines for Health Promotion 2006," revised to serve as a tool to help achieve the goal of Health Japan 21 (the second term).
2. "Physical activity" is defined as "all bodily movement that accompanies energy expenditure above resting energy expenditure" including both "activities of daily living" and "exercise."
3. Guidelines on "physical activity" now include the all-generation direction of " + 10 (add 10-min of activity to the current life)" in addition to age-specific criteria.
4. For exercise, performing "exercise" for ≥ 30 min at least 2 days/week in addition to "activities of daily living" was also shown to be desirable for individuals other than those in the 18-64 years age range.
5. In the " Japanese official physical activity guidelines for health promotion 2013," messages are sent to those who are likely to be at risk in the future and those who are currently at risk.

Appendix 2. Exercise Guidelines for Health Promotion 2006

[Chapter 4 2-5. Exercise Therapy]

Physical Activity

Any bodily movement that results in energy expenditure beyond resting expenditure

Exercise

Planned, structured, and purposeful in the sense that improvement or maintenance of physical fitness

Activities of Daily Living

Physical activities other than exercise

Moderate- or High-intensityExercise Brisk walking, jogging, playing tennis, swimming, etc.	**Moderate- or High-intensity Activities of Daily Living** Walking, floor cleaning, gardening, car washing, carrying bags, caregiving, climbing stairs, playing with children, etc.	**Moderate- or High-intensity**
Low-intensity Exercise Stretching, etc.	**Low-intensity Activities of Daily Living** Standing, cooking, doing laundry, working in office, playing the piano, etc.	**Low-intensity**

1. Physical activity is defined as any bodily movement that results in energy expenditure beyond resting expenditure

2. Physical activities are classified into two categories: "activities of daily living," such as physical labor, housework, and commuting to work/school in daily life, and "exercise" is a subset of physical activity that is planned, structured, and purposeful in the sense that improvement or maintenance of physical fitness is the objective.

3. Physical activities are classified according to intensity (i.e., physical activities of "moderate or higher intensity" and physical activities of "lower intensity").

4. Although the term "exercise" is used in the exercise therapy guidelines, exercise

Adapted/modified from: Ministry of Health, Labour and Welfare "Exercise guidelines for health promotion 2006"

Appendix 3. Method for Achilles Tendon Radiography

[Chapter 5: Diagnosis of familial hypercholesterolemia]

Imaging position

In the sitting and lateral positions, attach the lower thigh and lateral malleolus side of the ankle to the receiver surface so that the lower thigh and the sole form a 90° angle. Use radiographic aids whenever possible to improve reproducibility and accuracy of the position because extension, flexion, medial rotation, and external rotation of the ankle affect the measurements of Achilles tendon hypertrophy.

Imaging conditions

When using a digital system, use 50 kV and 5.0 mAs (e.g., 100 mA×0.05 s, 50 mA×0.1 s). Increase or decrease the mAs value as needed.

Imaging distance (distance from the focus of the X-ray tube to the X-ray receiver surface)

Use a distance of 120 cm to eliminate the impact of the magnification ratio on X-ray images as much as possible. If possible, take images with a lead scale or the like (known size and radio-opaque) placed at the same height as that of the Achilles tendon to correct the magnification ratio.

X-ray central line

The position of incidence is the posterior margin of the medial malleolus of the tibia perpendicular to the receiver surface.

Image processing conditions

Conditions for which it is possible to clearly detect the Achilles tendon, adipose tissue, and skin are recommended when a digital X-ray imaging system is used for evaluation.

Achilles tendon hypertrophy measurement

When measuring on an image reference terminal, measure the most thickened part of the Achilles tendon using a measurement tool. When measuring on a film, measure the thickening on an actual-size output using a caliper or a ruler. The development of measurement software programs for improved measurement accuracy is required.