Review

Executive Summary of Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases for Japanese

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Introduction

In Japan, a consensus conference on hyperlipidemia was held in 1987, and diagnostic criteria for hyperlipidemia were proposed. They were based on a consensus of experts and not necessarily on evidence in Japan. In the United States, National Cholesterol Education Program (NCEP) was announced as the evidence-based guideline in 1988[1]. Thereafter, with accumulation of clinical evidences, the NCEP underwent 2 major revisions in 1993[2] and 2001[3], and was partially revised in 2004[4] on the basis of evidence collected by the latest large-scale clinical studies. The concepts of the NCEP greatly affected clinical activities in Japan, but with increase of wishes for the development of original guidelines of Japan, the epidemiology of which differs from that in the United States, "The Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese Adults" were published on the basis of some Japanese evidences in 1997[5]. Thereafter, the importance of concurrence of risk factors was also established in Japan by the report of NIPPON DATA80[6] as well as of the Japan Lipid Intervention Trial (J-LIT)[7]. The announcement in 2002 of "The Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases"[8], which were developed by taking risk factors into consideration, set a major framework of guidelines in Japan.

Five years have passed since we issued "The Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases, 2002". During this period, new epidemiological and clinical studies have also been accumulated in Japan. Among them are the epidemiological studies, the current data[9] of NIPPON DATA80 and the clinical intervention studies, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA)[10] and Japan EPA Lipid Intervention Study (JELIS)[11]. Through these studies, it has also been shown in Japan that elevated LDL-cholesterol (LDL-C) is closely related to coronary artery disease (CAD) and that both CAD and cerebral infarction (CI) can be prevented by lowering LDL-C. Such evidence provided the basis for a revision of the guidelines.

For the establishment of guidelines in Japan, it is important to remember that Japan achieved remarkable economic development after World War II, and the associated urbanization caused marked changes in the living environment, i.e., westernization of lifestyle, which has led to increases in the obese, dyslipidemic, and diabetic populations. Hypertension also changed from the salt-dependent type to hypertension accompanied by metabolic abnormalities, consequently, with marked changes in the pathology of stroke, i.e. , from cerebral bleeding and lacuna type to ahterothrombotic CI[12]. Such changes in risk factors of atherosclerotic diseases have led to epidemiological trnsition in Japan.

In addition, the cholesterol level of Japanese continued to increase from the 1960s to 1990s, and it is approaching the mean of Americans, in whom the cholesterol level is decreasing due to improvements in lifestyle. Since several decades are needed for atherosclerotic diseases to develop and cause cardiovascular events, increases in the incidence of atherosclerotic diseases are expected for the future in Japan[13].

Our guidelines present standard treatments for the prevention of atherosclerosis. Dyslipidemia is a major risk factor of atherosclerosis along with hypertension, diabetes mellitus, and smoking. Total management of these risk factors is important for the prevention of atherosclerosis. Our guidelines propose measures for the management of dyslipidemia, which is

Table 1. Diagnostic criteria for dyslipidemia (Serum sampled after overnight fasting)

LDL-cholesterol	≥140 mg/dL
HDL-cholesterol	<40 mg/dL
Triglycerides	≥150 mg/dL

Diagnosis of dyslipidemia is made when either type of lipid abnormalities is present.
These diagnostic criteria are not intended for the beginning of drug therapy.
It is important to consider the indications of drug therapy only after evaluation of other risk factors.
LDL-C is evaluated bacically by calculation with the Friedewald equation.
[LDL-C = TC − HDL-C − TG/5 (when TG is <400 mg/dL)]
When the TG is ≥400 mg/dL or non-fasting state, the LDL-C should be determined by direct measurement.

closely related particularly to CAD among these risk factors, and we would like to remind their users that they are formulated on the assumption that other risk factors are under appropriate control.

1. Diagnostic criteria for dyslipidemia

In the current guideline, **Table 1** is titled "diagnostic criteria for dyslipidemia", changed from "diagnostic criteria for hyperlipidemia" in the previous edition because the table includes low HDL-cholesterol as a risk for atherosclerosis. This table of diagnostic criteria was prepared for the diagnosis of dyslipidemia and screening for a high-risk group of atherosclerotic diseases. And it should not be mistaken for criteria of dyslipidemia requiring drug therapy.

The diagnostic criterion for hypercholesterolemia here is LDL-C ≥140 mg/dL or TC ≥220 mg/dL. According to the relationship between TC and mortality due to CAD observed in the MRFIT[14], the NCEP of the United States proposed a TC level of 240 mg/dL (LDL-C 160 mg/dL)[2], at which the relative risk is doubled compared with 200 mg/dL (LDL-C 120 mg/dL), as the diagnostic criterion for hypercholesterolemia. In this guideline, a TC level of 220 mg/dL (LDL-C 140 mg/dL), at which the relative risk is increased by 1.5-fold compared to <160 mg/dL TC from the epidemiologic study of NIPPON DATA80[9], was proposed as the diagnostic criterion for the following reasons. First, the individuals with LDL-C levels between 140 and 160 mg/dL, at which the relative risk is 1.5～2 times higher, is already at a risk of developing atherosclerotic vascular diseases even without other risk factors, and therefore should be encouraged to modify their lifestyles. Second, when the LDL-C level falls in this range, intensive management of lipid may be required in the presence of other risk factors. Third, a trend toward an increase in CAD has been suggested in Japan[15]. Until recently, the incidence of atherosclerotic disease, typically CAD, has been relatively low in Japanese. However, a recent investigation indicated that the LDL-C level of Japanese tends to be increasing with changes in lifestyle[16]. It has also been confirmed in Japan that the relative risk of CAD rises continuously with increases in the LDL-C level[17], so that the incidence of CAD may also increase in Japan in the future.

An epidemiological study performed in Shiga Prefecture from 1988 to 1998 reported that the incidence of the initial episode of myocardial infarction was 55.5 persons/100,000 person/years in Japanese males aged 35～64 years and 9.1 persons/100,000 person/years in Japanese females of the same age range[15]. Therefore, the absolute incidence of CAD in Japan remains at 1/3 to 1/5 of the levels in Western countries[18-20]. The current diagnostic criterion is expected to be useful to maintain the incidence of CAD low in Japan. In Japan, mortality due to cerebrovascular diseases is approximately 2 times higher than that due to CAD. The management of LDL-C is also reported to be important for the prevention of atherothrombotic cerebral infarction, which is the major cause of cerebrovascular disease, by the recent large scale clinical studies including a Japanese study, MEGA[10].

For the above reasons, this guideline adopted LDL-C ≥140 mg/dL (TC ≥220 mg/dL) as a diagnostic criterion for high LDL-C to maintain the low incidence of atherosclerotic diseases in Japan. We would like to reiterate that the purpose of this criterion is to identify high-risk people for atherosclerotic diseases and is not merely a criterion for medication. In this guideline, LDL-C rather than TC is used to evaluate cholesterol level predicting the risk for atherosclerotic diseases. Since TC has long been used in general clinical practice in Japan, its replacement by LDL-C may invite considerable resistance. However, we consider that true risk of CAD can only be assessed through the measurement of LDL-C level.

However, as TC is commonly measured in general practice, we propose the following diagnostic procedure (**Table 1**). If the TC level exceeds 220 mg/dL, the LDL-C level is calculated using the Friedewald formula (LDL-C = TC − HDL-C − TG/5). This formula can be applied when serum TG level after overnight fasting is <400 mg/dL (determination of the LDL-C level by direct measurement is recommended when the TG level is ≥400 mg/dL). Calculated LDL-C level of ≥140 mg/dL, is considered to be hyper LDL-cholesterolemia. However, since the LDL-C level may be

Table 2. Lipid management goals based on risk assessment

Principle of therapeutic strategy	Category		Lipid management goals (mg/dL)		
		Major risk factors other than LDL-C*	LDL-C	HDL-C	TG
Primary prevention Lifestyle should be changed before consideration of drug therapy.	Ⅰ (Low-risk group)	0	＜160	≥40	＜150
	Ⅱ (Intermediate-risk group)	1～2	＜140		
	Ⅲ (High-risk group)	3 or more	＜120		
Secondary prevention Both drug therapy and lifestyle modification are considered .	History of coronary artery diseases		＜100		

Management of serum lipids as well as intervention of other risk factors (smoking, hypertention or diabetes) is necessary.
*Major risk factors other than LDL-C
Aging (male ≥45 years, female ≥55 years), hypertension, diabetes (including impaired glucose tolerance), smoking, family history of coronary artery disease, low HDL cholesterol (＜40 mg/dL)
• Category Ⅲ, if complicated by diabetes mellitus, cerebral infarction or arteriosclerosis obliterans.

≥140 mg/dL even when the TC level is ＜220 mg/dL, the use of the LDL-C level is recommended, in principle, for the diagnosis of dyslipidemia.

Low HDL-C has been established as a risk factor for atherosclerosis by many epidemiological studies in Japan as well as in Western countries. On the other hand, whether hypertriglyceridemia is a risk factor for atherosclerosis has been controversial. Though, a large scale cohort study showed the relationship between TG and atherosclerosis in Japan recently[21]. The current guideline defines HDL-C ＜40 mg/dL as hypo-HDL-cholesterolemia and TG ≥150 mg/dL as hypertriglyceridemia. Number of studies has demonstrated gender differences in the HDL-C level, but whether the gender difference should be reflected in the diagnosis of hypo-HDL-cholesterolemia must still remains to be discussed.

2. Management goals for dyslipidemic patients

When a patient is diagnosed to have dyslipidemia according to this diagnostic criterion, lifestyle modification is strongly recommended to prevent future atherosclerotic diseases, and it will be the basis of all treatments. Dyslipidemia often results from unhealthy lifestyles. Therefore, lifestyle modification alone may often be sufficient to improve lipids in many dyslipidemic patients relatively at the low risk.

We defined lipid management goals depending on different risk categories for patients diagnosed as having dyslipidemia (**Table 2**). First, the patients should be classified into those who have not developed CAD (primary prevention) and those with a history of CAD (secondary prevention). In secondary prevention, an intensive LDL-C goal (＜100 mg/dL) is proposed, and immediate initiation of drug therapy along with lifestyle modification should be considered.

In primary prevention, to prevent CAD in the future, patients are categorized into low-risk, intermediate-risk, and high-risk groups (Categories Ⅰ, Ⅱ, and Ⅲ, respectively) depending on the number of risk factors other than LDL-C. Major coronary risk factors other than LDL-C level confirmed to date are gender/aging, hypertension, diabetes mellitus (including impaired glucose tolerance), smoking, family history of CAD, and low HDL-C. Diabetic patients are classified in Category Ⅲ (high-risk group) by giving a greater weight to diabetes than to other risk factors. Patients with cerebral infarction (CI) or arteriosclerosis obliterans (ASO) are classified as Category Ⅲ (high-risk group), because they already have atherosclerotic lesions in arteries other than the coronary artery.

In primary prevention, indications of drug therapy should be considered, in principle, only after changing the lifestyle and evaluating its effects for 3 or 6 months. It is also emphasized that drug therapy should be introduced after sufficient evaluation of atherosclerosis risk in each patient, and this will considerably reduce the necessity of drug therapy in the low-risk group with few risk factors (**Fig. 1**). In case of Category Ⅰ (low-risk group) with no major coronary risk factor, management goal for LDL-C is ＜160 mg/dL. The goal for Category Ⅱ (intermediate-risk group) with 1-2 major coronary risk factors is ＜140 mg/dL, and ＜120 mg/dL for Category Ⅲ (high-risk group) with 3 or more major coronary risk factors as well as diabetes, CI or ASO. It should be note that achievement of these management goals are recommended, but not obligatory required.

While this guideline was intended to be applied

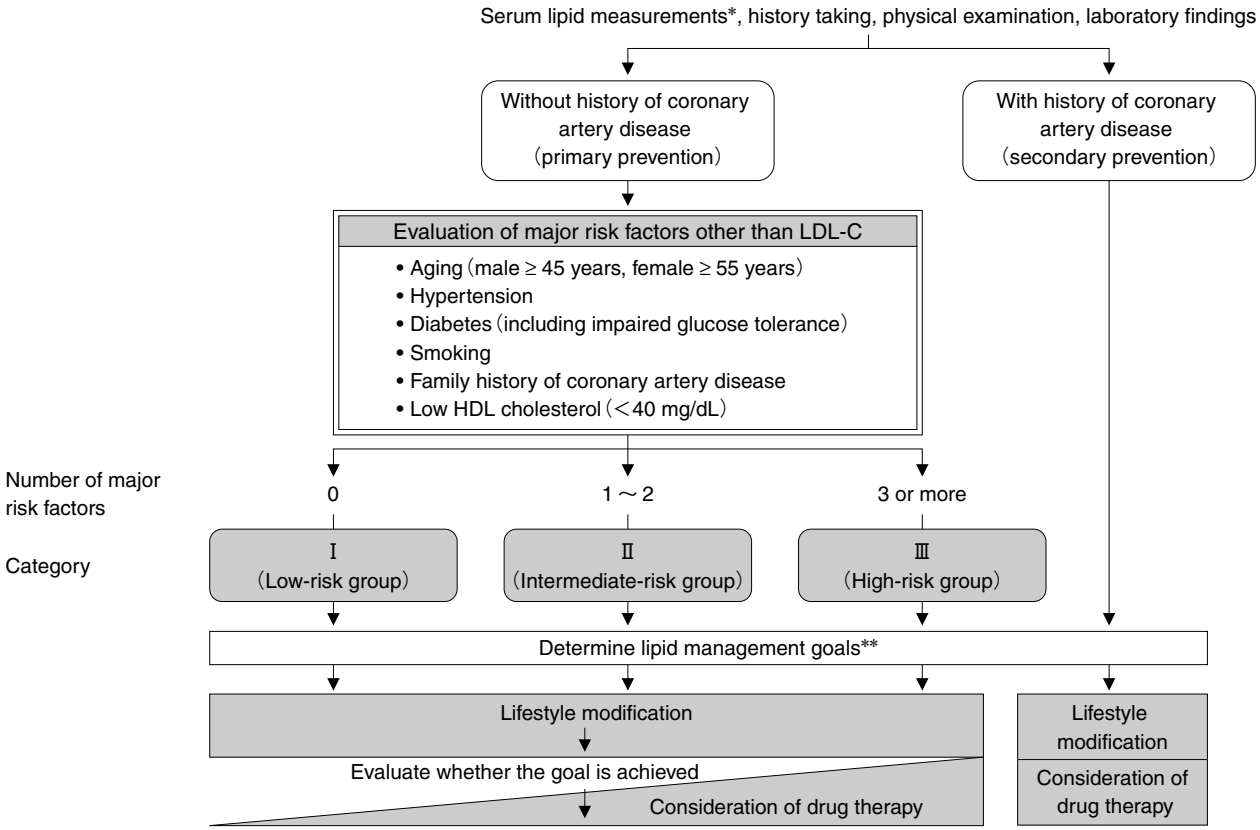

Fig. 1. Therapeutic strategies based on the categories and management goals

*Measurement of blood lipid levels: TC, LDL-C, HDL-C, and TG in serum after overnight fasting. See Table 1.
**Lipid management goals: See Table 2
Note: A patient with diabetes, cerebral infarction or arteriosclerosis obliterance is categorized into III even without other risk factors.

to adults younger than 65 years, it can also be applicable to the elderly at the age between 65～74 years. Since the incidence of CAD is low in females, elevated LDL-C should be managed with greater attention to the presence of other risk factors in females compared to males.

In 2005, diagnostic criteria for metabolic syndrome were published in Japan, and those based on the same concept had also been issued in other parts of the world. In the current guideline, metabolic syndrome is recognized as an important risk independent of LDL-C.

We hope that understanding of metabolic syndrome through this guideline will contribute to the prevention of atherosclerotic diseases.

3. Evaluation of atherosclerotic diseases

Atherosclerotic diseases that this guideline deals with are CAD, cerebral infarction (CI), and arteriosclerosis obliterans (ASO) based on atherosclerosis. Of these diseases, this guideline treats CAD mainly, which is most closely related to lipids, as the target disease. Recently, many large scale clinical studies including Japanese study showed significant decreases in CI by LDL- C lowering. This may be due to increase in the incidence of atherothrombotic cerebral infarction in Japan. So this guideline may also be applied to CI.

4. Asymptomatic atherosclerosis and its evaluation

In order to prevent atherosclerotic diseases, the presence or absence and severity of atherosclerosis must be evaluated before the clinical symptoms appear, and risk factors must be managed or treated in consideration of prevention of its progression. For this purpose, staging of atherosclerotic lesions is important. Presently, atherosclerosis is mainly evaluated by imaging techniques. Angiography, angioscopy[22, 23] and intravascular ultrasonography (IVUS)[24, 25] are invasive techniques to evaluate the degree of stenosis and qualitative estimation of vascular walls. Carotid artery ul-

trasonography is often used in general practice as non-invasive examination, since the degree of carotid arterial sclerosis has been shown to correlated with cerebrovascular disorders and CAD[26, 27]. Also, the development of multi-slice CT (MSCT) has facilitated the detection of coronary artery lesions readily and non-invasively[28].

In the near future, a guideline for the assessment of atherosclerosis that can be applied even before the appearance of clinical symptoms may become necessary Presently, however, evaluation of artherosclerotic lesions by above-mentioned imaging techniques has limitations, and atherosclerosis should be diagnosed as symptomatic atherosclerotic diseases.

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