Committee Report 3

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

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Introduction

Concerning the prevention of atherosclerotic diseases, there are risk factors that require intervention such as cigarette smoking, hypertension, diabetes mellitus, as well as dyslipidemia, and their comprehensive management is absolutely essential. There are guidelines concerning hypertension and diabetes mellitus introduced by Japanese medical associations specializing in these disorders, and patients should be treated according to the management goals of these guidelines. In addition, smoking cessation is the most essential management item for the prevention of atherosclerotic diseases.

It must also be sufficiently understood that dyslipidemia does not always require drug therapy. Particularly, lifestyle modification is important for the management of low HDL-cholesterol (HDL-C) and high triglyceride (TG), and sufficient correction of dyslipidemia is expected by itself. However, high TG may require drug therapy if the TG level is 500 mg/dL or higher in order to prevent acute pancreatitis. Also, patients with TG ≥ 300 mg/dL are accompanied frequently by various abnormalities of lipoprotein metabolism, and medical intervention is often necessary.

Herein, the background and rationale of patient categorization according to risk and management goals for various categories of dyslipidemia are discussed.

1. Categorization Based on Risk Factors

Management goals for categories based on the risk factors of atherosclerosis were set as management criteria for patients diagnosed as dyslipidemia (Table 1).

First, the patients must be classified into those who have not developed coronary artery disease (for primary prevention) and those who have a history of coronary artery disease (CAD) (for secondary prevention). Treatment for atherosclerosis is considered necessary for the latter, and the patients must be approached differently from the former patients. For secondary prevention, the management goals of LDL-C is set at a low level (LDL-C ≤ 100 mg/dL), and the appropriate initiation of drug therapy is necessary without delay along with lifestyle modification.

4S showed that the total mortality as well as mortality due to CAD can be lowered by reducing a high LDL-C level, and that lowering the LDL-C level is essential for secondary prevention. Thereafter, large-scale clinical studies (CARE and LIPID) showed that, for secondary prevention, reducing even an average LDL-C level is effective for the prevention of recurrence of CAD, reduction of total mortality, and reduction of stroke. Subsequently, the J-LIT, in which Japanese patients treated for hypercholesterolemia were followed up, reported the effect of lowering LDL-C levels for secondary prevention. J-LIT research group described that, in the patients with CAD, the recurrence of CAD was reduced by decreasing the LDL-C level to 100 mg/dL. Recently, also, the MUSASHI-AMI, another Japanese clinical study, reported that the recurrence of cardiovascular events could be reduced by the administration of statin in patients with acute myocardial infarction. These reports suggest that aggressive drug therapy accompanied by lifestyle modification should be recommended for secondary prevention. Recently, it has also been reported by large-scale clinical studies in Western countries that even more aggressive
Management of serum lipids as well as intervention of other risk factors (smoking, hypertension or diabetes) is necessary.

**Table 1. Lipid management goals based on risk assessment**

<table>
<thead>
<tr>
<th>Principle of therapeutic strategy</th>
<th>Category</th>
<th>Major risk factors other than LDL-C**</th>
<th>Lipid management goals (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (Low-risk group)</td>
<td>0</td>
<td>LDL-C ≥ 160</td>
</tr>
<tr>
<td>Lifestyle should be changed before consideration of drug therapy.</td>
<td>II (Intermediate-risk group)</td>
<td>1 ~ 2</td>
<td>&lt;140</td>
</tr>
<tr>
<td></td>
<td>III (High-risk group)</td>
<td>3 or more</td>
<td>&lt;120</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>History of coronary artery diseases</td>
<td></td>
<td>≥40</td>
</tr>
</tbody>
</table>

**Management of serum lipids as well as intervention of other risk factors (smoking, hypertension or diabetes) is necessary.**

**Four major risk factors other than LDL-C:**

- Male gender, age, hypertension, diabetes mellitus (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.

LDL-C reducing therapy is effective for the prevention of progression and recurrence of acute coronary syndrome. Similar results have been reported by the ESTABLISH study, performed in Japan.

In primary prevention, the main object is to prevent the future development of CAD in persons without history of such diseases, patients are categorized into low-, intermediate, and high-risk groups (Categories I, II, and III, respectively) according to the number of concurrent risk factors other than LDL-C. The concurrence of risk factors was also shown to be closely related to the occurrence of CAD by the Framingham study. The NIPPON DATABASE and J-LIT, which are conducted in Japan, have also established the importance of the concurrence of risk factors in the occurrence of CAD.

Major coronary risk factors other than LDL-C those have been confirmed to date are male gender, age, hypertension, diabetes mellitus (including abnormal glucose tolerance), cigarette smoking, family history of CAD, and low HDL-C. Whether diabetes mellitus should be regarded as a more important risk factor than the others is controversial. We classified diabetic patients in the high-risk group (category III), considering diabetes mellitus to be more important than other risk factors, because: 1) patients with type 2 diabetes mellitus are increasing rapidly, and the prognosis of established CAD is poor in diabetic patients; 2) the JDCS, which is a prospective study of patients with type 2 diabetes mellitus being conducted in Japan, showed that the incidence of CAD is similar to, or higher than, that of cerebral infarction, and that the LDL-C level is a top risk factor of CAD; 3) the UKPD study and other studies have concluded that treatment of hyperglycemia has not been sufficiently established in order to prevent the CAD in patients with type 2 diabetes mellitus.

Also, patients with cerebral infarction and arteriosclerosis obliterans were classified in the high-risk group (Category III), because they have already developed atherosclerotic disorders in vessels other than the coronary artery.

### 2. Goals of Dyslipidemia Management

For primary prevention, indications of drug therapy should be evaluated after making efforts to modify the lifestyle for a period long enough to assess its effects. At the initiation of drug therapy, its indications must be evaluated by sufficiently examining each patient for risk factors of atherosclerosis. It must be emphasized that the necessity of drug therapy is considerably lower in the low-risk group (Fig. 1). LDL-C goals should be less than 160 mg/dL without a major risk factor [Category I (low-risk group)], less than 140 mg/dL with 1 or 2 major risk factors [Category II (intermediate risk group)], and less than 120 mg/dL with 3 or more risk factors [Category III (high-risk group)]. Achievement of these goals are recommended, but it does not mean that the achievement is obligatory.

No consensus has been reached as to the goals of LDL-C level in patients with familial hypercholesterolemia (FH). This guideline proposes an LDL-C level of less than 100 mg/dL as a goal similarly to secondary prevention, because FH patients have a long history of high LDL-C from childhood and so are under serious risk of CAD. However, as sufficient management of LDL-C by drug therapy is often impossible in patients with such genetic disorders, it may be deserved as a goal to reduce LDL-C by more than 30%.
Since the treatment of FH patients is often difficult, and as they are at very high risk for developing atherosclerotic complications, we recommend consultation with an expert.

This guideline is originally prepared for the application to adults aged less than 65 years. However, it can also be applied to those aged 65-74 years. Also, as the incidence of CAD is low in females, females with high LDL-C must be managed with greater attention to other risk factors.

It might be proposed to set the goal for high LDL-C as a percent decrease in the LDL-C level rather than an absolute value. Since meta-analysis of studies in Western countries has shown that cardiovascular events decrease by 23% with a reduction in the LDL-C by 1 mmol/L (38.6 mg/dL), LDL-C must be controlled at a low level for the prevention of CAD. However, in patients with markedly high LDL-C level, typically FH, the goal proposed in this guideline may be difficult to achieve. The NCEP suggests that such patients should be treated with a 30-40% decrease in the LDL-C level as an alternative goal. Also, the results of the MEGA, which is a large-scale clinical study on primary prevention in Japan, suggest that coronary artery events can be reduced by about 30% by an approximate 20% reduction in the LDL-C level. On the basis of the above evidence, this guideline proposes a decrease in the LDL-C level of 20-30% in addition to an absolute level of LDL-C as possible treatment goals for primary prevention.

The HDL-C level should be managed to 40 mg/dL or above primarily through modification of lifestyle. The TG level, on the other hand, should be managed with sufficient consideration of background factors. Particularly, it should be managed strictly with less than 150 mg/dL as a goal if hypertriglyceridemia is accompanied by low HDL-C.

In this guideline, the LDL-C is used as an index of the management target. But there also is an argument that the non-HDL-C level (TC - HDL-C) is more convenient for the management of dyslipidemia in those who have high TG as a notable feature, such
as in metabolic syndrome. The NCEP sets the criterion for the non-HDL-C level at 30 mg/dL higher than that for the LDL-C level\textsuperscript{10}. This criterion should be referred to when treatment is conducted using the non-HDL-C level as an index.

References


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

<table>
<thead>
<tr>
<th>Lipid Type</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-cholesterol</td>
<td>≥140 mg/dL</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
</tbody>
</table>

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 basically by calculation with the Friedewald equation.

\[
[\text{LDL-C} = \text{TC} - \text{HDL-C} - \frac{\text{TG}}{5} \text{ (when TG is } < 400 \text{ mg/dL)}]
\]

When the TG is ≥400 mg/dL or non-fasting state, the LDL-C should be determined by direct measurement.