Committee Report 1

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan—2012 Version

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Committee for Epidemiology and Clinical Management of Atherosclerosis

Among the various atherosclerotic cardiovascular diseases (CVDs), these guidelines primarily deal with cerebrovascular disease, peripheral arterial disease (PAD) and coronary artery disease (CAD), which occur in association with atherosclerosis and is closely related to dyslipidemia.

1. Comprehensive Risk Management for the Prevention of Atherosclerotic CVD

To prevent CVD, it is important to manage dyslipidemia in addition to other risk factors. For this purpose, we propose comprehensive risk management for the prevention of CVD. Risk factors that should be considered include dyslipidemia, hypertension, diabetes mellitus, smoking, chronic kidney disease (CKD), a family history of premature CAD, a history of CAD, noncardiogenic cerebral infarction, PAD, age and sex. In this article, we describe the comprehensive management of CVD.

2. Diagnostic Criteria for Dyslipidemia

It has been shown in epidemiological studies conducted in Japan, as well as in Western countries, that the incidence of CAD increases in association with increases in the levels of LDL-cholesterol (LDL-C) and triglycerides (TGs) and decreases in the level of HDL cholesterol (HDL-C). Currently in Japan, the incidence of CAD is much lower than that observed in Western countries; however, this incidence is anticipated to increase in the near future due to the recent Westernization of the Japanese lifestyle. Therefore, the current guidelines provide screening criteria for dyslipidemia to prevent CVD with a specific emphasis on the prevention of CAD, as shown in Table 1.

Regarding the diagnosis of dyslipidemia, the total cholesterol (TC), TG and HDL-C levels should be measured after an overnight fast. The LDL-C level is then calculated using the Friedewald formula (LDL-C=TC−HDL-C−TG/5).

This formula cannot be used if blood is collected without fasting or if the TGs are ≥400 mg/dL. In such cases, using the non-HDL-C level is recommended, which is calculated by subtracting the HDL-C level from the TC level. Data obtained in Japan indicate that the non-HDL-C level is approximately 30 mg/dL higher than the LDL-C level. This view is shared by the National Cholesterol Education Program (NCEP). When lipids are evaluated based on the non-HDL-C level, the target value of non-HDL-C is determined by adding 30 mg/dL to the value of LDL-C (Table 2).

The incidence and mortality of CAD increase continuously in association with increases in the LDL-C level. At present, the incidence of CAD is lower in Japanese individuals than in Westerners. To maintain this low rate, efforts directed toward early prevention are required. Therefore, from the perspective of the prevention and treatment of CAD, the current guidelines propose an LDL-C level of 140 mg/dL as the reference value when screening Japanese individuals for hyper-LDL cholesterolemia. This value was selected because it corresponds to a TC level of 220 mg/dL, at which point the relative risk is approximately 1.5-fold higher than that observed at a TC level of <180 mg/dL, according to the NIPPON DATA80. Since the LDL-C goal may vary depending on concomitant risk factors, an LDL-C level between 120 and 139 mg/dL is defined as indicating borderline hyper-LDL cholesterolemia.

Hypo-HDL cholesterolemia has also been established to be a risk factor for CVD. The current guidelines define an HDL-C level of <40 mg/dL as indicating hypo-HDL cholesterolemia, as determined in

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for primary prevention according to the absolute risk calculated based on the results of the NIPPON DATA80. This study identified age, sex, diabetes mellitus, current smoking, systolic blood pressure and the TC level as risk factors and determined the absolute risk of death from CAD depending on the degree or existence of these factors.

How absolute risk categories should be determined is based on clinical consensus and/or conventional wisdom. The U.S. NCEP Adult Treatment Panel III classifies a 10-year risk of death from CAD or the development of nonfatal myocardial infarction of ≥20% (based on the Framingham score) as high risk, whereas European guidelines classify a 10-year risk of death from CVD (including strokes and CAD) of ≥5% as high risk. The current guidelines classify our previous guidelines. A number of studies have demonstrated sex differences in the HDL-C levels; however, it remains unclear whether these sex differences are reflected in the diagnosis of hypo-HDL cholesterolemia.

Hypertriglyceridemia has been found to occur in association with various conditions. Although some researchers insist that more intensive management is required in patients with certain diseases, such as diabetes mellitus, current smoking, systolic blood pressure and the TC level as risk factors and determined the absolute risk of death from CAD depending on the degree or existence of these factors.

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### Table 1. Dyslipidemia: Diagnostic Criteria for Screening (Fasting*)

| Low-density lipoprotein cholesterol (LDL-C) | ≥140 mg/dL | Hyper-LDL cholesterolemia |
| High-density lipoprotein cholesterol (HDL-C) | <40 mg/dL | Hypo-HDL cholesterolemia |
| Triglycerides (TG) | ≥150 mg/dL | Hypertriglyceridemia |

- The LDL-C level is calculated using the Friedewald formula (TC − HDL-C − TG/5) (for TG < 400 mg/dL).
- If the TG level is ≥400 mg/dL or non-fasting blood is used, the non HDL-C (TC − HDL-C) level should be used with a cutoff value of LDL-C + 30 mg/dL.
- Fasting is defined as deprivation of food for at least 10 to 12 hours; however, the ingestion of noncaloric beverages, such as water and tea, is allowed.
- If a patient is found to have borderline hyper-LDL cholesterolemia during screening, he/she should be examined for any high-risk conditions and the need for treatment should be considered.

### Table 2. Lipid Management Targets for Patients with Different Risk Levels

<table>
<thead>
<tr>
<th>Therapeutic principle</th>
<th>Management category</th>
<th>Lipid management target (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDL-C</td>
<td>HDL-C</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>Category I</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Drug therapy should be considered after lifestyle modification</td>
<td>Category II</td>
<td>&lt;140</td>
</tr>
<tr>
<td></td>
<td>Category III</td>
<td>&lt;120</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>Drug therapy should be considered, together with lifestyle modification</td>
<td>History of CAD</td>
</tr>
</tbody>
</table>

- For patients at low absolute risk, such as the young, the relative risk chart (Supplementary Table) should be used and changes in the absolute risk should be monitored carefully while encouraging the patient to modify their lifestyle.
- These values should be considered general, not mandatory, goals.
- A 20%-30% reduction in the level of LDL-C is considered to be a prime target for pharmacological intervention.
- The management target for the non HDL-C level is the secondary target to be used after a patient with hypertriglyceridemia has achieved the management target for the LDL-C level. The non HDL-C level should be used if blood is collected after meals or if the TG level is ≥400 mg/dL.
- For patients in any category, the management goals should generally be achieved via lifestyle modification.
- For patients in category I, drug therapy should be considered if the LDL-C level is ≥180 mg/dL.

3. Risk Stratification Based on Absolute Risk

The current guidelines stratify the risk of CVD...
patients with a 10-year risk of death from CAD of ≥2% as belonging to the high-risk group (category III), those with a risk of ≥0.5% to <2% as belonging to the intermediate-risk group (category II) and those with a risk of <0.5% as belonging to the low-risk group (category I), considering that there is little evidence of an association between hypercholesterolemia and cerebrovascular diseases in Japanese individuals. Since diabetes mellitus, CKD and a history of noncardiogenic cerebral infarction or PAD are considered to be important risk factors, patients with any of these conditions are classified as belonging to the high-risk group (Fig. 1).

The 10-year absolute risk of CAD-related death should be determined based on the risk assessment chart provided in the NIPPON DATA80. However, since this chart does not include hypo-HDL cholesterolemia, a family history of premature CAD or impaired glucose tolerance, the category should be raised if the patient meets one or more of these criteria (Fig. 2).

The chart obtained from the NIPPON DATA80 addresses the risk of CAD-related death in individuals between 40 and 79 years of age. While the current guidelines are intended for adults younger than 65 years of age, they can also be applied to persons between 65 and 74 years of age. To calculate the absolute risk for individuals ≥70 and <75 years of age, the table for individuals between 60 and 69 years of age should be used. For adults <40 years of age, the table for individuals between 40 and 49 years of age should be used.

When assessing the absolute risk, it should be noted that the absolute risk greatly depends on age. If a low absolute risk is obtained for a young individual with a risk factor, such as hypertension or smoking, the risk factors should be managed appropriately. When secondary prevention is required, each risk factor should be dealt with separately, as outlined in the previous guidelines.

4. Management Targets for Dyslipidemic Patients

The management targets for dyslipidemic patients are presented by category in Table 2. For primary prevention, drug therapy should be considered after lifestyle factors have been improved for a certain
It should be noted that achieving these targets is recommended but not obligatory. A meta-analysis of preventive clinical trials demonstrated that a 20%-30% reduction in the LDL-C level results in a decrease in the incidence of CAD of approximately 30%. Based on this finding, a 20%-30% decrease in

dL. It should be noted that achieving these targets is recommended but not obligatory. A meta-analysis of preventive clinical trials demonstrated that a 20%-30% reduction in the LDL-C level results in a decrease in the incidence of CAD of approximately 30%. Based on this finding, a 20%-30% decrease in
the LDL-C level can be considered a target. For secondary prevention, since the patient has already been diagnosed with CAD, the administration of drug therapy targeting an LDL-C level of <100 mg/dL is recommended in addition to lifestyle modification.

For the management of hypertriglyceridemia and hypo-HDL cholesterolemia, targeting a TG level of <150 mg/dL and an HDL-C level of ≥40 mg/dL is recommended, as in the previous guidelines.

Some researchers have the opinion that stricter targets should be established for high-risk patients (such as those with diabetes mellitus or CKD) or those who require secondary prevention, depending on the patient’s condition and severity of disease; however, there is insufficient evidence to support setting such goals. Nevertheless, the current guidelines also suggest that high-risk patients be stratified according to risk factors and that lower targets be established for such patients.

5. Treatment

Dyslipidemia should be treated with lifestyle modification, including smoking cessation and the administration of diet and/or exercise therapy. In primary prevention patients, drug therapy should only be considered when the lipid management targets are not achieved after sufficient effort has been made to improve lifestyle factors. In patients with a history of CAD, the use of drug therapy should be considered simultaneously with lifestyle modification.

When drug therapy is provided for patients with hyper-LDL cholesterolemia, statins are the first drug of choice. Resin, probucol and/or ezetimibe are used in combination with statins or selected when statins cannot be administered. The combination of statins and EPA is useful for treating high-risk patients with hyper-LDL cholesterolemia. For treating hypertriglyceridemia accompanied by hypo-HDL cholesterolemia, drugs such as fibrates and nicotinic acid derivatives should be considered.

6. High-Risk Conditions for CVD

The current guidelines include CKD in addition to a history of CAD (secondary prevention), diabetes mellitus, noncardiogenic cerebral infarction and PAD as high-risk conditions based on the findings of epidemiological studies, including evidence showing that the presence of CKD increases the incidence of CAD by at least two-fold. The previous guidelines classified a history of cerebral infarction as a high-risk condition, while the current guidelines classify a history of noncardiogenic cerebral infarction as a high-risk condition because cardiogenic cerebral infarctions are not caused by atherosclerotic disease.

7. Familial Hypercholesterolemia

Familial hypercholesterolemia occurs in approximately one in 500 individuals and is associated with a high risk of CAD. The current guidelines reference the diagnostic criteria for FH reported by the 2011 Primary Hyperlipidemia Research Group and set a target of an LDL-C level of <100 mg/dL or a decrease in the LDL-C level of at least 50%.

8. Evaluation of CVD

To prevent CVD, the presence or absence and severity of atherosclerosis must be evaluated before symptoms occur and risk factors must be managed or treated with the objective of preventing progression or possibly achieving regression. For this purpose, correctly staging CVD is important. At present, the degree of atherosclerosis is primarily evaluated using imaging techniques. Invasive techniques include angiography (to assess the severity of stenosis) as well as angioscopy and intravascular ultrasonography (to qualitatively assess the vessel walls). Noninvasive techniques include transcutaneous ultrasonography of the arteries, such as the carotid artery, to qualitatively and quantitatively evaluate the degree of atherosclerosis. Carotid artery ultrasonography is often used in general practice because the extent of carotid sclerosis has been shown to be correlated with the risk of cerebrovascular disease and/or CAD. The development of multidetector CT (MDCT) has allowed for easier detection of coronary artery lesions. At present, carotid artery ultrasonography and MDCT are less invasive and easier to perform than other imaging modalities. In the near future, developing guidelines for the assessment of atherosclerosis that can be employed before the onset of symptoms is necessary. At present, however, assessing the degree of atherosclerotic lesions using the above-mentioned imaging techniques is associated with some limitations. CVD should be diagnosed based on a clear understanding of these limitations.

Footnotes

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Disclosures


References


between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis, 2007; 190: 216-223

Supplementary Table. Relative Risk Charts for the Young, etc. with a Low Absolute Risk (based on the risk charts of the NIPPON DATA80)

<table>
<thead>
<tr>
<th>TC category (mg/dL)</th>
<th>Nonsmokers</th>
<th>Smokers</th>
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</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (≤140)</td>
<td>1.0*</td>
<td>1.3</td>
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<tr>
<td>140-159 mmHg</td>
<td>1.7</td>
<td>2.2</td>
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<tr>
<td>160-179 mmHg</td>
<td>2.2</td>
<td>2.8</td>
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<tr>
<td>Second-degree or higher hypertension (≥160 mmHg)</td>
<td>3.2</td>
<td>4.1</td>
</tr>
<tr>
<td>First-degree hypertension (140-159 mmHg)</td>
<td>2.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Normal (≤140 mmHg)</td>
<td>1.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>