Committee Report 3

Diagnostic Criteria for Dyslipidemia

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

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Epidemiological studies conducted in Japan as well as Western countries have shown that higher levels of LDL-cholesterol (LDL-C)\(^1\), total cholesterol (TC)\(^2\)-\(^7\), non HDL-cholesterol (non HDL-C)\(^8\), and triglyceride (TG)\(^9\),\(^10\) and lower levels of HDL-C\(^5\),\(^11\)-\(^13\) are associated with a higher risk of coronary artery disease (CAD) (Fig.1). At present, the absolute risk (incidence and mortality) of CAD in Japan is much lower than that observed in Western countries\(^14\)-\(^17\); however, due to recent increases in the LDL-C and TC levels in Japanese individuals as a result of Westernization of the Japanese lifestyle\(^18\),\(^19\), and the findings of a report showing that the incidence of CAD is increasing in some regions of Japan\(^19\),\(^20\), there is concern that the incidence of CAD will rise throughout Japan. Therefore, these guidelines define diagnostic criteria for assessing dyslipidemia during screening to prevent the development of arteriosclerosis from the perspective of preventing CAD, as shown in Table 1.

According to the diagnostic procedures, first, the TC, TG and HDL-C levels are measured in the morning after overnight fasting to calculate the LDL-C level using the Friedewald formula (LDL-C = TC - HDL-C - TG/5). This formula cannot be used in a non-fasting state or when the TG level is ≥ 400 mg/dL because large errors in the LDL-C level may occur. Although direct measurement methods for determining the LDL-C level have been applied clinically, significant problems have been found concerning variations in accuracy and the results obtained between kits, especially in cases of high TG levels\(^21\). Therefore, using the non HDL-C level is recommended when the TG level is ≥ 400 mg/dL. The non HDL-C level is calculated by subtracting the HDL-C level from the TC level.

Lipid standardization in clinical laboratories in Japan has been judged internationally to be very accurate for the TC levels and fairly accurate for the HDL-C levels\(^22\),\(^23\); thus, further standardization is warranted.

1. Hyper-LDL Cholesterolemia

The Framingham study and many other epidemiological studies conducted in Western countries have shown that the incidence and mortality of CAD increase in association with increases in the levels of TC and LDL-C. In addition, in Japan, epidemiological studies, such as the NIPPON DATA80\(^2\), Suita\(^3\), JALS\(^20\), CIRCS\(^1\), Hiroshima/Nagasaki\(^7\), MHW Primary Hyperlipidemia\(^26\), Okinawa cohort\(^27\) and Ehime epidemiological\(^10\) studies and epidemiological studies conducted in 76 workplaces in Japan (the 3M Study)\(^4\), have confirmed that the relative risk of CAD increases continuously in association with increases in the levels of LDL-C and TC.

The NIPPON DATA80, a prospective epidemiological study conducted in Japan, demonstrated that the relative risk of CAD-related death in individuals with a TC level of 200-219 mg/dL, 220-239 mg/dL, 240-259 mg/dL and ≥ 260 mg/dL is 1.4-, 1.6-, 1.8- and 3.8-fold higher, respectively, than that observed in individuals with a TC level of 160-179 mg/dL (Fig. 1a)\(^2\). In men, in particular, mortality from CAD increases continuously in association with increases in the TC (LDL-C) levels, with no distinct threshold.

Meanwhile, studies conducted in Western countries regarding interventions for hypercholesterolemia, including lifestyle modification, have revealed that
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that observed at a TC level of 200 mg/dL. As described above, the absolute risk of CAD in Japanese individuals is much lower than that observed in Westerners. In order to maintain this low risk, the use of early prevention measures is needed.

Based on the above findings, a TC level of 220 mg/dL, the level at which the relative risk shown in the NIPPON DATA80 is approximately 1.5-fold higher than that observed at a TC level of <180 mg/dL, was used as the cutoff value for screening Japanese individuals in terms of the prevention and treatment of CAD, and the corresponding LDL-C level of 140 mg/dL was defined as the cutoff value for the diagnosis of hyper-LDL cholesterol.

The CIRCS, an epidemiological study recently conducted in Japan, showed that the incidence of CAD in subjects with an LDL-C level of 80 to 99 mg/dL, 100 to 119 mg/dL, 120 to 139 mg/dL and ≥140 mg/dL is 1.4-, 1.7-, 2.2- and 2.8-fold higher, respectively, than that observed in subjects with a LDL-C level of <80 mg/dL. In the presence of multiple risk factors, the incidence of and mortality from CAD also increase in Japanese individuals. Since the incidence of and mortality from CAD in patients with multiple risk factors were found to be higher than those observed in patients without such factors, even at the same LDL-C levels, and patients with diabetes mellitus (DM) developed CAD at lower LDL-C levels of approximately 30 to 40 mg/dL as frequently as patients without DM in a subanalysis of primary prevention in the J-LIT study, it has been suggested that the degree of the increased risk of CAD associated with the LDL-C level changes depending on comorbidities. As a result of these concerns, these guidelines define an LDL-C level of 120-139 mg/dL as the borderline level at which the effects of other risk factors should be carefully considered when screening Japanese individuals for dyslipidemia.

2. Hypo-HDL Cholesterolemia

Having a low level of HDL-C places a patient at risk for developing CAD. Conversely, a higher HDL-C level is associated with a decreased risk of CAD. In the U.S., guidelines NCEP-ATP III, based on the relationship between the TC levels and CAD mortality reported in the MRFIT, the cutoff value for hypercholesterolemia is a TC level of 240 mg/dL, the level at which the relative risk is 2-fold higher than
Dyslipidemia Criteria

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

<table>
<thead>
<tr>
<th>Lipoprotein Type</th>
<th>Cutoff Value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein cholesterol (LDL-C)</td>
<td>≥140 mg/dL</td>
<td>Hyper-LDL cholesterolemia</td>
</tr>
<tr>
<td>HDL-C</td>
<td>120-139 mg/dL</td>
<td>Borderline hyper-LDL cholesterolemia**</td>
</tr>
<tr>
<td>Triglycerides (TGs)</td>
<td>&lt;40 mg/dL</td>
<td>Hypo-HDL cholesterolemia</td>
</tr>
<tr>
<td></td>
<td>≥150 mg/dL</td>
<td>Hypertriglyceridemia</td>
</tr>
</tbody>
</table>

* The LDL-C level is calculated using the Friedewald formula (TC − HDL-C − TG/5) (if 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. The cutoff value is LDL-C + 30 mg/dL.
* A “fasting state” is defined as having fasted for ≥ 10 to 12 hours. The consumption of liquids with no calories, such as water and tea, is permitted.
** If borderline hyper-LDL cholesterolemia is diagnosed during screening, the presence of high-risk conditions should be assessed and the need for treatment should be considered.

1.3- and 1.6-fold higher relative risk of CAD, respectively, than those with an HDL-C level of 40-49 mg/dL. Based on these findings, these guidelines define an HDL-C level of <40 mg/dL as the cutoff value for screening for hypo-HDL cholesterolemia. In general, women exhibit higher HDL-C levels than men36, 39, 40, however, there is currently insufficient evidence to support the existence of a relationship between sex differences in the HDL-C levels and the incidence of CAD. Therefore, these guidelines used the same cutoff value for both women and men.

3. Hypertriglyceridemia

Many reports have shown that a high TG level is associated with a risk of developing CAD in Asia, Oceania41 and Japan9, 10, 39, 42, 43 as well as in Western countries44. In some of these studies, the TG level was found to be associated with the risk of CAD even when the HDL-C level was corrected9, 41, 42, 44. In the U.S., hypertriglyceridemia is defined as a fasting TG level of ≥150 mg/dL based on the Framingham study39. Traditionally, the TG level has been measured using fasting blood; however, one report indicates that the non-fasting TG level more accurately predicts cardiovascular events46. Epidemiological studies conducted in Japan have shown that the incidence of CAD increases when the fasting TG is ≥150 mg/dL10, 39, 43 and that the incidences of myocardial infarction, exercise-induced angina and sudden death increase when the non-fasting TG level is ≥165 mg/dL (Fig. 1c)39. Moreover, many reports have also shown that hypertriglyceridemia is a risk factor for cerebral infarction, although this association is weaker than that observed for CAD39, 41, 47-49. Considering these findings, these guidelines define a TG level of ≥150 mg/dL as the cutoff value for screening for hypertriglyceridemia; however, hypertriglyceridemia often reflects other pathological conditions, such as increased levels of remnant lipoproteins or small, dense LDL, complications of hypo-HDL cholesterolemia and the presence of metabolic syndrome. Therefore, other conditions associated with increased TG levels should be carefully assessed.

4. Non HDL Cholesterol

If hypertriglyceridemia exists, especially when the TG level is ≥400 mg/dL, the correct LDL-C level cannot be calculated because the Friedewald formula is not applicable and the direct measurement method is problematic. In such cases, the non HDL-C level is a useful and simple index calculated by subtracting the HDL-C level from the TC level. Some investigators consider the non HDL-C level to be superior to the LDL-C level in terms of predicting the development of atherosclerotic diseases because the non HDL-C level incorporates all atherogenic lipoproteins, including remnant lipoproteins50, 51. Recently, many epidemiological studies have examined the relationship between the non HDL-C level and the risk of CAD in Japan8, 24, 25, 49, 52. The non HDL-C level exhibits the same relationship with the incidence of myocardial infarction as the LDL-C level, with both parameters demonstrating comparable ability to predict the development of myocardial infarction24. On the other hand, one study showed that the non HDL-C level is superior to the TC level in terms of predicting the incidence of myocardial infarction25. The incidence and mortality of CAD and myocardial infarction markedly increase in men with a non HDL-C level of ≥170-180 mg/dL, while no specific tendencies have been observed in women8, 24, 25, 52. One study investigated the risk of myocardial infarction associated with the non HDL-C level in the presence or absence of hypertriglyceridemia49. In that report, the risk of myocardial infarction markedly increased in the group with both hypertriglyceridemia (TG ≥150 mg/dL) and a
non HDL-C level of ≥190 mg/dL. In a subanalysis of the JELIS that compared the groups that achieved both LDL-C and non HDL-C management goals, the other groups exhibited higher incidences of CAD. Recently, it was demonstrated that the non HDL-C level in Japanese individuals is equal to LDL-C + 30 mg/dL, the same as that observed in the U.S. Based on these findings, these guidelines defined a non HDL-C level of ≥170 mg/dL as the cutoff value for screening.

**Footnotes**

This is an English version of the guideline from the Japan Atherosclerosis Society (chapter 3) published in Japanese in June, 2012.

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