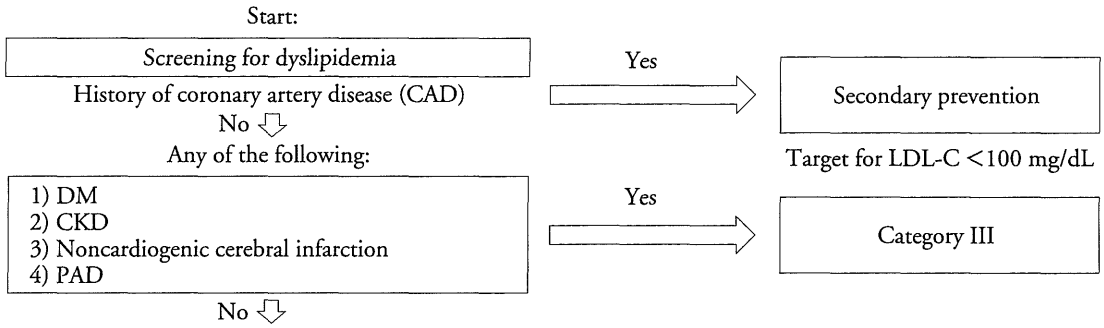
**Supplementary Table 2.** Simple Chart Based on Sex, Age and the Number of Risk Factors for Predicting the Absolute Risk of CAD




| Sex | Baseline risk: Age | Determined based on the number of risk factors: (1) Hypertension, (2) Smoking, (3) Hypo-HDL cholesterolemia (HDL-C < 40 mg/dL), (4) Family history of premature CAD (first-degree male relatives aged < 55 years or female relatives aged < 65 years), (5) Impaired glucose tolerance (excluding DM) | Absolute risk of CAD (%) | Category* |
|---|---|---|---|---|
| Men | 40-49 years (Also applied to persons aged 30-39 years) | 0 | 0.23 | Category I |
| | | 1-2 | 0.32-0.55 | Category II |
| | | ≥3 | 0.48-0.83 | Category III |
| | 50-59 years | 0 | 0.63 | Category II |
| | | 1 | 0.91-1.08 | Category II |
| | | ≥2 | 1.55 | Category III |
| | 60-69 years (Also applied to persons aged ≤74 years) | 0 | 1.78 | Category II |
| | | ≥1 | 2.55-4.31 | Category III |
| Women | 40-59 years | 0-1 | 0.10-0.20 | Category I |
| | | ≥2 | 0.24 | Category II |
| | 60-69 years (Also applied to persons aged ≤74 years) | 0-1 | 0.87-1.83 | |
| | | ≥2 | 2.19 | Category III |

In this simple chart, the serum level of LDL-C was set at 170 (TC=250), which exceeded the upper limit of the least strict management target (LDL-C=160). Then, the absolute risk of CAD death was calculated using the NIPPON DATA risk chart as follows:

1) For age, the median (men: 45, 55 and 65 years; women: 50 and 65 years) was used.
2) The number of risk factors was calculated according to the presence or absence of hypertension (presence: SBP=160; absence: SBP=120) and the presence or absence of smoking, of which the maximum number was 2.
3) In cases in which the number of risk factors was ≥3, the absolute risk was estimated based on the assumption that the third risk factor (other than hypertension and smoking) increases the risk 1.5-fold.

*Depending on the level of additional risk factors, the absolute risk may not always be within the same range as in Fig. 1. Furthermore, because the relative risk for patients in the same sex and age group is also taken into consideration, it should be noted that the category may not always be consistent with the range of the estimated absolute risk determined using the NIPPON DATA risk charts. This chart may be used as a convenient method if the NIPPON DATA risk chart is not readily available.

Management Category Target for the LDL-C level:
Category I < 160 mg/dL, Category II < 140 mg/dL, Category III < 120 mg/dL, Secondary prevention < 100 mg/dL

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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Committee for Epidemiology and Clinical Management of Atherosclerosis

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]. Nevertheless, the accuracy of TG and LDL-C measurements remains inadequate[22, 23]; thus, further standardization is warranted.

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### 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[24], JALS[25], 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

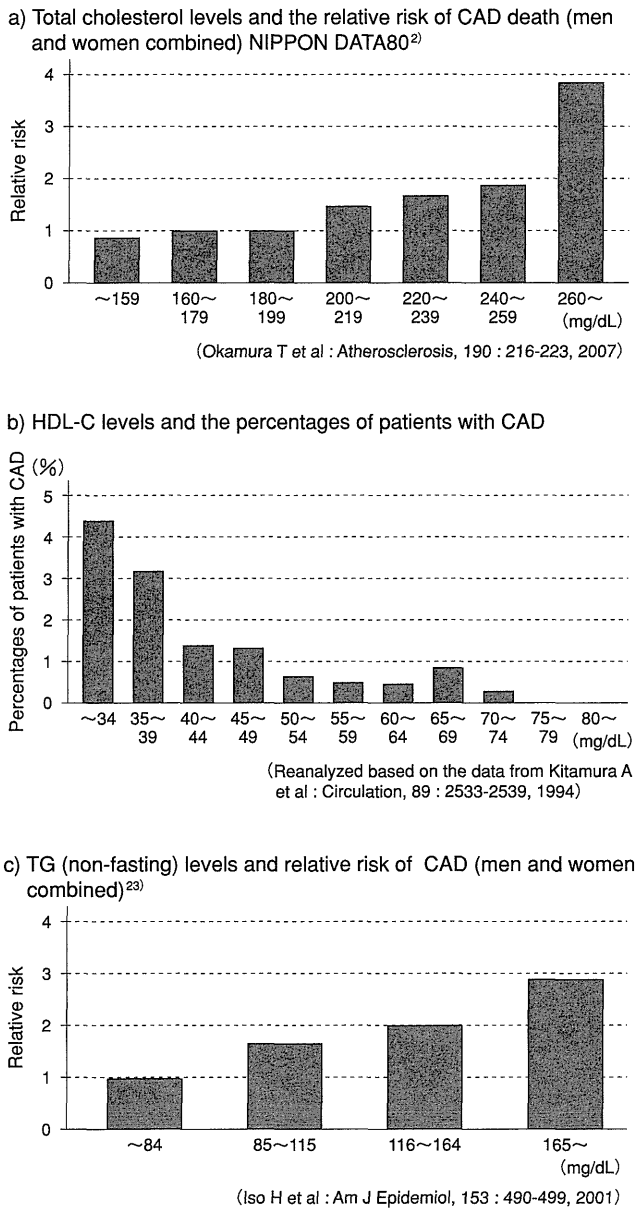


**Fig. 1.** Serum Lipids and Risk for CAD

intervention significantly decreases the incidence of CAD. In addition, in Japan, the results of large-scale clinical studies have recently shown that treatment for hyper-LDL cholesterolemia is clinically beneficial for Japanese individuals[28-31)].

In the U.S. guidelines NCEP-ATP Ⅲ, based on the relationship between the TC levels and CAD mortality reported in the MRFIT[32)], 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 that observed at a TC level of 200 mg/dL[33)]. 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 cholesterolemia.

The CIRCS, an epidemiological study recently conducted in Japan[1)], 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[34)], 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 (**Fig. 1b**)[11, 35)]. In the NIPPON DATA90, the HDL-C level was found to be significantly inversely correlated with overall mortality and stroke mortality during the 9.6-year observation period[36)]. Community and worksite-based cohort studies have shown that an HDL-C level <40 mg/dL is associated with an increased risk of CAD[11, 37-39)]. In the J-LIT, a cohort study, simvastatin-treated primary prevention patients[12)] and secondary prevention patients[13)] with an HDL-C level <40 mg/dL were found to have a

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

| | | |
|---|---|---|
| Low-density lipoprotein cholesterol (LDL-C) | ≥140 mg/dL | Hyper-LDL cholesterolemia |
| | 120-139 mg/dL | Borderline hyper-LDL cholesterolemia** |
| HDL-C | <40 mg/dL | Hypo-HDL cholesterolemia |
| Triglycerides (TGs) | ≥150 mg/dL | Hypertriglyceridemia |

• 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 men[36, 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, Oceania[41] and Japan[9, 10, 39, 42, 43] as well as in Western countries[44]. 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 corrected[9, 41, 42, 44]. In the U.S., hypertriglyceridemia is defined as a fasting TG level of ≥150 mg/dL based on the Framingham study[45]. Traditionally, the TG level has been measured using fasting blood; however, one report indicates that the non-fasting TG level more accurately predicts cardiovascular events[46]. Epidemiological studies conducted in Japan have shown that the incidence of CAD increases when the fasting TG is ≥150 mg/dL[10, 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**)[9]. Moreover, many reports have also shown that hypertriglyceridemia is a risk factor for cerebral infarction, although this association is weaker than that observed for CAD[39, 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 lipoproteins[50, 51]. Recently, many epidemiological studies have examined the relationship between the non HDL-C level and the risk of CAD in Japan[8, 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 infarction[24]. 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 infarction[25]. 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 women[8, 24, 25, 52]. One study investigated the risk of myocardial infarction associated with the non HDL-C level in the presence or absence of hypertriglyceridemia[49]. 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[53]. 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[54, 55]. 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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Committee Report 4

# Absolute Risk of Cardiovascular Disease and Lipid Management Targets

## 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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Traditionally, the relative risk has been primarily used to evaluate the strength of the associations between risk factors and cardiovascular disease (CVD) and the effects of treatment. In Western countries, scoring tables consisting of scores for each risk factor weighted according to their absolute risk and risk assessment charts in which squares at the points of intersection of the vertical and horizontal axes, each of which has a different risk factor at a different level, are expressed in different colors to represent the absolute risk have been developed to predict an individual's absolute risk in several guidelines. Typical examples are the U.S. Framingham risk score[1] and the European SCORE risk chart[2]. As the name implies, the Framingham risk score is a method for scoring sex (the weighting of each risk factor differs between men and women), age, total cholesterol (TC), the smoking status, high density lipoprotein cholesterol (HDL-C) and systolic blood pressure. The probability of developing coronary artery disease (CAD), coronary death and nonfatal myocardial infarction within 10 years is calculated from the sum of the scores. The SCORE is a risk assessment chart method used to calculate the probability of death due to all CVD, including stroke, within 10 years based on sex, age, TC, the smoking status and systolic blood pressure. Because the mortality of CVD differs between countries even at the same level of risk factors, the SCORE risk chart is classified into two types: one used in countries with low cardiovascular mortality (e.g., France and Italy) and the other used in countries with high mortality (e.g., the U.K. and Germany).

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In Japan, where the size of the aging population is increasing, the concept of absolute risk is important for the management of risk factors for CVD in terms of determining the priority of treatment options and promoting efficient preventive strategies. In addition to the J-LIT chart for dyslipidemia[3], many risk assessment tools for predicting CVD based on cohort studies in the general population have recently been published in Japan[4-9]. This chapter explains the background and rationale of classifying patients according to absolute risk and the management targets for dyslipidemia in each category.

### 1. Establishing the Absolute Risk

In this guideline, the NIPPON DATA80 risk chart[5] was used as source data to establish the absolute risk for the following reasons:

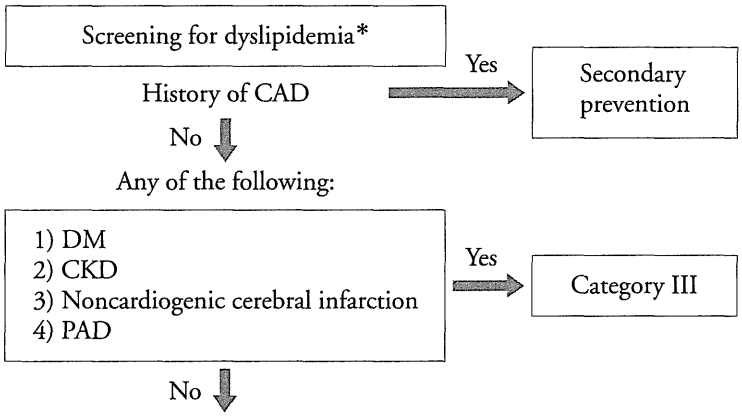
1) There was no regional bias, as approximately 10 thousand people living in 300 districts were randomly selected throughout Japan for the evaluation;

2) At the time of TC measurement (1980), the administration of medications to treat hyperlipidemia was uncommon, and statins, in particular, which strongly affect the prognosis, had not been launched;

3) The health examinations for community residents (health checkups based on the Health and Medical Service Act for the Aged) first introduced the measurement of TC in 1986, hence the TC levels were measured with almost no interventions, including lifestyle modification, suggesting that these levels reflected the natural conditions of Japanese individuals;

4) The participation rate observed in the baseline survey when the Basic Resident Register was used as the denominator was high, at approximately 75%;

5) The follow-up rate was >90%; and




Management categories based on absolute risk for the primary prevention of CAD

| 10-year probability (absolute risk) of CAD death derived from NIPPON DATA80 | Additional risk factors | |
|---|---|---|
| | No additional risk factors | One or more of the following:<br>(1) Hypo-HDL cholesterolemia (HDL-C <40 mg/dL)<br>(2) Family history of premature CAD in first-degree relatives (a man aged <55 years or a women aged <65 years)<br>(3) Impaired glucose tolerance |
| < 0.5% | Category I | Category II |
| ≥0.5% < 2.0% | Category II | Category III |
| ≥2.0% | Category III | Category III |

*This flow chart is not applicable to patients with FH.

**Fig. 1.** Flow Chart for Establishing the Management Targets for LDL-C.

6) The measurement of TC was internationally standardized.

The limitations of the chart include:

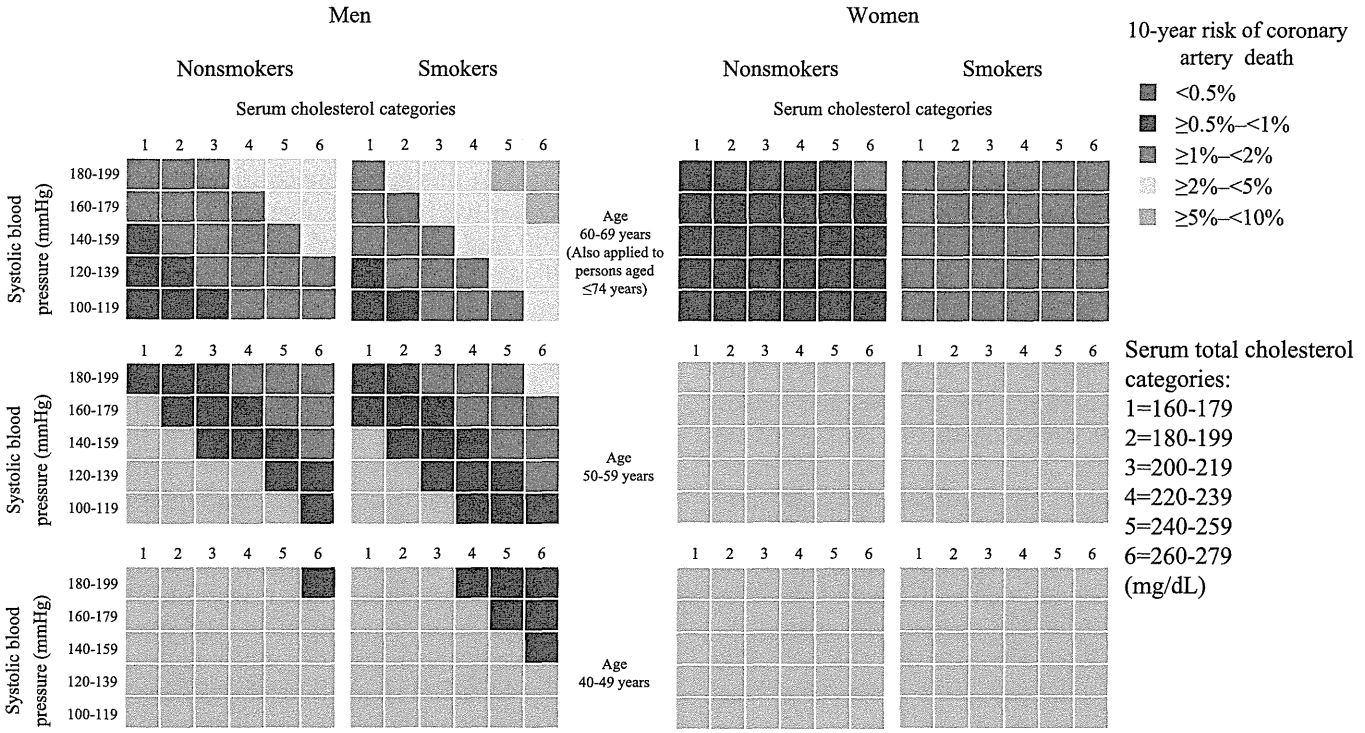
1) The end point was death, although incidence was preferable if possible;

2) Information on low-density lipoprotein cholesterol (LDL-C) and HDL-C is lacking; and

3) Blood was collected in a non-fasting state.

The advantages and disadvantages may be paradoxical. At present, there are no risk assessment tools that meet all ideal conditions required to establish guidelines.

With regard to the guidelines for primary prevention, it is difficult to perform a cohort study in a large population or urban area if accuracy of the end point is pursued. In particular, the majority of epidemiological studies in which the end point is the incidence of CVD have been conducted in non-urban areas. For example, the pooled analysis of a cohort study called the JALS-ECC, in which the end point was myocardial infarction morbidity and information on the HDL-C levels was provided[4], included almost no urban areas. The crude incidence of myocardial infarction in the JALS-ECC was approximately 0.6 per 1,000 person-years, whereas that observed in the Suita study of a cohort of only urban dwellers was 1.4 per 1,000 person-years, a rate that is two-fold or more higher (no significant differences were observed in sex, age composition or the initial year of follow-up)[10]. In this case, it cannot be determined which study is more representative of the Japanese population, and estimating the absolute risk based on the data obtained for only one area is not recommended.




The section of hyperglycemia from the NIPPON DATA80 risk assessment chart is omitted here. These charts cannot be applied to high-risk patients, such as those with DM or CKD.

**Fig. 2.** Absolute risk assessment charts for death from coronary artery disease (primary prevention).

Absolute risk should be reassessed at least once a year since it may be affected by either risk factors or aging.

Step 1: The applicable portion of the above figures should be used based on gender, age, the present smoking status, systolic blood pressure (mmHg) and the TC level (mg/dL).
Absolute risk ≥2% → Category Ⅲ
Absolute risk <2% → To Step 2
Step 2: The presence of any of the following conditions: Hypo-HDL cholesterolemia (<40 mg/dL), a family history of CAD and/or impaired glucose tolerance
Absolute risk ≥0.5% <2% +Yes → Category Ⅲ
Absolute risk ≥0.5% <2% +No → Category Ⅱ
Absolute risk <0.5% +Yes → Category Ⅱ
Absolute risk <0.5% +No → Category Ⅰ
Supplementary notes
(1) The TC category 160-179 mg/dL should be used in patients with a TC level of <160 mg/dL.
(2) The TC category 260-279 mg/dL should be used in patients with a TC level of ≥280 mg/dL.
(3) The systolic blood pressure category of 100-119 mmHg should be used in patients with a systolic blood pressure of <100 mmHg, while the systolic blood pressure category of 180-199 mmHg should be used in patients with a systolic blood pressure of ≥200 mmHg.
(4) These guidelines cannot be applied to persons 75 years of age or older. For patients <40 years of age, the relative risk charts (Supplementary Table 1) should be used.
(5) Blood pressure should be managed according to the guidelines established by the Japanese Society of Hypertension, and diabetes mellitus should be managed according to the guidelines established by the Japan Diabetes Society.
(6) It is desirable to encourage smokers to stop smoking, irrespective of the level of absolute risk.

## 2. Categorical Classification Based on Absolute Risk

It is impossible to statistically determine the cut-off point for the absolute risk at which patients are at a high risk; the criteria must be determined based on clinical consensus or socially accepted ideas. The U.S. NCEP ATP Ⅲ[11] defines a high risk as a ≥20% risk of developing fatal CAD or nonfatal myocardial infarction within 10 years based on the Framingham risk score. However, because the incidence of CAD greatly differs between Japan and the U.S., it is not appropri-

ate to use this absolute risk criterion as a reference.

Meanwhile, the European guidelines using the SCORE risk chart[12] are similar to the NIPPON DATA in that they both use the end point of death. The European guidelines that are based on the SCORE risk chart define a high risk as a ≥5% risk of cardiovascular disease death within 10 years. The chart for all CVD deaths in the NIPPON DATA80 employs almost the same end point as that used in the SCORE risk chart. However, strokes account for a high proportion of CVD in Japan, and similar to most cohort studies conducted in Japan, the NIPPON DATA80 shows no relationship between the TC level and stroke mortality. The ratio of stroke death to CAD death in Japan is approximately 2:1. The purpose of these guidelines is to promote the comprehensive prevention of CAD and provide lipid management goals for Japanese individuals. Therefore, in reference to these categories, these guidelines define Category I (low risk) as a <0.5% risk of CAD mortality, Category II (intermediate risk) as a ≥0.5% to <2% risk of CAD mortality and Category III (high risk) as a ≥2% risk of CAD mortality.

A flow chart for establishing management targets for LDL-C based on the absolute risk is shown in **Fig. 1**. First, after screening for dyslipidemia, a check is performed to determine whether the patient is a candidate for secondary prevention. Next, it is necessary to determine whether the patient has a condition that by itself classifies the patient into Category III, such as diabetes mellitus (DM, excluding impaired glucose tolerance), chronic kidney disease (CKD), noncardiogenic cerebral infarction and peripheral arterial disease (PAD). If no such conditions are observed, then the clinician can proceed to using the absolute risk assessment chart for the primary prevention of CAD. Referring to **Fig. 2**, it is possible to classify patients into the respective management categories, i.e., Categories I to III, according to the magnitude of the absolute risk based on the patient's laboratory findings. Regarding these categories, if at least one of the following conditions (hypo-HDL cholesterolemia, a family history of premature CAD or impaired glucose tolerance (excluding DM)) is observed, the category moves up one level (however, if the patient is classified into Category III, the category does not change). Because the absolute risk changes depending on age and the risk factor level, the absolute risk should be reassessed and the management categories should be reviewed on an annual basis, at minimum.

In the NIPPON DATA80 chart used in the assessment of absolute risk, sex, age, hypertension[13], smoking[14], DM (a random glucose level)[15] and TC[16] are included in the criteria for absolute risk. With respect to DM, because the absolute risk greatly depends on the presence or absence of complications and severe patients tend to be managed at medical institutions and are less likely to participate in community-based cohort studies, this guideline considers DM separately and does not use the DM category (a random glucose level ≥200 mg/dL) included in the original NIPPON DATA80 chart. Although the guidelines used in Western countries define patients with DM as high-risk as secondary prevention patients (patients with a history of CAD), at present there is no clear evidence suggesting that patients with DM correspond to secondary prevention patients in Japan. Therefore, in the same way as patients with noncardiogenic cerebral infarction or PAD, those with DM (excluding impaired glucose tolerance) are assigned to Category III, regardless of other factors, in this guideline. Recently, evidence that CKD is an important risk factor for CVD among Japanese has been reported[17-21], and patients with CKD are also considered as being at high risk according to the SCORE chart. Therefore, these guidelines classify patients with CKD into Category III, regardless of other factors.

As described above, a history of premature CAD in a first-degree relative is not included in the NIPPON DATA80 chart; thus, if this factor exists, the management category should be moved up to the next level. However, age (the age of the family member at the onset of disease) is important when recording the family history. Accordingly, this guideline defines a family history of premature CAD as <55 years of age for men and <65 years of age for women. Note that because patients or their family members may have vague memories, the patient should be carefully monitored if they have a family history of CAD, even if the CAD is not known to be premature.

### 3. Patient Management Based on the Relative Risk

Some women and young people exhibit a remarkably higher relative risk depending on the number or level of their risk factors compared with people of the same generation or same sex, even when they are classified into Category I. In principle, the lifestyles of such subjects should be modified immediately, even if the absolute risk is low. Because the absolute risk rapidly increases with age, careful monitoring is required. In order to motivate such subjects, relative risk charts are prepared using the NIPPON DATA80 risk chart (**Supplementary Table 1**). We recommend using this chart for patient instruction as needed.

**Table 1.** Lipid Management Targets for Patients with Different Risk Levels

| Therapeutic principle | Management category | Lipid management target (mg/dL) | | | |
|---|---|---|---|---|---|
| | | LDL-C | HDL-C | TG | Non HDL-C |
| Primary prevention<br>Drug therapy should be considered after lifestyle modification | Category I | <160 | ≥40 | <150 | <190 |
| | Category II | <140 | | | <170 |
| | Category III | <120 | | | <150 |
| Secondary prevention<br>Drug therapy should be considered, together with lifestyle modification | History of CAD | <100 | | | <130 |

- For patients at low absolute risk, such as the young, the relative risk charts (Supplementary Table 1) 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 as general goals, 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 non HDL-C is the secondary target to be used after a patient with hypertriglyceridemia has achieved the management target for LDL-C. 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 through lifestyle modification.
- For patients in category I, drug therapy should be considered if the LDL-C level is ≥180 mg/dL.

## 4. Management Targets for Dyslipidemia

The management targets for dyslipidemia for each category are shown in **Table 1**. For primary prevention, in principle, lifestyle factors should be modified for three to six months in order to assess the effects, then the administration of medications should be considered. However, if the LDL-C level continues to be ≥180 mg/dL in a patient in Category I, medication administration may be considered together with lifestyle modification. The management targets for Category I (low absolute risk) is an LDL-C level <160 mg/dL, that for Category II in an LDL-C level <140 mg/dL and that for Category III (high absolute risk) is an LDL-C level of <120 mg/dL. These targets are the same as the management targets for each category in the previous guidelines; however, the previous guidelines defined the categories simply based on the number of risk factors, while these guidelines define the categories based on the absolute risk. These management targets reflect the typical goals; in some cases, such as patients with very high LDL-C levels, it is difficult to achieve these management goals[22, 23]. A meta-analysis of randomized controlled trials of statins showed that a 20% to 30% reduction in the LDL-C level results in approximately a 30% reduction in the incidence of CAD[22, 23]. Therefore, considering the long-term efficacy and safety, a 20% to 30% reduction in the LDL-C level can be used as the management target. Note that this guideline cannot be applied to patients with familial hypercholesterolemia (FH). It is recommended that FH patients be referred to specialists because treating FH is difficult, and such patients are at very high risk for CAD.

Although we assume that these guidelines will generally be applied to adults <65 years of age, they can also be applied to the young old <75 years of age (the absolute risk should be calculated according to the category of 60 to 69 years of age). For patients <40 years of age, the need for lipid management is left to the discretion of the attending physician; if management is judged to be necessary, the absolute risk should be calculated according to the category of 40 to 49 years of age.

Because a substantial portion of the absolute risk is determined based on sex, age and other factors, achieving the management goals may not result in sufficient decreases in the risk of CAD leading to changes in the category of absolute risk; however, the absolute risk itself will certainly decrease.

In contrast, secondary prevention patients with a history of CAD, who likely require treatment for CVD, should be managed completely separately from primary prevention patients. The management targets for LDL-C for secondary prevention should be established at lower levels than those for primary prevention. Large-scale clinical studies conducted in Western countries have shown that reducing the level of LDL-C, even in subjects with average LDL-C levels, is effective in preventing the recurrence of CAD and the development of strokes and reducing total mortality. Subsequent observational and clinical studies conducted in Japan have shown that the likelihood of recurrence of CAD decreases in association with a decrease in the LDL-C level to 100 mg/dL[24, 25]. The

administration of drug therapy together with lifestyle modification is desirable in secondary prevention patients. In Japan, there is little evidence regarding whether the management target for LDL-C should be set at a lower level than < 100 mg/dL. Therefore, for secondary prevention, these guidelines define the management target as an LDL-C level of < 100 mg/dL, which is the same as that used in the previous guidelines.

Similar to the previous guidelines, it is recommended that the management target for TG and HDL-C be defined as < 150 mg/dL and ≥ 40 mg/dL, respectively, for both primary and secondary prevention patients. Although these guidelines use the LDL-C level as an index for the management goals, the non HDL-C level, which is calculated by subtracting HDL-C from TC, rather than LDL-C, is useful for managing lipid abnormalities in which hypertriglyceridemia is predominant, and the accumulation of such evidence has also occurred in Japan[10, 26-29]. The NCEP-ATP Ⅲ defines the cutoff for the non HDL-C level as 30 mg/dL higher than the LDL-C level, and the findings in Japan are similar[10, 30, 31]. Accordingly, these guidelines define the management targets for the non HDL-C level to be 30 mg/dL higher than those for the LDL-C level. The management targets for non HDL-C are secondary targets applicable to patients with hypertriglyceridemia who have achieved the management targets for LDL-C. If the TG level is ≥ 400 mg/dL or blood is collected after meals, the non HDL-C target should be used initially.

These guidelines have been used to determine the categories for lipid management targets based on absolute risk. Absolute risk can be also estimated to some extent by counting the number of risk factors and considering the sex and age of the patient. Please refer to the illustration presented (**Supplementary Table 2**). If an absolute risk chart is not readily available, the management targets can be expediently established using this illustration.

## Footnotes

This is an English version of the guideline from the Japan Atherosclerosis Society (chapter 4) published in Japanese in June, 2012.

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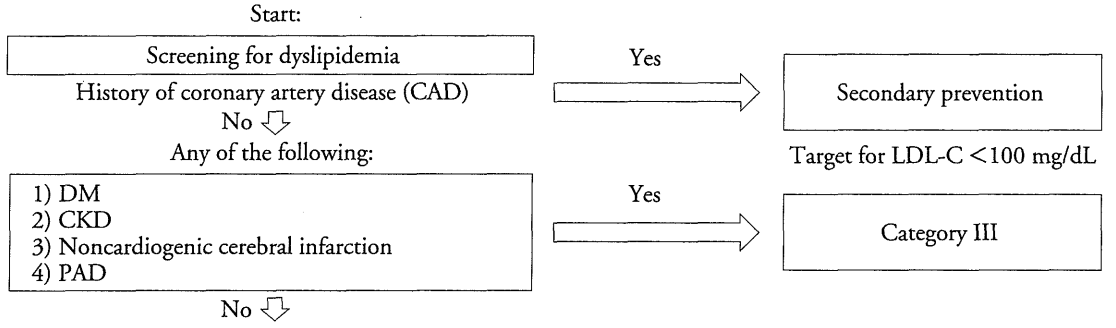
**Supplementary Table 1.** Relative Risk Charts for Patients with a Low Absolute Risk (based on the risk charts of the NIPPON DATA80)

| | | | Nonsmokers | | | |
|---|---|---|---|---|---|---|
| Systolic blood pressure | | | | | | |
| Second-degree or higher hypertension (≥160 mmHg) | 2.2 | 2.8 | 3.6 | 4.6 | 5.8 | 7.4 |
| First-degree hypertension (140-159 mmHg) | 1.7 | 2.2 | 2.8 | 3.5 | 4.5 | 5.7 |
| Normal (≤140 mmHg) | 1.0* | 1.3 | 1.6 | 2.1 | 2.6 | 3.4 |
| TC category (mg/dL) | 160-179 | 180-199 | 200-219 | 220-239 | 240-259 | 260+ |
| | | | Smokers | | | |
| Systolic blood pressure | | | | | | |
| Second-degree or higher hypertension (≥160 mmHg) | 3.2 | 4.1 | 5.2 | 6.6 | 8.4 | 10.7 |
| First-degree hypertension (140-159 mmHg) | 2.5 | 3.1 | 4.0 | 5.1 | 6.5 | 8.2 |
| Normal (≤140 mmHg) | 1.4 | 1.8 | 2.3 | 3.0 | 3.8 | 4.8 |
| TC category (mg/dL) | 160-179 | 180-199 | 200-219 | 220-239 | 240-259 | 260+ |

*Reference group
To calculate the relative risks used in this table, the representative values in each risk factor category were used. The representative values in each TC category were set at 160, 190, 210, 230, 250 and 270, the representative values in each systolic blood pressure category were set at 110 (normal), 150 (degree I) and 170 (degree II) and the patients were assumed to not have DM. The relative risk for patients who are nonsmokers with a TC level of 160 to 179 and a normal blood pressure was used as the reference value (i.e., relative risk: 1.0). For the sake of convenience, the relative risks were calculated assuming that the patients were men 40 years of age because the values cannot be calculated if the sex and age are not fixed. If the TC level cannot be used, the LDL-C + 80 value should be used.

**Supplementary Table 2.** Simple Chart Based on Sex, Age and the Number of Risk Factors for Predicting the Absolute Risk of CAD




| Baseline risk | | Determined based on the number of risk factors | | |
|---|---|---|---|---|
| Sex | Age | (1) Hypertension<br>(2) Smoking<br>(3) Hypo-HDL cholesterolemia (HDL-C < 40 mg/dL)<br>(4) Family history of premature CAD (first-degree male relatives aged < 55 years or female relatives aged < 65 years)<br>(5) Impaired glucose tolerance (excluding DM) | Absolute risk of CAD (%) | Category* |
| Men | 40-49 years (Also applied to persons aged 30-39 years) | 0 | 0.23 | Category I |
| | | 1-2 | 0.32-0.55 | Category II |
| | | ≥3 | 0.48-0.83 | Category III |
| | 50-59 years | 0 | 0.63 | Category II |
| | | 1 | 0.91-1.08 | Category II |
| | | ≥2 | 1.55 | Category III |
| | 60-69 years (Also applied to persons aged ≤74 years) | 0 | 1.78 | Category II |
| | | ≥1 | 2.55-4.31 | Category III |
| Women | 40-59 years | 0-1 | 0.10-0.20 | Category I |
| | | ≥2 | 0.24 | Category II |
| | 60-69 years (Also applied to persons aged ≤74 years) | 0-1 | 0.87-1.83 | |
| | | ≥2 | 2.19 | Category III |

In this simple chart, the serum level of LDL-C was set at 170 mg/dL (TC=250 mg/dL), which exceeded the upper limit of the least strict management target (LDL-C=160 mg/dL). Then, the absolute risk of CAD death was calculated using the NIPPON DATA risk chart as follows:

1) For age, the median (men: 45, 55 and 65 years; women: 50 and 65 years) was used.
2) The number of risk factors was calculated according to the presence or absence of hypertension (presence: SBP=160 mmHg; absence: SBP=120 mmHg) and the presence or absence of smoking, of which the maximum number was 2.
3) In cases in which the number of risk factors was ≥3, the absolute risk was estimated based on the assumption that the third risk factor (other than hypertension and smoking) increases the risk 1.5-fold.

*Depending on the level of additional risk factors, the absolute risk may not always be within the same range as in Fig. 1. Furthermore, because the relative risk for patients in the same sex and age group is also taken into consideration, it should be noted that the category may not always be consistent with the range of the estimated absolute risk determined using the NIPPON DATA risk charts. This chart may be used as a convenient method if the NIPPON DATA risk chart is not readily available.

Management Category Target for the LDL-C level:
Category I < 160 mg/dL, Category II < 140 mg/dL, Category III < 120 mg/dL, Secondary prevention < 100 mg/dL

Committee Report 5

# Cardiovascular Disease Risk Factors Other than 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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### 1. Hypertension

Hypertension is an important risk factor for atherosclerotic cardiovascular diseases (CVDs), such as cerebrovascular disease, coronary artery disease (CAD), heart failure and chronic kidney disease (CKD). Among them, it especially exhibits a strong association with cerebrovascular disease[1, 2]. Hypertension is a stronger risk factor for cerebral hemorrhage than for cerebral infarction and the incidences of both cerebral hemorrhage and infarction increase in association with in the blood pressure category[3, 4]. The Hisayama study demonstrated that the incidence of cerebral infarction significantly increased in patients with grade 1 hypertension (140 to 159/90 to 99 mmHg) compared with that observed in patients with an optimal blood pressure (<120/80 mmHg)[5]. According to "Health Japan 21" report, an increase in systolic blood pressure of 10 mmHg is associated with an increased risk of morbidity and mortality from cerebrovascular disease of 20% in men and approximately 15% in women[6].

Hypertension is also involved in the development of CAD, although the relationship is weaker than that observed with cerebrovascular disease. It has been reported that an increase in systolic blood pressure of 10 mmHg is associated with a greater risk of morbidity and mortality from CAD of approximately 15% in men[6]. Furthermore, in the 19-year follow-up period in the NIPPON DATA80 study, the hazard ratio for CVD mortality significantly increased in association with a rise in blood pressure in subjects 30 to 64 and 65 to 74 years of age, as well as in the elderly ≥ 75 years of age[3]. In the J-LIT study, the relative risk of developing CAD in primary prevention patients with hypertension was 2.5-fold for women and 2.3-fold for men compared with that observed in patients without hypertension[7].

Although blood pressure is usually measured in the office (in a medical environment), it has been reported that home blood pressure and 24-hour ambulatory blood pressure monitoring (ABPM) are more accurate in predicting the development of cardiovascular events than office blood pressure measurements[8-10].

The reference values for hypertension differ for office blood pressure, 24-hour ABPM and home blood pressure. Hypertension is defined as an office blood pressure of ≥ 140/90 mmHg, a home blood pressure of ≥ 135/85 mmHg and a 24-hour ABPM of ≥ 130/80 mmHg[11].

### 2. Diabetes Mellitus (DM)

DM is an important risk factor for CVD[12-14]. In the Hisayama study, the relative risks of developing CAD and cerebral infarction in patients with DM were higher, with values of 2.6 and 3.2, respectively, than those observed in subjects with normal glucose tolerance[15]. The relative risks are the same as those seen in Western patients with DM[16], while the absolute risks are lower than those observed in Westerners by approximately 30% to 70%[17, 18]. The increased risk of developing CAD due to DM is higher in women than in men[19]. Patients with DM also have an increased risk of developing peripheral arterial disease (PAD)[20]. The risk of developing CVD increases from the onset of impaired glucose tolerance (IGT) before the development of DM[21, 22]; however, it is unclear

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whether patients with IGT are at the same risk level as those with DM.

## 3. Smoking

Many reports, including the Framingham, MRFIT and Honolulu Heart Program studies, have stated that smoking is a risk factor for CAD and cerebrovascular disease[23-30]. In Japan, this finding has been reported in large-scale cohort studies, including the Hisayama[31], Hiroshima/Nagasaki[32], NIPPON DATA80 (**Figs. 1** and **2**)[33], JACC[34] and JPHC[35, 36] studies. Smoking is also a well-known risk factor for PAD[37-40].

Meanwhile, a meta-analysis demonstrated that even short-term passive smoking affects the platelet and vascular endothelial functions and the development of atherosclerosis and oxidative stress at levels of approximately 80% to 90% of those observed with chronic active smoking and that the relative risk of developing CAD in passive smokers is 1.3 (95% CI: 1.2 to 1.4)[41]. It has also been shown that passive smoking is a risk factor for stroke[42, 43].

The result of a meta-analysis of 25 prospective cohort studies, including four Japanese studies, that evaluated the relationship between active smoking and the incidence of type 2 DM, showed a risk of 1.4 (95% CI: 1.3 to 1.6)[44]. A meta-analysis of 54 cross-sectional studies, including two Japanese studies, revealed that the HDL-C levels are significantly lower (by 5.7%) in smokers than in nonsmokers in a dose-dependent manner[45]. Furthermore, it was shown that the HDL-C levels in smokers increase to those observed in nonsmokers following smoking cessation[46]; thus, smoking directly affects lipid metabolism. In Japan, a cross-sectional study reported that the risk of developing metabolic syndrome in smokers increases in association with increases in the number of cigarettes smoked, while the risks observed in ex-smokers decrease in association with increases in the duration of smoking cessation[47]. Moreover, a cohort study reported that the risk of developing metabolic syndrome rises in accordance with the number of cigarettes smoked[48]. Among smokers with metabolic syndrome, atherosclerosis progresses and the risk of developing CAD and/or cerebral infarction increases[49, 50]. Smoking is by itself a risk factor for CVD; it increases the risk of developing DM, dyslipidemia and metabolic syndrome and is associated with an increased risk of CVD.

## 4. Age and Sex

Age is a strong risk factor for CVD in Japan as well as Western countries[51, 52]. Regarding CAD, the U.S. data[53], NIPPON DATA80[54], "Annual Statistical Report of National Health Conditions"[55], Hiroshima/Nagasaki[32], 3M study in workplaces[56] and Takashima study in Shiga prefecture[57] studies demonstrated that the mortality and incidence of CAD increase starting from age 45 for men and age 55 for women and that the risk of CVD markedly increases in association with increases in age class.

The incidence and mortality of CAD in women are lower than those observed in men in all age classes. Considering the increased risk associated with age, the increase in the risk of CAD in women occurs more slowly, by approximately 10 years, than that observed in men[27, 55]. In epidemiological studies conducted in Okinawa and Shiga prefectures, the age-adjusted incidence of myocardial infarction in women 35 to 65 years of age was found to be markedly lower than that observed in men[2, 57]. The vital statistics prepared by the Ministry of Health, Labour and Welfare reported that the mortality of myocardial infarction in women is 22% to 25% among women in their 50s, 25% to 33% among women in their 60s and 41% to 48% among women in their 70s compared to that observed in men[55]. In women, the postmenopausal period is considered to reflect the point at which the risk of CAD increases. Patients who have undergone bilateral oophorectomy should be considered to be at risk of developing CAD, even if they are $<55$ years of age.

## 5. Family History

In Western countries, it has been reported since the 1970s that a family history of CAD is a risk factor for the disease[59-66]. A family history of CAD, especially that in a first-degree relative (parent, child, brother or sister), and a family history of premature CAD (age of onset: $<55$ years for men, $<65$ years for women) are strong risk factors for CAD.

The Framingham study reported that if at least one parent has CAD, the age-adjusted odds ratio for developing CAD was 2.6 and 2.3 for men and women, respectively, and 2.0 and 1.7 for men and women following adjustment for all variables in a multivariate analysis[62]. In Japan, the J-LIT study showed that a family history of CAD increases the relative risk of developing CAD by approximately three-fold[7]. The recent CREDO-Kyoto study also reported that a family history of CAD contributes to the development of major cardiovascular events at an early

age[67].

Traditional risk factors (hyper-LDL cholesterolemia, hypo-HDL cholesterolemia, hypertension, DM and smoking) are associated with genetic predispositions and are affected by the habits of the household. In other words, a family history of CAD is considered to include both genetic and environmental risk factors, a fact that is already well known. Lp(a), small dense LDL and homocysteine have recently received attention as other risk factors to consider, all of which are genetically influenced. However, because family history remains a strong risk factor even after adjusting for all traditional risk factors in a multivariate analysis[58, 60-62, 68], it is assumed that a patient's family history includes many unknown genetic factors[64].

Therefore, most studies of family history have concluded that a family history of CAD is an independent risk factor for CAD, and a family history of premature CAD (age of onset: <55 years for men, < 65 years for women), in particular, should be considered a risk factor.

## 6. Other Risk Factors or Markers to Consider

Aside from the established risk factors described above, the other parameters listed in **Table 1** have been proposed to be risk factors or markers for CVD. It should be noted that these parameters include not only factors that are true risk factors for the development of atherosclerosis, but also factors that are simply markers of atherosclerosis.

### 1) Lp(a)

Lp(a) is a class of LDL in which apo(a) is attached to apo B-100 by a disulfide bond. It has been reported that the plasma levels of Lp(a) as well as the size of apo(a) are independent risk factors for CAD and strokes[69-76]. Several atherogenic properties of Lp(a) have been clarified[78, 79]. For example, apo(a) proteins are highly homologous to plasminogen[77], promote thrombus formation by interfering with plasminogen[80, 81], easily bind to oxidized phospholipids[78] and tend to be anchored to the arterial wall[82].

### 2) Remnant Lipoproteins

Remnant lipoproteins, which are commonly observed in patients with postprandial hyperlipidemia, have been proposed to play a pivotal role in the development of CAD[83]. Remnant lipoproteins are intermediate lipoproteins that are produced during the metabolism of chylomicrons and VLDLs and are deposited in the vascular intima, leading to the development of atherosclerosis[84]. The pathophysiological conditions under which the amount of remnant lipoproteins is increased include familial combined hyperlipidemia, familial type Ⅲ hyperlipidemia, DM and metabolic syndrome.

### 3) Small Dense LDL

Small dense LDL particles[85, 86] are subfractions of LDL particles that are small in size and high in density. Many reports have shown that increased levels of small dense LDL are related to CAD[87-91] and associated with PAD and aneurysm formation[92, 93]. The proposed mechanisms underlying the strong atherogenicity of small dense LDL include the following: small dense LDL particles are easily oxidized[94] and processed by pathways other than those for LDL receptors[95]; and the particles are easily incorporated into the arterial wall[96] where they tend to bind to the matrix[97]. The presence of small dense LDL is closely associated with hypertriglyceridemia and hypo-HDL cholesterolemia[98]. An increase in the level of small dense LDL is found in conditions such as type 2 DM, metabolic syndrome and insulin resistance[99].

### 4) Oxidized LDL and MDA-LDL

Oxidized LDL, in which lipids (e.g., phospholipids) and apolipoproteins are oxidatively modified, is involved in a broad range of processes related to atherosclerosis, such as vascular endothelial cell injury, enhancement of infiltration of monocytes into the vessel walls and foam cell formation. Assays to measure the level of MDA-LDL, a class of oxidized LDL in which apoB-100 is modified by malondialdehyde (MDA), are commercially available.

### 5) Apo B

Apo B is an apolipoprotein contained in atherogenic lipoprotein particles, such as LDL and remnant lipoproteins. Because there is one apo B molecule per lipoprotein particle, the apo B level is proportionate to the number of atherogenic lipoprotein particles. Therefore, even if the LDL-C level remains constant, an increase in the number of LDL particles caused, for instance, by the existence of small dense LDL particles will result in a higher level of apo B. A meta-analysis of epidemiological studies revealed that the apo B level is a stronger marker of cardiovascular events than the levels of LDL-C and HDL-C[100].

### 6) Ratios of Lipids and Apoproteins

The lipid levels, such as those of LDL-C and HDL-C, are strong risk factors for the development of CVD; however, several studies have proposed that the proportion of cholesterol in each lipoprotein or the

ratio of apolipoproteins, i.e., the TC/HDL-C ratio, the non HDL-C/HDL-C ratio, the LDL-C/HDL-C ratio and the apo B/AI ratio, may be stronger markers of CVD than the lipid or apolipoprotein levels themselves[101-104]. It should be noted that most of these data are derived from Western countries; thus, in Japan, the current management goals should be evaluated using the absolute value of each lipid level.

**7) CRP and Inflammation-Related Markers**

Inflammation plays an important role in the formation of atherosclerotic lesions[105, 106]. C-reactive protein (CRP) is an acute-phase protein that is usually used as an inflammatory marker. It has recently been reported that the high-sensitivity CRP (hsCRP) level observed under a steady state can be used as a marker for the primary/secondary prevention of CAD[107-112]. It has also been reported that the CRP level is an independent risk factor for CAD, cerebral infarction and vascular death and is a stronger marker than systolic blood pressure or the non HDL-C level[113]. However, an analysis of CRP genotypes in patients with CAD revealed that the genotypes that result in high levels of CRP are not associated with the development of CVD; thus, CVD is considered to be associated with the inflammatory state reflected by the CRP level[114].

Similar to CRP, Lp-PLA2, an enzyme produced in atherosclerotic lesions, and amyloid A, an acute-phase protein, have been reported to be markers of CVD[110, 115, 116]. Infections with organisms such as Chlamydophila pneumoniae and cytomegalovirus have been proposed to be related to the development of atherosclerosis via the effects of local and/or systemic inflammation[117]. A recent study also indicated that periodontal disease is associated with atherosclerosis[118].

**8) Homocysteine**

Many reports have indicated that increased plasma levels of homocysteine are a risk factor not only for CAD, but also for strokes and PAD[119-121]. For example, the Physicians' Health Study showed that increased homocysteine levels are associated with an increased relative risk of myocardial infarction[122]. In addition, a recent analysis suggested that homocysteine is a stronger predictor of cardiovascular events than CRP[123]. On the other hand, the administration of vitamin supplementation therapy to lower the plasma homocysteine levels fails to reduce the incidence of cardiovascular events[124]. Furthermore, a recent study clarified that there is no relationship between CVD and gene mutations that genetically increase the plasma homocysteine levels[125]. Therefore, further investigations are warranted to determine whether the plasma levels of homocysteine are simply a marker or a true causal risk factor for CVD.

**9) Blood Coagulation and Fibrinolytic Factors**

Plaque rupture and subsequent thrombus formation are important events in the pathogenesis of CAD[126]. Fibrinogen, a coagulation factor, has been shown to be a risk marker for CVD since the 1970s[127]. The fibrinogen level is correlated with other risk factors, such as age, the smoking status, the LDL-C level and the physical activity level[128]; however, even when corrected for these factors, the fibrinogen level has been shown to be a marker of CVD[129-132]. It has also been proposed that fibrinolytic factors, such as t-PA[129] and PAI-1[78], are involved in the pathogenesis of CVD. The PAI-1 level is associated with the severity of several conditions, including visceral fat accumulation and insulin resistance[133, 134]; thus, it has been speculated that the presence of these conditions affects the association observed between the PAI-1 level and the development of CAD. The activities of coagulation and fibrinolytic factors are thought to be linked with each other, thereby contributing to the formation of atherosclerotic lesions[135].

## Footnotes

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