Committee Report 2

Comprehensive Risk Management for the Prevention of Cardiovascular Disease

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

Dyslipidemia is one of the most important risk factors for cardiovascular disease (CVD), and managing dyslipidemia is extremely important for preventing CVD. Appropriately managing other major risk factors for which intervention is possible, including smoking, hypertension and diabetes mellitus (DM), is also important for treating dyslipidemia.

A “Comprehensive Risk Management Chart for the Prevention of Cardiovascular Disease” is shown in Fig. 1. This chapter describes the procedures for diagnosis, assessment and intervention that are required for the comprehensive management of risk factors to prevent CVD, particularly coronary artery disease (CAD).

Special attention should therefore be paid to cerebrovascular disease as well as CAD in Japan. Correcting dyslipidemia, along with hypertension, smoking and DM, plays an important role in preventing cerebrovascular disease, particularly noncardiogenic cerebral infarction.

1. Screening

Step 1: Screening for the Assessment of Risk Factors for Cardiovascular Disease

• A thorough assessment of the major risk factors for CVD, all of which must be considered, careful recording of medical/family history and examinations, including blood chemistry tests, are important.

• Regarding laboratory tests, fasting venous blood* should be collected, in principle.

* A “fasting state” is defined as fasting for ≥ 10 to 12 hours. Liquids with no calories, such as water and tea, can be consumed.

The subjects described in this section are primarily those who are initially diagnosed as “requiring further investigation” of risk factors for atherosclerosis. In addition, subjects with a history of CVD, such as CAD, as well as patients who have already been treated or followed up for dyslipidemia, DM or hypertension, should periodically undergo screening tests according to the methods described in this section, and their risk factors and management should be reassessed over time.

The interview items, important physical findings and screening test results required to assess the risk of CVD among individual patients are shown in Table 1. For patients with a history of CVD or symptoms or those who are expected to have a higher risk because they are being treated for dyslipidemia, hypertension or DM or because they have remained untreated for a long period, the tests (including diagnostic imaging) shown in Table 2 should be considered.

If familial hypercholesterolemia (FH) is suspected based on an LDL-C level of ≥ 180 mg/dL or the patient’s medical history, obtaining a soft tissue X-ray film of the Achilles tendon is recommended. Detecting small dense LDL on polyacrylamide gel electrophoresis (PAGE) of plasma lipoproteins and/or measuring the apo B/LDL-C ratio is useful for making a diagnosis of familial combined hyperlipidemia, while detecting broad β, measuring the level of apo E and/or analyzing isoforms of apo E is useful for diagnosing familial type III hyperlipidemia. Primary hyperlipidemia, including FH, requires strict management from the early stage of the disease, and screening family members (relatives) of the patient is essential.
Step 1: Screening
(interview, physical findings and examination findings)

Step 2: Assessment of risk factors
(History of CAD, noncardiogenic cerebral infarction, PAD, DM, CKD, age, sex, dyslipidemia, hypertension and family history of premature CAD)

Step 3: Risk stratification based on absolute risk
(Management categories should be determined according to the “Absolute Risk Chart for CAD” and additional risks)

Step 4: Determination of therapeutic strategies appropriate for the risk

Step 5: Goal of management of each disease

5A: Dyslipidemia
LDL-C: Category I: <160 mg/dL
Category II: <140 mg/dL
Category III: <120 mg/dL
Secondary prevention: <100 mg/dL
HDL-C: ≥ 40 mg/dL
TG: <150 mg/dL

5B: Hypertension
Young/middle aged: <130/85 mmHg
Elderly (≥ 65 years): <140/90 mmHg
DM, CKD, or after MI: <130/80 mmHg
Cerebrovascular disease: <140/90 mmHg

5C: DM
HbA1C (NGSP): <7.0%
FBG: <130 mg/dL
2-h PBG: <180 mg/dL

5D: Other conditions
Metabolic syndrome, Obesity, Hyperuricemia, etc.

Step 6: Lifestyle modification (smoking cessation, anti-obesity measures, dietary therapy, exercise therapy, etc.)

Step 7: Drug therapy (Step 6 should be continued)

7A: Dyslipidemia
Statins, anion-exchange resin, small intestinal cholesterol transporter inhibitors, fibrates, nicotinic acid derivatives, EPA, probucol, etc.

7B: Hypertension
Ca-antagonists, ARBs, ACE inhibitors, diuretics, β-blockers, etc.

7C: DM
SUs, α-glucosidase inhibitors, biguanides, thiazolidines, DPP-4 inhibitors, insulin, etc.

7D: Other conditions
Antiplatelet therapy (aspirin), etc.

Fig. 1. Comprehensive Risk Management Chart for the Prevention of Cardiovascular Disease.
**Table 1. Screening Tests (Basic Tests)**

**Step 1a: Screening Tests (Basic Tests)**

### Medical history
- Type(s), time of onset and time-course of changes of symptoms (anginal pain, intermittent claudication, amaurosis, aphasia, transient quadriplegia, abdominal pain, etc.)
- Lifestyle (smoking, drinking, dietary habits, regular exercise, etc.) and regular medication
- Medical history (particularly CVD) and weight change
- Family history (CVD, lifestyle-related diseases, sudden death, premature death, etc.) and consanguineous marriage or not

### Physical findings
- Height, body weight, BMI and waist circumference
- Pulse rate and blood pressure† (presence or absence of asymmetry)
- Arcus corneae, Achilles tendon hypertrophy, cutaneous or tendon xanthoma (extensor surfaces of joints, wrist, buttocks, etc.), goiter, carotid bruits, heart sound, abdomen (pulsatile mass and arterial bruits) and limbs (arterial palpation, edema and motor or sensory disturbance)

### Laboratory tests‡
- Peripheral blood count and routine urinalysis
- Serum lipids (TC, LDL-C, HDL-C and TG)
- Blood chemistry tests: AST, ALT, LDH, γ-GTP, ALP, cholinesterase, CK, BUN, CRE, eGFR,* Na, K, UA, FBS and HbA1c
- Thyroid function tests (TSH, free T3 and free T4)

### Physiological tests
- ECG

### Imaging
- Chest radiography (cardiothoracic ratio and aortic calcification)

† Office blood pressure measurement should follow the “Guidelines for the Management of Hypertension JSH 2009” issued by the Japanese Society of Hypertension.

‡ Fasting blood should be collected, in principle. Appropriate tests should be performed in each patient.

§ Calculated with the Friedewald formula: LDL-C = TC – HDL-C – TG/5 (in cases of fasting blood collection and TG < 400 mg/dL).

* Men: eGFR (mL/min/1.73m²) = 194 × Cṙc −1.094 × age −0.287
  Women: eGFR (mL/min/1.73m²) = 194 × Cṙc −1.094 × age −0.287 × 0.739 (“Clinical Practice Guidebook for the Diagnosis and Treatment of Chronic Kidney Disease 2009” issued by the Japanese Society of Nephrology)

**Table 2. Screening Tests (Selective/Additional Tests)**

**Step 1b: Screening Tests (Selective/Additional Tests)**

### Diagnostic imaging
- Soft X-ray imaging (Achilles tendon)
- Carotid ultrasonography
- Echocardiography
- Vascular ultrasonography (limbs)
- Coronary CT and chest and abdominal CT
- Magnetic resonance imaging (MRI) and magnetic resonance (MR) angiography

### Physiological tests
- Ankle-brachial index (ABI), brachial-ankle pulse wave velocity (baPWV) and cardio-ankle vascular stiffness index (CAVI)

### Laboratory tests
- Agarose gel electrophoresis of lipoproteins and polyacrylamide gel electrophoresis (PAGE)
- Apolipoproteins (A1, AII, B, CII, CIII and E)
- Small dense LDL, lipoprotein (a) (Lp[a]), remnant lipoprotein cholesterol (remnant-like particle-cholesterol [RLP-C] and remnant lipoprotein cholesterol [RemL-C]), lipoprotein lipase (LPL), hepatic lipase (HL) and lecithin cholesterol acyltransferase (LCAT)
- Urine microalbumin
- Pituitary/adrenal hormones
- Other tests (MDA-LDL, etc.)
Screening for primary hyperlipidemia is extremely important; therefore, referring the patient to a specialist is desirable if primary hyperlipidemia is suspected.

If secondary hyperlipidemia is suspected (the major causes of this disease are shown in Table 3), tests required to make a diagnosis of this condition should be added. In patients with goiters or the elderly, attention should be paid to the possibility of hypothyroidism.

### 2. Assessment of Risk Factors

**Step 2: Risk Factors Requiring Consideration**

- **CAD**
- **DM/impaired glucose tolerance**
- **CKD**
- **Noncardiogenic cerebral infarction/PAD**
- **Age and sex**
- **Dyslipidemia**
- **Hypertension**
- **Smoking**
- **Family history of premature CAD in a first-degree relative**

Significant risk factors for absolute risk assessment and risk stratification of cardiovascular disease include a history of CAD, DM/impaired glucose tolerance, chronic kidney disease (CKD), the presence or history of other types of CVD, such as noncardiogenic cerebral infarction or peripheral arterial disease (PAD), age, sex, dyslipidemia, hypertension, smoking and a family history of premature CAD in a first-degree relative (men < 55 years of age or women < 65 years of age). Regarding a family history of CAD, it is often unclear whether CAD is premature. If a first-degree relative has a history of CAD or sudden death, further consideration is therefore required regarding risk stratification and management.

### 3. Risk Stratification Based on Absolute Risk

**Step 3: Risk Stratification**

- **First**, it should be determined whether a patient requires secondary prevention or primary prevention according to the presence or absence of a history of CAD.
- **For primary prevention**, a patient is classified as belonging to category III if he/she has any of the following: (1) DM, (2) CKD, (3) noncardiogenic cerebral infarction or (4) PAD.
- **If a patient does not have any of the above-mentioned conditions (1) to (4), the absolute risk (10-year risk of CAD death) should be determined based on the patient’s age, sex, TC level, systolic blood pressure and smoking status according to the “Absolute Risk Charts for CAD (Primary Prevention)” section. Subsequently, the presence or absence of any of the following additional risks should be assessed to determine each patient’s risk management category: (1) hypo-HDL cholesterolemia (HDL-C < 40 mg/dL), (2) family history of premature CAD and (3) impaired glucose tolerance (excluding DM).
- **For low-risk patients**, such as young individuals and premenopausal women, the relative risk chart should be applied to predict the future risk.

Based on the information obtained in Steps 1 and 2, it should first be determined whether a patient requires secondary prevention. If a patient requires primary prevention, the risk management category should be determined according to the presence of additional risk factors, and the “Absolute Risk Charts for CAD (Primary Prevention)” (10-year risk of CAD death) should be used to stratify the risk for each patient (Fig. 2).

The absolute risk and management category will vary depending on the age and risk factors of the patient. Therefore, the progression of organ damage due to atherosclerosis and/or each individual risk factor should be periodically and objectively reassessed at least annually (refer to section “1. Screening” in this report) to review the absolute risk and management categories.

Patients with a history of CAD require strict risk management as “secondary prevention patients.” Along with a history of CAD, smoking, a history of DM (including impaired glucose tolerance) or CKD, a history of or complications associated with noncardiogenic cerebral infarction or PAD, metabolic syndrome and the presence of more than one major risk factor places the patient at a higher risk and

### Table 3. Major Secondary Hyperlipidemia

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Renal failure/uremia</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Obstructive jaundice</td>
</tr>
<tr>
<td>DM</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Autoimmune diseases (systemic lupus erythematosus, etc.)</td>
</tr>
<tr>
<td>Drug-induced (diuretics, β-blockers, corticosteroids, estrogen, retinoic acid, cyclosporin, etc.)</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

The diagnostic criteria for hypertension\(^1\), DM\(^2\) and CKD\(^3\) should conform to the clinical practice guidelines released by relevant societies.

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\(^1\) Hypertension
\(^2\) DM
\(^3\) CKD

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**Fig. 2.** Absolute Risk Charts for CAD (Primary Prevention)
requires stricter management (Table 4).

For primary prevention, a patient is classified into “category III” if the absolute risk is ≥2% or, regardless of the absolute risk, he/she has any of the following: DM (excluding impaired glucose tolerance), CKD, noncardiogenic cerebral infarction or PAD.

If patients with DM have microangiopathy, such as retinopathy or nephropathy, persistent poor glycemic control, such as an HbA1c (NGSP) level of ≥8.4%, a current history of smoking, a history of or current noncardiogenic cerebral infarction or PAD, metabolic syndrome or more than one major risk factor, they are at higher risk of developing CAD or death, and comprehensive strict management of each risk factor, including dyslipidemia, should be performed starting from an early stage (Table 5).

Even if the absolute risk is <2%, if a patient has at least one of the following additional risk factors, hypo-HDL cholesterolemia, a family history of premature CAD (a first-degree male relative <55 years of age or a female relative <65 years of age) or impaired glucose tolerance (excluding DM), the risk management category increases to the next higher category.

4. Determination of Appropriate Therapeutic Strategies for Each Risk Category

Step 4: Therapeutic Strategies Appropriate for the Risk
- Lifestyle modification, including dietary therapy, exercise and smoking cessation, forms the basis for the prevention of CVD. All patients should be provided adequate guidance regarding lifestyle modification.
- A management/treatment goal should be determined for each disease, such as dyslipidemia, hypertension and DM, according to each patient’s risk.
- Even if a patient has a low risk, intervention for or adequate management of each risk factor should be considered early in anticipation of a future increase in risk.

Lifestyle modification provides the basis for the prevention of cardiovascular disease. Regardless of the patient’s risk category, all patients should be provided adequate guidance regarding lifestyle modification.

Although younger patients and some women may have a lower absolute risk in their current state, atherosclerosis can advance asymptotically, and both CAD and cerebrovascular disease occur more frequently with age. Therefore, a management goal should be determined for each risk factor in anticipation of a future increase in risk. It is desirable to utilize “the relative risk chart” in order to anticipate future risks and provide continuous observation and patient guidance (Supplementary Table 1 “Relative Risk Charts for Patients with a Low Absolute Risk”). The absolute risk can also be estimated to some extent according to the “Simple Chart Based on Sex, Age and Number of Risk Factors and Predicted Absolute Risk of CAD,” which is shown in Supplementary Table 2. Lifestyle modification is an effective tool that can be used for intervention, even in low-risk patients.

5. Goals of Management

Step 5A: Management Targets for Dyslipidemia (Fasting Venous Blood)
- Management of lipids should be performed as described in Fig. 2 and Table 6.

The LDL-C level should be calculated using the Friedewald formula, in principle. However, if the TG level is high (≥400 mg/dL) or if collecting a fasting blood sample is difficult, the non HDL-C level should be used as the target, instead of the LDL-C level. The targets for LDL-C and non HDL-C are shown in Table 6.

The target LDL-C level for each patient should be determined by comprehensively considering the duration of exposure to risk factors, including dyslipidemia (duration of the disease), and the clustering of risks.

These targets can be considered general goals for the long term. The immediate target should be at least a 20% to 30% reduction in the level of LDL-C. In

Table 4. Patient Conditions Requiring Stricter Management in Secondary Prevention

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>DM</td>
</tr>
<tr>
<td>CKD</td>
</tr>
<tr>
<td>Noncardiogenic cerebral infarction/PAD</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>More than one major risk factor</td>
</tr>
</tbody>
</table>

Table 5. Diabetic Patients at Higher Risk of Developing CAD

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microangiopathy (retinopathy, nephropathy, etc.)</td>
</tr>
<tr>
<td>Persistent poor glycemic control*</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Noncardiogenic cerebral infarction/PAD</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>More than one major risk factor</td>
</tr>
</tbody>
</table>

*HbA1c (NGSP) ≥8.4%
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In patients with secondary hyperlipidemia, clinicians should aim to achieve the targets (Table 4 and 5).

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Management categories based on absolute risk for the primary prevention of CAD (For absolute risk, refer to Fig. 2 in Committee Report 1)

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

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

**Fig. 2.** Flow Chart for Setting Management Targets for LDL-C.

**Table 6.** 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>Primary prevention</td>
<td>Category I</td>
<td>LDL-C &lt;160</td>
</tr>
<tr>
<td>Drug therapy should be considered after lifestyle modification</td>
<td>Category II</td>
<td>HDL-C &lt;140</td>
</tr>
<tr>
<td></td>
<td>Category III</td>
<td>TG &lt;170</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>History of CAD</td>
<td>Non HDL-C &lt;150</td>
</tr>
<tr>
<td>Drug therapy should be considered, together with lifestyle modification</td>
<td>Category I</td>
<td>LDL-C &lt;100</td>
</tr>
<tr>
<td></td>
<td>Category II</td>
<td>HDL-C &lt;120</td>
</tr>
<tr>
<td></td>
<td>Category III</td>
<td>TG &lt;150</td>
</tr>
</tbody>
</table>

high-risk patients, such as those with DM and poor glycemic control or organ damage (e.g., retinopathy, nephropathy or PAD) and those receiving secondary prevention, clinicians should aim to ensure achievement of the targets (Table 4 and 5).
Comprehensive Risk Management

pressure measurements. Home blood pressure measurement is not only useful for assessing hypotensive effects, but also preventing complications due to excessive decreases in blood pressure. Home blood pressure values are generally lower than casual blood pressure values measured in outpatient clinics or during health screenings; thus, the target home blood pressure is lower than the target office blood pressure.

Elderly patients ≥75 years of age often have organ damage; therefore, careful management with antihypertensive therapy is needed taking into consideration the QOL, using an intermediate target blood pressure of 150/90 mmHg. Patients with a high pulse pressure are expected to have advanced atherosclerosis, which means that a slow and careful reduction of blood pressure should be achieved.

Step 5C: DM Management Goals
• Targets for the index of glycemic control and management of blood glucose should be set for each patient taking into consideration their age and disease condition. Generally, the target should be an HbA1c (NGSP) level of <7.0%.

As a risk factor for CVD, DM occupies a very important position along with dyslipidemia and hypertension. Patients with persistent poor glycemic control, such as an HbA1c (NGSP) level of ≥8.4% or complicating hypothyroidism or steroid therapy, the treatment of the primary disease should be given priority, and management of lipid abnormalities should be performed according to the individual circumstances and requirements. With respect to transient hypercholesterolemia associated with pregnancy, drug therapy is not needed, in principle.

Step 5B: Management Targets for Hypertension
• In young or middle-aged patients <65 years of age, the target office blood pressure should be <130/85 mmHg (home blood pressure <125/80 mmHg).
• In elderly patients ≥65 years of age, the target office blood pressure should be <140/90 mmHg (home blood pressure <135/85 mmHg).
• In patients with DM, CKD or a history of MI, the target office blood pressure should be <130/80 mmHg (home blood pressure <125/75 mmHg).
• In patients with cerebrovascular disease, the target office blood pressure should be <140/90 mmHg (home blood pressure <135/85 mmHg).

Although this section describes the target office blood pressure (Fig. 1 and Table 7), home blood pressure measurements are essential for diagnosing masked hypertension and/or white coat hypertension and diagnosing and treating refractory hypertension and are of equal or greater clinical value than office blood pressure measurements. Home blood pressure measurement is not only useful for assessing hypotensive effects, but also preventing complications due to excessive decreases in blood pressure. Home blood pressure values are generally lower than casual blood pressure values measured in outpatient clinics or during health screenings; thus, the target home blood pressure is lower than the target office blood pressure.

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Table 7. Stratification of cerebrovascular/cardiovascular risk in four categories on the basis of (clinic) blood pressure classification and risk strata

<table>
<thead>
<tr>
<th>Blood pressure classification</th>
<th>High-normal blood pressure 130-139/85-89 mmHg</th>
<th>Grade I hypertension 140-159/90-99 mmHg</th>
<th>Grade II hypertension 160-179/100-109 mmHg</th>
<th>Grade III hypertension ≥180≥110 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk stratum-1 (no other risk factors)</td>
<td>No additive risk</td>
<td>Low risk</td>
<td>Moderate risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Risk stratum-2 (one to two risk factors (other than diabetes) or metabolic syndrome)</td>
<td>Moderate risk</td>
<td>Moderate risk</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Risk stratum-3 (three or more risk factors, diabetes, CKD, target organ damage/cardiovascular disease)</td>
<td>High risk</td>
<td>High risk</td>
<td>High risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

Abbreviation: CKD, chronic kidney disease.

a When obesity and dyslipidemia are present in the absence of other risk factors, risk factors other than the blood pressure level are counted as two, and the risk is classified as the risk stratum-2. However, when other risk factors are present, the total of risk factors is calculated as three or more, and the risk is classified as the risk stratum-3.

b Metabolic syndrome in risk stratum-2 indicates patients with an abnormal plasma glucose level (an impaired fasting plasma glucose level of 110-125 mg/dL and/or impaired glucose tolerance that does not lead to diabetes), or abnormalities in lipid metabolism in addition to a high-normal or higher blood pressure level and abdominal obesity (males: ≥85 cm, females: ≥90 cm).

c Treatment in moderate- and high-risk groups with high-normal blood pressure values is based on the algorithm for treatment of hypertension at initial visit. The management of common cardiovascular risks is important here. (The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). Hypertens Res 2009; 32: 3-107)
organ damage (e.g., retinopathy, nephropathy or PAD) have an especially high risk (Table 5). The risk of developing CVD is much higher in women with DM than in women without DM.

To prevent the development/progression of CVD in patients with DM, obtaining good glycemic control alone is insufficient, and comprehensive and strict management of risk factors, such as dyslipidemia, hypertension, obesity (visceral fat accumulation) and smoking, is required.

**Step 5D: Management of Other Conditions**
- Metabolic syndrome is based on the excessive accumulation of visceral fat and is characterized by a cluster of risk factors for CVD. Simultaneous with treating each risk factor, reducing obesity, particularly visceral fat, should be a management target.
- In order to address other diseases closely associated with lifestyle, such as hyperuricemia, an appropriate treatment/management goal to prevent CVD should be set for each patient.

Epidemiological studies performed in Western countries and Japan have shown that the clustering of risk factors, such as that observed in metabolic syndrome, is associated with an increased risk of CVD. In addition to managing each risk factor, reducing visceral fat, the accumulation of which is the basis for metabolic syndrome (i.e., reducing obesity and waist circumference), should be considered. For such patients, active guidance on anti-obesity measures should be provided, with a 5% decrease in body weight or waist circumference after three to six months being the immediate target, and achievement of the target should be assessed over time.

The serum uric acid level is an independent predictor of future hypertension and is associated with the development and/or progression of CKD. An elevated uric acid level reflects an increased frequency of metabolic syndrome. Therefore, even in cases of asymptomatic hyperuricemia without gout or renal calculi, therapeutic intervention should be considered if there is a history of hypertension, DM or CAD and the uric acid level is $\geq 8.0$ mg/dL. Lifestyle modification is also the basis of treatment in such cases.

**Table 8. Lifestyle Modification for the Prevention of CVD**

1. Stop smoking and avoid passive smoking.
2. Refrain from overeating and maintain an ideal body weight.
3. Reduce intake of meat fat, dairy products and egg yolk and increase the intake of fish and soy products.
4. Increase intake of vegetables, fruit, unrefined grains and seaweed.
5. Reduce intake of food containing too much salt.
6. Avoid excessive alcohol consumption.
7. Perform aerobic exercise for at least 30 min daily.

Lifestyle modification forms the basis of the prevention of CVD, and introducing drug therapy without careful consideration should be avoided. After drug therapy is commenced, continued guidance on lifestyle modification should be provided (Table 8).

Smoking is one of the most important factors that can be targeted for intervention among the causes of CVD. In order to prevent CVD, smoking cessation should be recommended for people of all ages and both sexes. The increased risk of CAD observed in nonsmokers due to passive smoking is also a serious issue.

A BMI of $\geq 25$ is considered to indicate obesity. For obese individuals, particularly patients with visceral fat accumulation (metabolic syndrome), a 5% decrease in body weight and/or waist circumference should be the immediate target.

Optimizing the total energy intake and nutrient balance and modifying inappropriate dietary habits and eating behaviors form the basis of treatment in patients with risk factors, such as dyslipidemia, hypertension, DM and obesity. Soluble dietary fiber should be consumed abundantly, while the intake of cholesterol and saturated fatty acids should be reduced. Patients with hypertension are recommended to limit their intake of salt to $<6$ g/day.

It has been demonstrated that exercise can improve dyslipidemia (e.g., increase the level of HDL-C) as well as exert hypotensive effects, improve insulin resistance and achieve hypoglycemic effects. Engaging in moderate aerobic exercise (approximately 50% of maximum oxygen uptake) for at least 30 minutes per day at least three times per week (daily if possible) or at least 180 minutes per week is desirable. For patients with hypertension, except those with mild to moderate blood pressure elevation (160 to 179/100 to 109 mmHg) and no CVD, prior medical examinations are needed. In DM patients with poor glycemic control...
(e.g., positive urine ketones), retinopathy, CVD, renal failure, peripheral neuropathy or autonomic neuropathy, a specialist should be consulted regarding the appropriateness or need for restricting exercise therapy. In this context, a meta-analysis of patients with a history of CAD demonstrated that exercise therapy alone can improve the prognosis.

7. Therapy (Drug Therapy)

Following the initiation of drug therapy, lifestyle modification (Step 6) should be continued.

Step 7A: Drug Therapy for Dyslipidemia

- If a patient cannot achieve their target LDL-C level following adequate lifestyle modification in primary prevention, drug therapy should be considered according to the weight of the risk.
- If a patient in category I persistently has an LDL-C level of ≥ 180 mg/dL, drug therapy should be considered.
- Statins are recommended for the treatment of hyper-LDL cholesterolemia.
- In patients with high-risk hyper-LDL cholesterolemia, the use of ezetimibe in combination with a statin should be considered.
- In patients with high-risk hyper-LDL cholesterolemia, the use of eicosapentaenoic acid (EPA) in combination with a statin should be considered.
- In patients with hypertriglyceridemia accompanied by hypo-HDL cholesterolemia, drug therapy with fibrates, niacinic acid derivatives or other similar drugs should be considered according to the weight of the risk.

There is abundant evidence that LDL-C-lowering therapy with statins can prevent CVD. If a patient with dyslipidemia cannot achieve their target level with a single drug, dose escalation of the drug or the use of combination therapy should be considered. The Japan EPA Lipid Intervention Study (JELIS) conducted in Japanese patients with hyper-LDL cholesterolemia revealed that those who received statins in combination with EPA developed significantly fewer major coronary events compared with patients who received statins alone.

In patients with renal dysfunction, since rhabdomyolysis occurs more frequently with the use of statins or fibrates, the combination therapy of statins and fibrates is contraindicated.

Step 7B: Drug Therapy for Hypertension

- In patients with hypertension, drug therapy should be considered if the office blood pressure is > 140/90 mmHg (home blood pressure: 135/85 mmHg) after a certain period of adequate lifestyle modification (three months in low-risk patients or one month in moderate-risk patients). In high-risk patients with hypertension complicated by DM, CKD, CVD or organ damage, the initiation of drug therapy should be considered while the patient is encouraged to modify their lifestyle.

- One of the following five types of drugs should be selected as the first choice: Ca-antagonists, angiotensin II-receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACE inhibitors), diuretics or β-blockers (including α/β-blockers). The drug should be selected according to each patient's condition while giving due consideration to the positive indications, relative contraindications and contraindications of each drug.

- Combination therapy is required in many cases to achieve the goal of hypertension treatment. Recommended combination therapies include renin-angiotensin (RA) inhibitors (ARBs or ACE inhibitors) and Ca-antagonists, RA inhibitors and diuretics, Ca-antagonists and diuretics and Ca-antagonists and β-blockers.

- When antihypertensive treatment is administered, appropriate drugs should be selected according to each patient's condition.

- RA inhibitors are recommended as the first-line drugs for patients with organ damage, such as those with proteinuria or renal dysfunction, heart failure, old myocardial infarctions (MIs) or DM. However, for patients with renal dysfunction (a serum creatinine level of > 2.0 mg/dL), careful administration is desirable since the renal function may be worsened. The administration of such drugs in pregnant or lactating women is contraindicated. When RA inhibitors are used in combination with K-sparing diuretics, attention should be paid to the possibility of hyperkalemia. In patients with bilateral renovascular hypertension, caution should be exercised since rapid progression of renal dysfunction may be observed following the administration of RA inhibitors.

- β-blockers are not used as first-line drugs in the elderly or patients with impaired glucose tolerance, since monotherapy or combination therapy with diuretics may exacerbate glucose/lipid metabolism. Generally, the combination of β-blockers and diuretics is not recommended.

Step 7C: Drug Therapy for DM

- In patients with non-insulin-dependent type 2 DM, drug therapy should be considered if good glycemic control cannot be achieved after two to three months of lifestyle modification, including adequate diet and exercise therapy.

- However, drug therapy may be administered in the early stage of the disease in patients exhibiting a poor
response to lifestyle modification or a certain degree of metabolic disorder.

- Available oral drugs include sulfonylureas (SUs), fast-acting insulin secretagogues, α-glucosidase inhibitors, biguanides, thiazolidines and dipeptidyl peptidase-4 (DPP-4) inhibitors.
- Glucagon-like peptide (GLP)-1-receptor agonists are available in injectable forms.
- Insulin therapy should preferably be initiated after consulting diabetes specialists. Insulin may be administered in combination with oral drugs.

When drug therapy is prescribed, attention should always be paid to hypoglycemia, and the patient should be provided adequate guidance.

For insulin-dependent diabetic patients, such as those with type 1 DM, insulin therapy is required; therefore, referral to and close cooperation with a specialist during ongoing treatment is needed. For patients with type 2 DM who have severe metabolic derangement, severe infection or a history of invasive surgery, insulin therapy is required, and a specialist should be consulted.

For other non-insulin-dependent patients, adequate education should be provided regarding lifestyle modification, such as appropriate diet and exercise therapy. If the target for glycemic control cannot be achieved after two to three months of treatment, the initiation of drug therapy should be considered. The glycemic control target will vary for each patient according to the patient’s condition.

In patients with increased insulin resistance, such as those with obesity, biguanides and thiazolidines are good choices. For patients with a decreased insulin secretory capacity, SUs and DPP-4 inhibitors are indicated. To correct postprandial hyperglycemia, fast-acting insulin secretagogues, α-glucosidase inhibitors and DPP-4 inhibitors are good options.

GLP-1-receptor agonists are analogs of the incretin GLP-1 that promote insulin secretion and decrease both fasting blood glucose and postprandial blood glucose.

Attention should be paid to adverse reactions specific to each drug, including weight gain with SUs, gastrointestinal symptoms (such as abdominal bloating and diarrhea) with α-glucosidase inhibitors, reactions to the use of iodinated contrast agents with biguanides and heart failure or edema caused by thiazolidines.

Various insulin preparations with different durations of action and dosage forms are available. Insulin therapy should be initiated after consulting with a diabetes specialist, if possible. Selecting the proper insulin preparation and adjusting the timing and number of injections according to the patient’s lifestyle is required. Providing guidance regarding the procedures of injection and self-monitoring of blood glucose is also important.

**Step 7D: Other Drug Therapy**

- Antiplatelet therapy is effective for the secondary prevention of CAD and noncardiogenic cerebral infarction. Attention should always be paid to the development of adverse drug reactions, such as hemorrhagic complications, during the administration of this regimen.

The inhibitory effects of low-dose aspirin (75 to 150 mg/day) on cardiovascular events in patients with a history of MI were demonstrated in a meta-analysis\(^\text{13}\), and the effectiveness of this medication in Japanese individuals was shown in the Japanese Antiplatelet Myocardial Infarction Study (JAMIS)\(^\text{14, 15}\).

However, the results of a recent meta-analysis revealed that the inhibitory effects of aspirin treatment on cardiovascular death in the primary prevention of CVD may be offset by an increased risk of hemorrhagic complications\(^\text{16}\), suggesting that administration without careful consideration should be avoided\(^\text{17}\).

Among Japanese individuals, the J-PAD showed no inhibitory effects of low-dose aspirin on cardiovascular events in patients with type 2 DM\(^\text{18}\), while a subanalysis demonstrated inhibition of cardiovascular events in elderly subjects ≥65 years of age and patients with moderate renal dysfunction\(^\text{18}\).

To prevent the recurrence of noncardiogenic cerebral infarctions, such as atherothrombotic and lacunar infarctions, the administration of low-dose aspirin or clopidogrel is recommended. Cilostazol is also effective for decreasing the recurrence of cerebrovascular disease. However, managing blood pressure is the most important measure for preventing the recurrence of lacunar infarctions\(^\text{19}\).

Cilostazol is effective to some extent in improving the symptoms of PAD, such as intermittent claudication. The administration of aspirin is effective for improving patency following revascularization or endovascular treatment. Furthermore, aspirin and clopidogrel have been demonstrated to be effective for preventing cerebrovascular death in patients with PAD\(^\text{20, 21}\).

**Footnotes**

This is an English version of the guidelines of the Japan Atherosclerosis Society (chapter 2) published in Japanese in June 2012.
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References

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

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

*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

<table>
<thead>
<tr>
<th>Start:</th>
<th>Yes</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Screening for dyslipidemia</td>
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<td></td>
</tr>
<tr>
<td>History of coronary artery disease (CAD)</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any of the following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Noncardiogenic cerebral infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4) PAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary prevention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target for LDL-C &lt; 100 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category III</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.