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Supplemental Table 1. 5A Approach

Step
Step 1: Ask (Identify all smokers systematically at each examination.)
Step 2: Advise (Clearly, strongly, and individually advise all smokers to stop smoking.)
Step 3: Assess (Assess the desire to smoking cessation.)
Step 4: Assist (Assist patients in smoking cessation.)
Step 5: Arrange (Arrange a schedule of follow-up examinations.)

Strategies for implementation

Step 1

- Prepare a system within the medical organization to ensure that all patients are asked about smoking at each examination and the answers are recorded.
- Add a space for smoking (to distinguish current, former, and non-smokers) to the section of vital signs such as the blood pressure, heart rate, body temperature, and body weight. Alternatively, attach a sticker indicating the smoking status to all charts.

Step 2

- Clearly: "It is important for you to stop smoking now. I am ready to help you." or "It is not enough to cut back on smoking only when you are sick."
- Strongly: "As your attending physician, I must let you know that smoking cessation is the most important step you can take to protect your health. I and the hospital staff are ready to help you."
- Individually: Relate smoking with the current state of health/disease, social and economic cost, motivation/desire to quit smoking, and impact on children and family.

Step 3

- Ask all smokers if they are willing to stop smoking now (within 30 days).
  If they are, support them in cessation.
  If they are not, motivate them to cessation.

Step 4

Assist patients to make a plan of smoking cessation.

- Set a date to start smoking cessation (preferably within 2 weeks)
- Tell family, friends, and colleagues about smoking cessation and ask for their understanding and support.
- Mentally prepare for problems that will arise in smoking cessation (particularly during the first few weeks) in advance. They include nicotine-withdrawal symptoms.
- Eliminate tobacco from the environment on smoking cessation. Before smoking cessation, avoid smoking in places where you spend prolonged periods of time such as the office, home, and car.

Counsel the patients (training in problem-solving skills)

- It is important not to smoke even a single cigarette: Not even a puff is permitted after the day you start to quit.
- History of smoking cessation: Look back on what helped and interfered with smoking cessation during past attempts.
- Alcohol: Since alcohol consumption may lead to a resumption of smoking, patients should reduce or give up drinking during smoking cessation.
- Smokers in the family: Smokers in the family make smoking cessation difficult. Persuade these family members to quit smoking at the same time or not to smoke in the patient's presence.

Provide social support in medical activities

- Say, "I and my staff are always ready to help you."

Help the patients to receive social support from people other than medical professionals.

- Say, "Ask your spouse/partner, friends, and colleagues for social support."

Recommend undergoing drug therapy

- Recommend the use of drugs with established efficacy. Explain how these drugs increase the success rate of smoking cessation and alleviate withdrawal symptoms.
- Use a nicotine-replacing agent and bupropion hydrochloride SR (not approved in Japan) as the first choices.

Provide supplementary study materials

- Select study materials appropriate for the characteristics of the patient from those published by the government or NPOs.

Step 5

- Timing: The first follow-up examination should be scheduled immediately after the beginning of smoking cessation, within 1 week if possible. The second should be scheduled within 1 month. Make a schedule for subsequent follow-ups.
- What should be done in follow-up examinations: Congratulate the patient on smoking cessation. If the patient has started smoking again, study the situation, and advise them to try again. Advise the patient to regard the failure as a chance to learn for future success. Anticipate problems that have actually arisen and those expected to arise.
- Assess the use of drug therapy and its problems. Evaluate the possibility of the use of, or suggestion to use, stronger treatments.

Supplemental Table 2. Classification of Overweight and Diagnostic Criteria for Obesity

Definition of overweight

A state in which fatty tissue is excessive and BMI is ≥ 25 kg/m^2.

Classification of overweight

Overweight should be classified according to the table below based on the body mass index: BMI = body weight (kg)/[height (m)]^2.

Overweight index

BMI (kg/m^2)	Category	WHO criteria
< 18.5	Low weight	Under weight
18.5 ≤ - < 25	Normal weight	Normal range
25 ≤ - < 30	Overweight (grade I)	Pre-obese
30 ≤ - < 35	Overweight (grade II)	Obese class I
35 ≤ - < 40	Overweight (grade III)	Obese class I
40 ≤	Overweight (grade IV)	Obese class III

Note 1: It should be noted that overweight (BMI ≥ 25) is not always a state that medically requires weight loss. The standard body weight (ideal body weight) should be calculated with the following formula: standard body weight (kg) = height (m)^2 × 22. This is based on a BMI of 22, which is most unlikely to be associated with disease.

Note 2: BMI ≥ 35 should be defined as severe overweight.

Definition of obesity

Obesity is a state in which health problems have been caused by or are related to overweight, or a state in which weight loss is indicated medically because problems are anticipated, and should be treated as a disease entity.

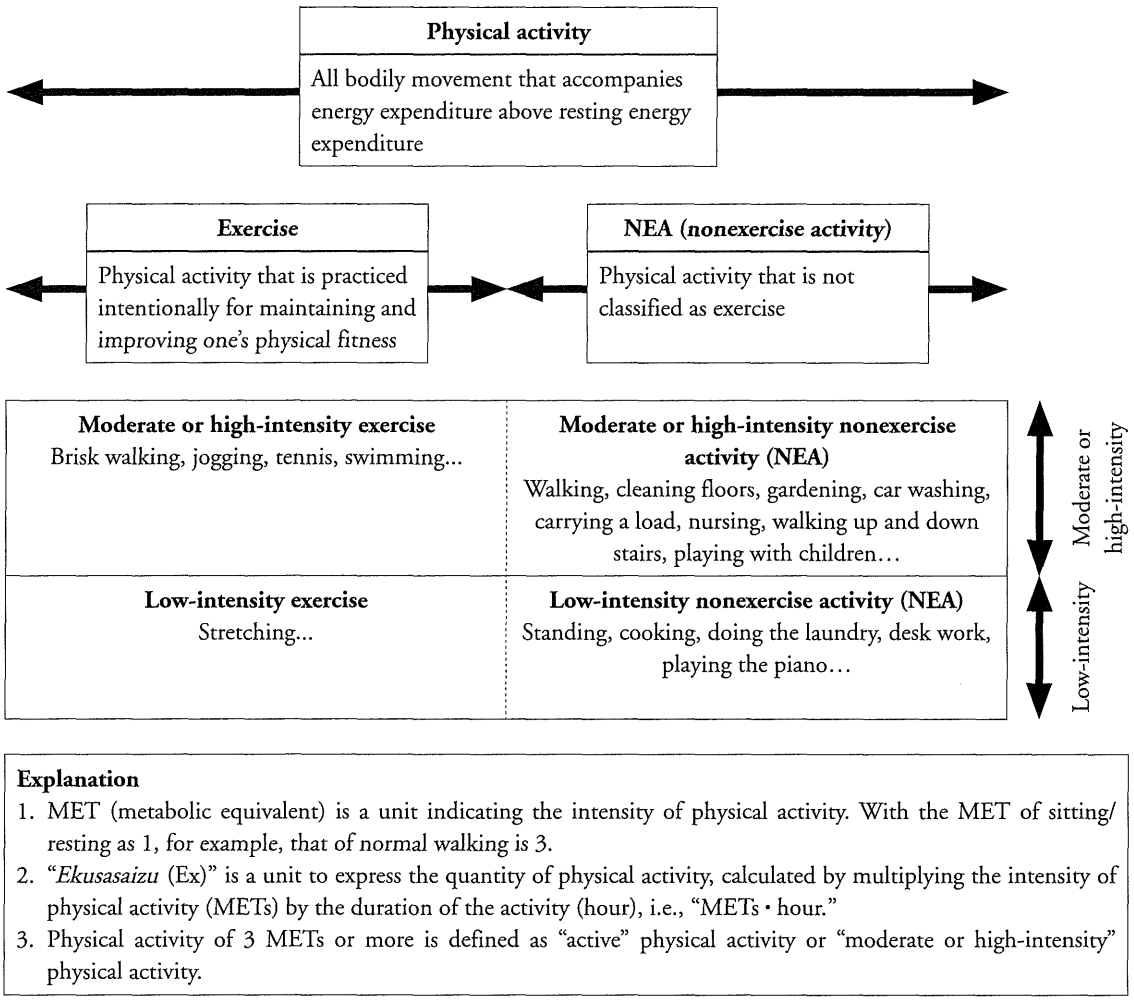
Diagnosis of obesity

The patient is overweight (BMI ≥ 25) and meets any of the following criteria:

1. The patient has health problems caused by or related to overweight and weight loss is required (the problems can be improved or progression can be prevented by weight loss).
2. There is a high risk of health problems if the patient does not lose weight.
   Visceral fat accumulation is suspected by screening of the waist circumference and visceral obesity is definitively diagnosed by abdominal CT scanning.

Japan Society for the Study of Obesity, ed.: 2011 Diagnostic Guidelines for Obesity. Study of Obesity, 2011:17 (extra edition) opening chart P1, Table A

Supplemental Table 3A.



Explanation

1. MET (metabolic equivalent) is a unit indicating the intensity of physical activity. With the MET of sitting/resting as 1, for example, that of normal walking is 3.
2. "*Ekusasaizu* (Ex)" is a unit to express the quantity of physical activity, calculated by multiplying the intensity of physical activity (METs) by the duration of the activity (hour), i.e., "METs • hour."
3. Physical activity of 3 METs or more is defined as "active" physical activity or "moderate or high-intensity" physical activity.

Adapted from the Ministry of Health, Labour and Welfare's "Exercise and Physical Activity Guide for Health"

Supplemental Table 3B. Goals for the Quantity of Physical Activity to Prevent Lifestyle-Related Diseases

Basic goal	23 Ex (METs • hour) per week by physical activity, of which 4 Ex is active exercise.
Goal to reduce visceral fat	About 10 Ex/week or more of exercise is required to ensure a reduction in visceral fat.
Specific examples of physical activity	Example 1) Physical activity corresponding to 23 Ex per week: walking 8,000 to 10,000 steps per day 7 days per week Example 2) Exercise corresponding to 4 Ex: brisk walking for 60 mins or tennis for 40 min Example 3) Exercise corresponding to 10 Ex: 30 min brisk walking 5 days per week

(Examples of exercise and physical activity corresponding to 1 Ex are shown in Supplemental Table 4)

Adapted from the Ministry of Health, Labour and Welfare's "Exercise and Physical Activity Guide for Health Promotion 2006."[123]

Supplemental Table 3C. Examples of Physical Activity Corresponding to 1 Ex

	Activities	Time(min)
Examples of exercise corresponding to 1 Ex	Bowling, volleyball, frisbee, weight lifting (light or moderate effort)	20
	Brisk walking, radio calisthenics, golf (using a power cart), table tennis, badminton, aquabics, Tai Chi	15
	Light jogging, weight lifting (vigorous effort), jazzercise, aerobics, basketball, swimming (leisurely), soccer, tennis, skiing, skating	10
	Running, swimming, judo, karate	7~8
	Walking, sweeping the floor, loading/unloading a car, childcare, car washing	20
Examples of NEA corresponding to 1 Ex	Brisk walking, cycling, nursing, gardening, walking/running - playing with child(ren), moderate intensity	15
	Mowing the lawn, walking, using a power mower; moving furniture; climbing stairs; shoveling snow by hand	10
	Carrying heavy loads	7~8

Cited from the Ministry of Health, Labour and Welfare's "Exercise and Physical Activity Guide for Health Promotion 2006."[123]

Explanation

In 2006, the preparation committee proposed the creation of an exercise reference and exercise guide for health promotion[124]. In this guide, "physical activity" is defined as "all bodily movement that accompanies energy expenditure above resting energy expenditure," and is classified into "exercise" that is practiced intentionally for maintaining and improving one's physical fitness and "nonexercise activity (NEA)" (Supplemental Table 3A). To prevent lifestyle-related diseases, walking about 8,000 to 10,000 steps per day or corresponding physical activity and moderate exercise suitable for individuals (e.g., brisk walking for 60 minutes per week, tennis for 40 minutes) is recommended (Supplemental Tables 3B and 3C). Trying to use the stairs instead of an escalator or lift is considered to be an effective way to increase muscle strength in daily living. Furthermore, exercise involving 30 minutes brisk walking 5 times a week is required to ensure a reduction in visceral fat.

Committee Report 7-B

Treatment B) Drug Therapy

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. Drug Therapy

"Evidence-based medical therapy from the results of large-scale clinical trials" has been emphasized, and drug therapy is widely used for both primary and secondary prevention. However, with respect to the prevention of atherosclerotic cardiovascular disease (CVD), the basis for treatment is lifestyle modification, such as changing dietary habits, increasing physical activity, maintaining an ideal body weight and quitting smoking. In particular, in primary prevention, the risk factors for atherosclerosis should be evaluated correctly and treatment should be selected depending on the patient's risk. In other words, it is important to not only ascertain the presence or absence of coronary artery disease (CAD) and measure the LDL-cholesterol (LDL-C) level, but also identify other major risk factors, including complications of CVD other than CAD, such as non-cardiogenic cerebral infarction, peripheral arterial disease (PAD) and carotid atherosclerosis, and complications of diabetes mellitus (DM) or chronic kidney disease (CKD), and then to perform an absolute risk evaluation and provide lipid management based on the guidelines. On the other hand, in secondary prevention, providing strict lipid management is essential, and the need for drug therapy is significant. Additionally, in secondary prevention patients, risks should be stratified, and more strict lipid-lowering therapy should be considered in those at a higher risk of recurrence.

2. Indications for Drug Therapy

1) LDL-C-Lowering Drugs

The absolute risk of CAD in the Japanese population is relatively low compared to that observed in Western populations, while the relative risk of LDL-C and CAD in Japanese patients is similar to that observed in Western patients. In the MEGA study[1], a large-scale clinical trial in Japan, the significance of LDL-C-lowering therapy using statins for primary prevention in patients with hypercholesterolemia was confirmed in a Japanese population. However, in primary prevention, drug therapy should not be selected without carefully considering the individual's risk; such therapy should be considered only in patients with a high absolute risk. Low-risk patients without any additional risk factors, young individuals and premenopausal women at low absolute risk can be followed up with lifestyle modification only, even if the management target is not achieved. Following strict lifestyle modification, and only if the management target is not achieved, drug therapy should be considered according to the level of risk. However, if a patient persistently has an LDL-C level of ≥ 180 mg/dL, considering drug therapy given the possibility of familial hypercholesterolemia (FH) is appropriate (see committee report 9: **Familial Hypercholesterolemia**).

Meanwhile, if type 2 diabetes, CKD, non-cardiogenic cerebral infarction or PAD is observed, the disease itself puts the patient at high risk for cardiovascular events. In such cases, strict lipid management based on the treatment/management guidelines is therefore required, and strict LDL-C-lowering therapy involving drug therapy should be considered at an early stage.

Large-scale clinical trials in secondary prevention patients, including the 4S, CARE and LIPID trials, have reported that LDL-C-lowering therapy using statins is effective. Subsequently, the safety and effectiveness of statin treatment in reducing cardiovascular

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events after acute coronary syndrome were reported[2-5]. Providing early strict lipid management is important for the long-term inhibition of cardiovascular events[4, 6, 7]. The development of statins with more potent LDL-C-lowering effects has improved the rates of achievement of LDL-C management targets in Western countries and Japan, while the rates of achievement of management targets in secondary prevention patients remain insufficient. Therefore, in order to achieve the target of LDL-C <100 mg/dL in the setting of secondary prevention, the use of lifestyle modification along with drug therapy is required. In secondary prevention, among patients at higher risk, such as those with acute coronary syndrome, current smoking habits, CAD complicated by metabolic syndrome, type 2 diabetes, non-cardiogenic cerebral infarction, PAD or CKD, achieving the LDL-C target (<100 mg/dL) is essential and providing early, strict LDL-C management using drug therapy is important.

2) TG-Lowering Drugs and HDL-C-Increasing Drugs

Large-scale clinical studies in patients with high triglyceride (TG), low HDL-C and normal LDL-C levels have not shown as much positive evidence as that for LDL-C-lowering therapy[8-12]. However, the subanalysis of the ACCORD Lipid Trial[13] revealed that combination therapy with fibrates and statins is effective in patients with high TG and low HDL-C levels; thus, further investigation is warranted. If the TG level is high, using the non HDL-C level as the lipid management target is recommended; however, there is little evidence with respect to using non HDL-C as a target, and thus continued discussion is required. In case of primary prevention, encouraging lifestyle modification with the primary goal of lipid management using the LDL-C level as a target is important. In patients with a remarkably increased TG level of ≥1,000 mg/dL, dietary interventions, such as lipid restriction and alcohol abstinence, along with treatment with fibrates should be considered, because they have a high risk for acute pancreatitis.

Additionally, in patients with a history of CAD, similar to that observed in primary prevention, there is insufficient evidence for the use of drug therapy for dyslipidemia without hyper-LDL cholesterolemia. However, in secondary prevention patients at higher risk for recurrence of cardiovascular events, in addition to providing management of the LDL-C level at <100 mg/dL, the use of combination drug therapy with drugs other than statins, such as fibrates and nicotinic acid derivatives, can be considered according to the type of dyslipidemia.

There are many reports regarding treatment evidence, suggesting the appropriateness of drug therapy. These reports are summarized in the reference tables at the end of the guidelines.

3. Characteristics and Criteria for Selecting Various Drugs

The classification of drugs used to treat dyslipidemia according to efficacy is shown in **Table 1**. The efficacy of these drugs was confirmed using a double-blind method in Japan. The characteristics and efficacy of various drugs should be understood, and selecting safe and effective drugs should be undertaken taking into consideration the presence of comorbidities and the possibility for drug interactions. The characteristics of various drugs used to treat dyslipidemia are described below.

1) HMG-CoA Reductase Inhibitors (Statins): Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, Pitavastatin and Rosuvastatin

Statins are indicated for the treatment of dyslipidemia with a high LDL-C level.

Since the effect was shown in FH patients[14], statins are the most effective in decreasing the LDL-C level among the lipid-lowering drugs. Statins competitively inhibit HMG-CoA reductases, the rate-limiting enzymes of cholesterol synthesis, inhibit cholesterol synthesis[15], promote the synthesis of LDL receptors and decrease serum LDL-C[16]. The degree of LDL-C-lowering ranges from 20% to 50%. Furthermore, the inhibition of VLDL synthesis and secretion in the liver due to decreased cholesterol synthesis also results in a decreased TG level[17]; however, the degree of lowering is only approximately 10% to 20%. Reported adverse drug reactions include hepatic disorders and myopathic symptoms, such as increased creatinine kinase (CK) and muscular weakness. Rhabdomyolysis characterized by increased myoglobin in the blood and urine has also been reported, although this complication is very rare. This risk is increased by combining statins with fibrates, nicotinic acid derivatives, cyclosporine or erythromycin.

Previous reports have demonstrated that patients who use statins incidentally during early pregnancy can experience suspected teratogenicity[18]; therefore, at present, statins should not be used in women who wish to become pregnant and patients in pregnancy.

2) Anion Exchange Resins (Resins): Colestimide and Cholestyramine

Resins are indicated for the treatment of dyslipidemia with a high LDL-C level (type IIa). Although the first-line drugs for hyper-LDL cholesterolemia are

Table 1. Classification of Drugs Used to Treat Dyslipidemia According to Efficacy

Classification	LDL-C	TG	HDL-C	Non HDL-C	Major generic name
Statins	↓↓↓	↓	↑	↓↓↓	pravastatin,* simvastatin,* fluvastatin,* atorvastatin,* pitavastatin* and rosuvastatin
Anion exchange resins	↓↓	↑	↑	↓↓	colestimide and cholestyramine
Small intestine cholesterol transporter inhibitor	↓↓	↓	↑	↓↓	ezetimibe
Fibrates	↓	↓↓↓	↑↑	↓	bezafibrate,* fenofibrate, clinofibrate* and clofibrate*
Nicotinic acid derivatives	↓	↓↓	↑	↓	niceritrol, nicomol* and tocopheryl nicotinate*
Probucol	↓	–	↓↓	↓	probucol*
ω3PUFA	–	↓	–	–	ethyl icosapentate* and omega-3-acid ethyl esters

*A generic drug is available. PUFA: polyunsaturated fatty acid
↓↓↓: ≤ −25%; ↓↓: −20 to −25%; ↓: −10 to −20%; ↑: 10 to 20%; ↑↑: 20 to 30%

statins, resins may be the first-line drugs in patients who cannot tolerate statins due to adverse drug reactions and pregnant women or women of childbearing potential who require drug therapy. The greatest benefit of resin treatment lies in the use of combination therapy with statins.

Cholestyramine is a drug whose inhibitory effects on the development of CAD were first proven in large-scale clinical studies[19, 20]. Resin adsorbs bile acids in the intestines and inhibits the intestinal circulation of bile acids via reabsorption, thereby promoting catabolism from cholesterol to bile acids. This catabolism leads to decreased sterol pools in the body and enhanced synthesis of LDL receptors in the liver, resulting in decreased LDL-C[21]. However, at the same time, HMG-CoA reductases may be activated in the liver, thereby enhancing cholesterol synthesis. Therefore, combining these drugs with statins is extremely reasonable. In contrast, bile acids act as ligands for the nuclear receptor FXR and are involved in regulating TG metabolism by inhibiting the SREBP1c expression and enhancing the lipoprotein lipase (LPL) activity; thus, resin treatment results in a decreased LDL-C level, together with synthesis of VLDL and an increased serum TG level, resulting from the absorption of bile acids. Adverse drug reactions primarily include gastrointestinal symptoms, such as constipation and bloating; however, no serious reactions have been observed because these drugs are nonabsorbable. Resins have been shown to absorb concomitant drugs, such as statins, digitalis, warfarin, thiazide diuretics and thyroid gland preparations; therefore, when these drugs are concomitantly used, instructions to take the drugs at a suitable interval must be provided to ensure drug efficacy.

3) Probucol

Probucol is indicated for the treatment of dyslipidemia with a high LDL-C level (type IIa). This drug is characterized by its effects of regression on xanthomas. However, this drug decreases both the LDL-C and HDL-C levels.

The degree to which probucol lowers LDL-C is 15% to 25%. The mechanism underlying this phenomenon is thought to involve enhanced LDL catabolism, particularly via the promotion of cholesterol excretion in bile. In contrast, the mechanism underlying the decreased HDL-C level is thought to involve the inhibition of ABCA1, a membrane protein essential for HDL production. Other possible mechanisms include the enhanced activity of cholesterol ester transfer proteins (CETPs) and enhanced activity of SR-BI, an HDL receptor. From the viewpoint of cell biological factors[22, 23], immunohistological factors[24, 25] and other factors, LDL-C oxidation is clearly an important aspect of the pathogenic mechanisms of atherosclerosis. Probucol is taken up by lipoproteins, after which it exerts potent antioxidant effects due to its structure in which two fat-soluble butylated hydroxytoluene (BHT) antioxidants are bound. An early clinical study demonstrated that cholestyramine treatment in combination with additional probucol exerts no inhibitory

effects on the progression of atherosclerosis in the femoral artery on angiography[26]. However, subsequent clinical studies and observational studies demonstrated inhibitory effects on restenosis[27, 28] and improvements in long-term survival[29] following percutaneous transluminal coronary angioplasty (PTCA), inhibitory effects on the progression of the carotid intima-media thickness (IMT), inhibitory effects on cardiovascular events[30] and secondary prevention effects in patients with heterozygous FH[31]. In any case, because no large-scale clinical studies have been conducted, the use of probucol is limited to combination therapy with statins and monotherapy in patients who cannot tolerate statins. Adverse drug reactions include gastrointestinal symptoms, hepatic disorders, rashes, QT prolongation and torsade de pointes on electrocardiograms.

4) Nicotinic Acid Derivatives: Niceritrol, Nicomol and Tocopheryl Nicotinate

Nicotinic acid derivatives are indicated for the treatment of hyper-LDL cholesterolemia, hypertriglyceridemia and dyslipidemia accompanied by increased remnant lipoproteins.

The mechanism of action of these drugs involves the inhibition of hormone-sensitive lipases, thereby inhibiting lipolysis in peripheral fatty tissue and decreasing the influx of free fatty acids into the liver, resulting in the inhibition of lipoprotein synthesis in the liver. In addition, these drugs exert HDL-C-increasing effects by inhibiting apolipoprotein A-I catabolism. The rate of decrease in TG following nicotinic acid monotherapy (3.0 g/day) is 26%[32]. Nicotinic acid derivatives also have Lp(a)-lowering effects[33-35]. Major adverse drug reactions include itching and hot flashes due to peripheral vasodilation. Because insulin resistance may be exacerbated, these drugs should be carefully administered in patients with DM.

5) Fibrates: Bezafibrate and Fenofibrate

Fibrates are most effective for hypertriglyceridemia. In particular, fibrates are markedly effective for type Ⅲ hyperlipidemia because they enhance the catabolism of remnant lipoproteins. These drugs are also highly effective in increasing HDL-C.

The major mechanism of action is the activation of PPARα, a nuclear receptor, by fibrates acting as a ligand for PPARα[36, 37], which results in the following: (i) enhanced beta-oxidation of fatty acids and decreased TG production in the liver; (ii) increased LPL production; (iii) decreased Apo C-Ⅲ production and enhanced LPL activity, leading to the promotion of TG degradation and catabolism from VLDL to LDL; and (iv) increased production of Apo A-I and A-Ⅱ. As a result, the TG level decreases and the HDL-C level increases. Bezafibrate has a TG-lowering effect of 30% to 40%, a TC-lowering effect of approximately 10% and an HDL-C-increasing effect of 35% to 45%. Fenofibrate is characterized by a long half-life, exerts an effect on lipids and has a uric acid-lowering effect. Regarding major adverse drug reactions, rhabdomyolysis is likely to occur in patients with renal dysfunction; the incidence of this complication increases in combination with statins.

6) EPA: Ethyl Icosapentate

EPA is indicated for the treatment of dyslipidemia accompanied by increased TG, especially for type Ⅱb and Ⅳ hyperlipidemia. EPA inhibits VLDL synthesis in the liver, thereby decreasing the TG level, and has a slight HDL-C-increasing effect. The results of epidemiological studies and secondary prevention studies have demonstrated that the intake of fish oil and n-3 polyunsaturated fatty acids helps to prevent cardiovascular events. The JELIS[38] study conducted in Japan found that patients who received statins in combination with additional EPA exhibited a significant reduction in the incidence of major cardiovascular events compared to patients who received statin monotherapy, indicating the efficacy of EPA. In addition to its effects on lipids, EPA is expected to have antiplatelet and anti-inflammatory effects in preventing atherosclerosis. Regarding major adverse drug reactions, gastrointestinal symptoms, such as diarrhea and bleeding, should be noted.

7) Small Intestine Cholesterol Transporter Inhibitor: Ezetimibe

This drug inhibits Niemann-Pick C1-Like 1 (NPC1L1), a small intestine cholesterol transporter that exists in the small intestinal mucosa and inhibits the absorption of cholesterol in the small intestine derived from diet and bile, thereby exerting a serum cholesterol-lowering effect[39]. Unlike resins, this drug is absorbed in the body and enters the intestinal circulation, although approximately 78% of the drug is excreted in feces. Because this drug selectively inhibits cholesterol absorption, the absorption of fat-soluble vitamins, such as vitamins A and D, is not affected. The usual dose (10 mg/day) decreases the LDL-C level by approximately 18%, and, similar to resins, this drug enhances cholesterol synthesis in the liver. Therefore, the use of combination therapy with statins is ideal and also provides a synergistic effect; combination therapy with 10 mg of ezetimibe and a statin at a usual dose decreases the LDL-C level by approximately

35% to 50%[40-42], which is equivalent to the effects achieved using a maximum dose of statin monotherapy. Furthermore, the HDL-C level is increased by 8% to 9%, while the TG level is decreased by 20% to 30%. Major adverse drug reactions include gastrointestinal symptoms; however, no significant differences are observed compared to a placebo. Similar to that observed with statins, myopathic symptoms, such as increased CK and muscular weakness, although rare, have been reported, and there are no reports indicating that the use of combination therapy with statins increases the incidence of adverse drug reactions.

4. Combination Therapy

If the therapeutic target values for dyslipidemia are not achieved with treatment with a single agent, increasing the dose or administering combination therapy with other lipid-lowering drugs can be considered. In particular, in secondary prevention, when the target LDL-C value is less than 100 mg/dL, achieving the therapeutic goal with a single agent is sometimes difficult. In such cases, the use of combination therapy with several classes of agents should be considered. Upon the initiation of combination therapy, the characteristics of each drug described above should be fully considered in order to achieve maximal benefits and minimal adverse effects. Several studies performed in Western countries have shown that combination therapy is effective in inhibiting the progression or inducing the regression of atherosclerotic lesions. In these studies, combination therapy with statins and resins[39] decreased the total cholesterol (TC) and LDL-C levels by 34% and 46%, respectively, while combination therapy with high dose of resins and nicotinic acid derivatives[40, 44] decreased the LDL-C and TG levels up to 43% and 22%, respectively. Likewise, in Japan, combination therapy with pravastatin and colestimide[41, 43] has been reported to decrease the TC and LDL-C levels by 26% and 37%, respectively, and increase the HDL-C level by 21%, thus indicating the efficacy of combination therapy.

Combination therapies that have been proven to be effective in improving serum lipid profiles in Japanese populations include the following: (1) statins and resins[43, 45, 46]; (2) statins and fibrates[47, 48]; (3) statins and probucol[49]; (4) statins and nicotinic acid derivatives[50]; (5) probucol and nicotinic acid derivatives[51]; (6) statins, probucol and resins[52, 53]; and (7) statins and ezetimibe. The administration of statins in combination with ezetimibe or resins is theoretically the most effective means of decreasing the LDL-C level. Furthermore, the combination of statins and ezetimibe exerts TG-lowering and HDL-C-increasing effects. Combination therapy with statins and nicotinic acid derivatives results in decreased cholesterol and increased HDL-C levels. Among the above mentioned combination therapies, the combination of statins and fibrates should be administered with caution because this combination has a high risk of inducing rhabdomyolysis. According to the postmarketing survey conducted under the instructions of the Ministry of Health, Labour and Welfare, most patients who develop rhabdomyolysis following the coadministration of statins and fibrates have renal disorders; thus, if laboratory tests reveal an abnormal renal function, the use of combination therapy with statins and fibrates should be avoided.

5. Follow-Up of Drug Therapy

Following the initiation of pharmacological intervention, the efficacy and side effects of the agent should be monitored. In general, monitoring the patient every month for the first three months and at least every three months thereafter is recommended.

In order to detect side effects using blood tests, performing liver function tests [AST (GOT), ALT (GPT), LD (LDH), ALP, γGTP and total bilirubin], renal function tests (urinalysis, serum creatinine and BUN) and assessments of CK and blood cell counts is recommended.

6. Combination Therapy with Lipid-Lowering Drugs and Other Agents to Prevent Atherosclerosis

1) Precautions for Drug Combination

Fat-soluble drugs are excreted after being catabolized to water-soluble compounds by cytochrome P450 (CYP) in the liver. Among statins, drugs other than pravastatin and rosuvastatin are fat-soluble and metabolized by CYP. Because hypertension and dyslipidemia are common diseases, many patients suffer from both conditions; thus, the frequency of prescribing both antihypertensive and lipid-lowering agents is estimated to be high. Most calcium channel blockers (CCBs) and some angiotensin II receptor blockers (ARBs) are catabolized by CYP (**Table 2**); therefore, the coadministration of agents metabolized by the same CYP may increase the blood concentration of each agent, resulting in an increased incidence of adverse reactions. Thus far, no reports have documented an increased incidence of adverse events following the administration of combination therapy with statins and either CCBs or ARBs; however, attention must always be paid to possible drug interactions when these medications are coadministered.

Bile acid-binding resins adsorb drugs with negative charges. As a consequence, resins may cause

Table 2. Statins and Cardiovascular Drugs Metabolized by CYP

CYP	Statin	Cardiovascular drug
CYP2C9	Fluvastatin (Pitavastatin)* (Rosuvastatin)*	ARBs (losartan, valsartan, and candesartan) and warfarin
CYP3A4	Simvastatin Atorvastatin	Ca-antagonists (diltiazem, verapamil, nifedipine, amlodipine, cilnidipine, azelnidipine, and benidipine) and warfarin

*Pitavastatin and rosuvastatin are also minimally metabolized by CYP2C9.

delayed and/or decreased absorption of beta-blockers and thiazide diuretics. Furthermore, because resins theoretically inhibit the absorption of hydrophobic agents, they may inhibit the absorption of fat-soluble drugs, such as statins, CCBs and ARBs. Therefore, in patients who can adhere to a somewhat sophisticated medication schedule, taking fat-soluble drugs one to four hours before or ≥4 hours after taking a resin is recommended.

Warfarin is one of the most commonly prescribed agents for CVD; however, it interacts with many drugs. Therefore, caution should be taken when prescribing warfarin with other drugs. When warfarin is administered together with simvastatin, fluvastatin, rosuvastatin or fibrates, its effects are augmented. In contrast, the effects of warfarin are reduced when administered with resins. Physicians must also keep in mind that the co-administration of EPA together with warfarin may increase the risk of hemorrhagic events, as EPA inhibits platelet aggregation.

2) Evidence for CVD Treatment Using Combination Therapy Consisting of Lipid-Lowering Agents and Antihypertensive Drugs

The ASCOT-LLA study is a large-scale clinical trial with a 2×2 design; the patients were assigned to receive either amlodipine or atenolol to treat hypertension, and each group was allocated to receive either atorvastatin or a placebo for lipid management. This study found that there were no differences in the efficacy of amlodipine and atenolol, while the incidence of CAD events was significantly decreased in the amlodipine-atorvastatin group compared to that observed in the atenolol-atorvastatin group[54].

Beta-blockers have been shown to be effective in inhibiting atherosclerosis. At present, no large-scale clinical trials have elucidated the effects on the rate of cardiovascular events following the coadministration of beta-blockers and lipid-lowering drugs. Nevertheless, the add-on administration of beta-blockers to statins has been demonstrated to exert inhibitory effects on the progression of IMT[55, 56] and and cause a regression of atherosclerotic plaques, as assessed on intravascular ultrasonography (IVUS)[57].

Regarding renin-angiotensin system (RAS) inhibitors, studies evaluating coronary stenosis[58] or stent restenosis[59, 60] on angiography have reported that combination therapy using RAS inhibitors together with statins results in favorable outcomes compared to that observed with monotherapy with either drug.

7. Adherence

Dyslipidemia is the largest risk factor for CVD. However, most patients, except for those undergoing secondary prevention therapy, do not experience symptoms. Therefore, a high proportion of patients do not recognize dyslipidemia as a disease. In addition, accepting the need to treat dyslipidemia unless provided an appropriate explanation by a medical professional is difficult. The rate of recognition of dyslipidemia has been reported to be lower than that of hypertension[61].

The basic therapy for preventing CVD is lifestyle modification, including diet therapy, exercise therapy and smoking cessation[62]. In order for patients to appropriately achieve these lifestyle modifications, physicians and medical professionals must first establish a good relationship with the patient and their family members and fully explain the relationships between CVD, dyslipidemia and lifestyle factors. Furthermore, physicians and medical staff must confirm that the patient understands the explanation. Several techniques have been proposed to improve patient adherence, including the following: devising a feasible lifestyle modification program together with the patient; helping the patient to resolve problems encountered in daily life; advising and encouraging the patient; or instructing the patient to take gender into account[63]. Furthermore, the benefits of lipid-lowering agents, if administered, are expected to be at their highest when the patient adequately achieves the lifestyle modifications.

In order to improve medication adherence, explaining the need to take medications is important[64]. In general, improvements in medication adherence lead to improvements in the benefits of the medication[65-67]. The use of a simpler dosing regimen involving the minimum number of tablets and the least complicated administration plan (once daily is best[68]) results in improved adherence[69-71]. However, even the administration of once-daily drugs, such as statins, is associated with the following: the longer the treatment period, the lower the adherence over time[72]; patients without complications tend to exhibit decreased adherence[73]; and patients with good adherence one to two years after the initiation of drug therapy continue to exhibit good adherence to medication[74]. Therefore, explaining the need for drug treatment periodically and continuously is important. In addition, confirming the efficacy of the drug using blood tests following the initiation of treatment is necessary. Monitoring the data periodically (approximately every three months) to determine whether the therapeutic target has been reached and explaining the results to the patient is crucial for improving adherence[75]. With regard to drugs with relatively good adherence, such as statins, measuring the cholesterol levels is helpful for determining whether medication adherence is suitable[76, 77]. However, it is important not to be content with simply measuring the LDL-C level, but rather to also assess each patient's level of understanding regarding his/her current medical condition and the need for medication in the routine clinical setting[74].

Among the various risk factors for atherosclerosis, dyslipidemia and hypertension are conditions that can be effectively managed with pharmacological intervention. Recently, a combination drug that includes a statin and CCB has become available in Japan. In Japan, 40% to 50% of patients with hypertension suffer from dyslipidemia. Of these patients, approximately 60% have been reported to receive treatment for dyslipidemia; however, ≥ 60% of patients receiving treatment have been reported to not achieve the therapeutic target values described in the guidelines issued in 2002. In particular, ≥ 80% of patients with a history of CAD have been reported to have not achieved the target[78]. Studies conducted in Western countries have shown that adherence to medications can be improved by changing to the aforementioned combination drug from the use of statins and CCBs separately[79, 80] and that adherence is notably better in patients who have previously taken either drug[80].

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 7-B) published in Japanese in June 2012.

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Committee Report 8

Metabolic Syndrome

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

Japanese eating habits and dietary components have clearly changed in recent years[1]. Lifestyles that include overnutrition and physical inactivity are threatening to increase the incidence of coronary artery disease (CAD) and stroke. Among the conditions underlying the development of atherosclerotic cardiovascular diseases (CVD), particular importance is ascribed to a cluster of multiple risk factors, including hyperglycemia, dyslipidemia, and elevated blood pressure, which are closely related to lifestyle.

This pathologic condition used to be called "Syndrome X,"[2] "the deadly quartet,"[3] "visceral fat syndrome,"[4], or "insulin resistance syndrome,"[5] but those terms were unified as "metabolic syndrome"[6] in 1999. Metabolic syndrome is recognized as a condition in which the risk factors of atherosclerosis cluster on the basis of obesity, particularly visceral fat accumulation, due to overnutrition and physical inactivity[7, 8].

1. Importance of Accumulated Risk Factors

The Group of 'The Research for the Association between Host Origin and Atherosclerotic Diseases under the Preventive Measure for Work-related Diseases of the Japanese Ministry of Labour' performed a case-control study in approximately 120,000 office workers[9, 10]. The records of annual medical health checkups performed 10 years prior to the onset of CAD were reviewed for 94 individuals who developed CAD during a 3-year observation period and were compared to those of age- and gender-matched controls who were randomly selected from the same workplace of the patient. The surveys revealed that the blood pressure, fasting blood glucose, total cholesterol (TC), triglyceride (TG), and uric acid levels were significantly higher in cases compared with those in controls for the evaluated 10-year period, even though these abnormalities were mild or moderate. It was of particular interest that the body mass index (BMI) remained higher in cases compared to controls for a long period of time. The NIPPON DATA80 also showed that the relative risk of death due to CAD and stroke increased with the number of combined risk factors (**Fig. 1**)[9-12]. These results clearly indicate the importance of a cluster of multiple risk factors in the development of CAD in Japan, even if the severity of each risk factor is mild. According to a survey of middle-aged and elderly Japanese, the odds ratio of having any one risk factor (hypertension, impaired glucose tolerance/diabetes mellitus, hypertriglyceridemia, or hypo-HDL-cholesterolemia) and the frequency of having multiple risk factors were high in both obese and non-obese subjects with visceral fat accumulation compared with non-obese subjects without visceral fat accumulation[13]. The odds ratio was not significant in obese subjects without visceral fat accumulation. The Japan Society for the Study of Obesity proposed a definition of "obesity disease" based on susceptibility to the clustering of obesity-associated risk factors[14, 15]. The fat distribution in CAD patients (observed using CT) revealed that approximately half of the patients had excess visceral fat accumulation with multiple risk factors[16]. A 10-year follow-up study of middle-aged and elderly Japanese-American men revealed that approximately 30% of subjects developed CAD and that the accumulation of visceral fat, hypertension, and hyperglycemia were important risk factors[17].

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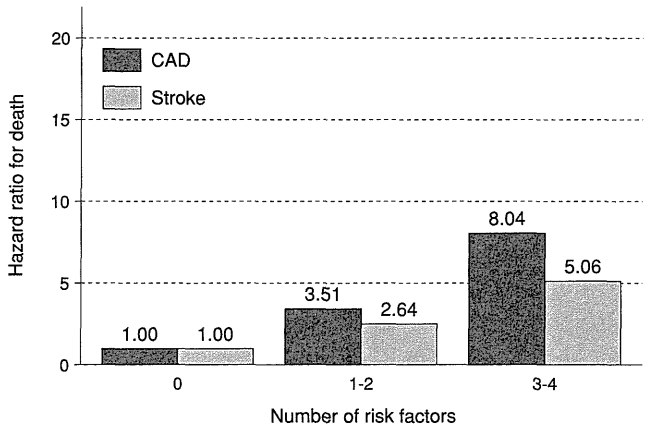

Fig. 1. Relationship between the number of concurrent risk factors and death due to coronary artery disease and stroke (NIPPON DATA80: 1980-1994)[11]

Risk factors: Obesity, hypertension, hyperglycemia, hypercholesterolemia
(Nakamura Y, et al: Circ J, 2006; 70:960-964)

Table 1. Japanese diagnostic criteria for metabolic syndrome[7]

Visceral fat accumulation	
Waist circumference	Men ≥ 85 cm Women ≥ 90 cm
(The values for both men and women correspond to visceral fat ≥ 100 cm^2.)	
Two or more of the items mentioned below in addition to the above	
Hypertriglyceridemia and/or Hypo-HDL-cholesterolemia	≥ 150 mg/dL <40 mg/dL for both men and women
Systolic blood pressure and/or Diastolic blood pressure	≥ 130 mmHg ≥ 85 mmHg
Fasting hyperglycemia	≥ 110 mg/dL

- Measurement of visceral fat by methods such as CT scanning is recommended.
- The waist circumference is measured at the umbilical level in the standing position during light breathing. If the umbilicus is displaced due to marked fat accumulation, measurement is performed at the level of the midpoint between the lower costal margin and iliac crest.
- If a diagnosis of metabolic syndrome has been made, a glucose tolerance test is recommended, but it is not essential for the diagnosis.
- If the examinee is undergoing drug treatments for hypertriglyceridemia, hypo-HDL-cholesterolemia, hypertension, and/or diabetes mellitus, each item is considered to be positive.

(Evaluation Committee on Diagnostic Criteria for Metabolic Syndrome: Internal Medicine, 2005; 94:794-809)

2. Diagnostic Criteria for Metabolic Syndrome

The definition of metabolic syndrome in Japan, which is characterized by the accumulation of visceral fat accompanied by the concurrence of multiple risk factors including elevated blood pressure, dyslipidemia, and hyperglycemia, was established in 2005 (**Table 1**). In the diagnostic criteria, waist circumference is used as an index of visceral fat accumulation for practical convenience, and individuals with metabolic syndrome are defined as those having visceral fat accumulation demonstrated by increased waist circumference and 2 or more risk factors[7]. The International Diabetes Federation also published diagnostic criteria for metabolic syndrome based on the same concept[8].

The joint statement of NCEP-ATP Ⅲ and several societies in Western countries proposed that individuals with three of the five risk factors, including abdominal obesity, hypertriglyceridemia, hypo-HDL-cholesterolemia, high blood pressure, and high blood glucose, should be diagnosed as having metabolic syndrome[18]. The Western diagnostic criteria consider the absolute risk for the development of cardiovascular events and type 2 diabetes.

In contrast to the Western criteria, the Japanese criteria emphasize that the syndrome develops based on visceral fat accumulation. The purpose of the Japanese criteria is to decrease risk factors through interventions to reduce visceral fat. The compulsory measurement of waist circumference in workplace annual health checkups and the specific health examination began in 2008; this action was intended to prevent diabetes and atherosclerotic CVD based on the concept of metabolic syndrome.

According to a recent large-scale cross-sectional study conducted in Japan on visceral fat area and accumulated risk factors, the average number of obesity-related cardiovascular risk factors (dyslipidemia, high blood pressure, and high blood glucose) was more than 1.0 at 100 cm^2 for visceral fat area in both men and women[19, 20]. The criteria for waist circumference in Japan were determined by the absolute visceral fat area of 100 cm^2; this differs from the Western criteria, which are based on the value corresponding to the obesity criteria in each country.

3. Disease Concept of Metabolic Syndrome and its Significance

Conditions, such as metabolic syndrome, that involve the clustering of multiple risk factors (using WHO or NCEP-ATP Ⅲ definition) have been shown to increase the risk of CVD in comparison to a single risk factor in epidemiological studies in Japan, includ-

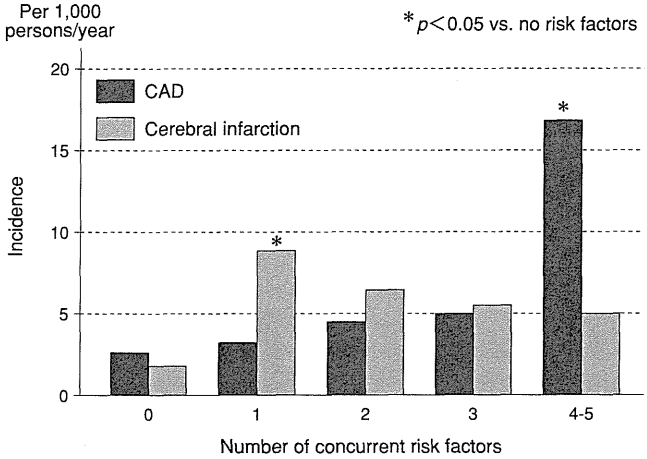

Fig. 2. Relationship between the number of concurrent risk factors and incidences of coronary artery disease and cerebral infarction[12]

Components of metabolic syndome: Obesity, impaired glucose tolerance, lipidosis, hypertension, hyperinsulinemia
After adjustment for age, 5-year (1988-1993) follow-up of 1097 men and women aged ≥ 60 years in Hisayama-machi
(Reproduced from Ken Okubo, et al: Rinsho to Kenkyu 2004; 81:1736-1740 with partial modification)

ing the Tanno and Sobetu Study[21] and the Hisayama Study[12], as well as in foreign epidemiological studies, including NHANES II[22] and SAHS[23] in the United States, the Botnia study[24] and the KIHD study[25] in Finland and Sweden, respectively and a meta-analysis that included Japanese epidemiological studies[26] (**Fig. 2**). Concerning the secondary prevention of CAD, it was also reported that the presence of metabolic syndrome increased the incidence of subsequent cardiac events in a study of long-term outcomes in 748 patients who underwent percutaneous coronary intervention[27].

Metabolic syndrome develops due to visceral fat accumulation and subsequent insulin resistance. The accumulation of visceral fat leads to the dysregulation of adipocyte-derived biologically active products (adipocytokines), resulting in pathologic conditions such as impaired glucose metabolism, dyslipidemia, and hypertension.

Metabolic syndrome is significant because the accumulation of visceral fat is related not only to the development of each risk factor but also to the clustering of risk factors, which substantially increases the risk of CVD, even though the severity of each risk factor is not particularly high. Inevitably, without visceral fat accumulation, patients with hyperglycemia, hypertension, and dyslipidemia are at high risk for atherosclerotic CVD. Conventionally, some patients with multiple risk factors were treated for each of the concurrent factors using multiple pharmaceutical regimens. Through the establishment of the concept of metabolic syndrome, the significance of visceral fat reduction by lifestyle modification (e.g., guidance based on lifestyle characteristics; diet and exercise therapy in accordance with the guidance; and behavior therapy for effective continuance) has become strengthened as the first step in the management of individuals with visceral fat accumulation[28].

4. Relationship to Hyper-LDL-Cholesterolemia

A global consensus has been reached that high-LDL-cholesterolemia is a major risk factor for atherosclerotic CVD, and its management protocol has been established. Metabolic syndrome has been proposed as a high-risk condition for CVD independent of high-LDL-cholesterolemia[7]. Therefore, the diagnostic criteria of metabolic syndrome include no criterion concerning the LDL-C level. However, subjects with metabolic syndrome sometimes also present an elevated level of plasma LDL-C. The combination of metabolic syndrome and high-LDL-cholesterolemia will further increase the risk of CVD. Therefore, strong recommendations to reduce visceral fat and a comprehensive approach for multiple risk factor control, including high-LDL-cholesterolemia, are necessary in such cases.

Footnotes

This is an English version of the guideline from the Japan Atherosclerosis Society (chapter 8) published in Japanese in June, 2012.

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