Ⅲ. 研究成果の刊行物・別刷

Committee Report 1

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

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Committee for Epidemiology and Clinical Management of Atherosclerosis

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

1. Comprehensive Risk Management for the Prevention of Atherosclerotic CVD

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

2. Diagnostic Criteria for Dyslipidemia

It has been shown in epidemiological studies conducted in Japan, as well as in Western countries, that the incidence of CAD increases in association with increases in the levels of LDL-cholesterol (LDL-C)[1] and triglycerides (TGs)[2, 3] and decreases in the level of HDL cholesterol (HDL-C)[4-7]. Currently in Japan, the incidence of CAD is much lower than that observed in Western countries[2, 3, 8, 9]; however, this incidence is anticipated to increase in the near future due to the recent Westernization of the Japanese lifestyle. Therefore, the current guidelines provide screening criteria for dyslipidemia to prevent CVD with a specific emphasis on the prevention of CAD, as shown in **Table 1**.

Received: November 2, 2012
Accepted for publication: December 17, 2012

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

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

The incidence and mortality of CAD increase continuously in association with increases in the LDL-C level. At present, the incidence of CAD is lower in Japanese individuals than in Westerners. To maintain this low rate, efforts directed toward early prevention are required. Therefore, from the perspective of the prevention and treatment of CAD, the current guidelines propose an LDL-C level of 140 mg/dL as the reference value when screening Japanese individuals for hyper-LDL cholesterolemia. This value was selected because it corresponds to a TC level of 220 mg/dL, at which point the relative risk is approximately 1.5-fold higher than that observed at a TC level of <180 mg/dL, according to the NIPPON DATA80[10]. Since the LDL-C goal may vary depending on concomitant risk factors, an LDL-C level between 120 and 139 mg/dL is defined as indicating borderline hyper-LDL cholesterolemia.

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

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

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

- The LDL-C level is calculated using the Friedewald formula (TC − HDL-C − TG/5) (for TG <400 mg/dL).
- If the TG level is ≥400 mg/dL or non-fasting blood is used, the non HDL-C (TC − HDL-C) level should be used with a cutoff value of LDL-C + 30 mg/dL.

*Fasting is defined as deprivation of food for at least 10 to 12 hours; however, the ingestion of noncaloric beverages, such as water and tea, is allowed.

**If a patient is found to have borderline hyper-LDL cholesterolemia during screening, he/she should be examined for any high-risk conditions and the need for treatment should be considered.

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

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

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

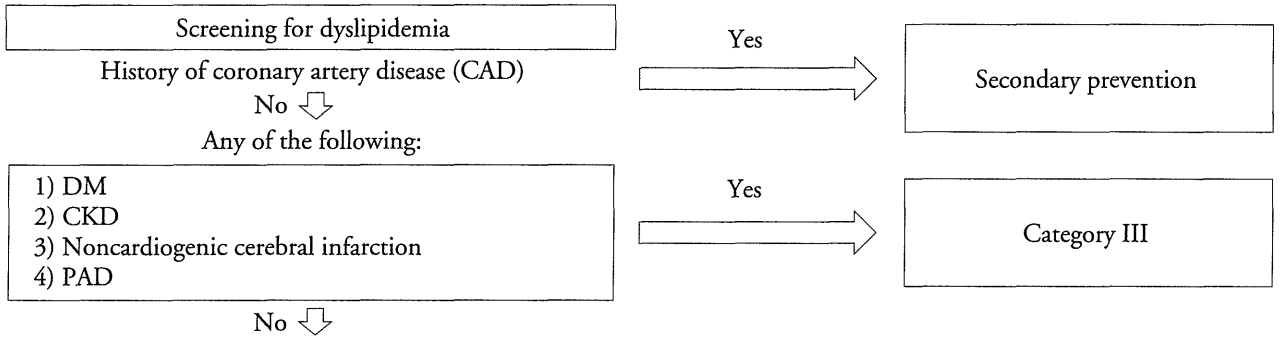
our previous guidelines. A number of studies have demonstrated sex differences in the HDL-C levels; however, it remains unclear whether these sex differences are reflected in the diagnosis of hypo-HDL cholesterolemia.

Hypertriglyceridemia has been found to occur in association with various conditions. Although some researchers insist that more intensive management is required in patients with certain diseases, such as diabetes mellitus, the current guidelines define a TG level of ≥150mg/dL as indicating hypertriglyceridemia, based on epidemiological data obtained during screenings of the general population.

3. Risk Stratification Based on Absolute Risk

The current guidelines stratify the risk of CVD for primary prevention according to the absolute risk calculated based on the results of the NIPPON DATA80[11]. This study identified age, sex, diabetes mellitus, current smoking, systolic blood pressure and the TC level as risk factors and determined the absolute risk of death from CAD depending on the degree or existence of these factors.

How absolute risk categories should be determined is based on clinical consensus and/or conventional wisdom. The U.S. NCEP Adult Treatment Panel III classifies a 10-year risk of death from CAD or the development of nonfatal myocardial infarction of ≥20% (based on the Framingham score) as high risk[12], whereas European guidelines classify a 10-year risk of death from CVD (including strokes and CAD) of ≥5% as high risk[13]. The current guidelines classify



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

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

This flow chart is not applicable to patients with FH.

Fig. 1. Flow chart for setting management targets for LDL cholesterol

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

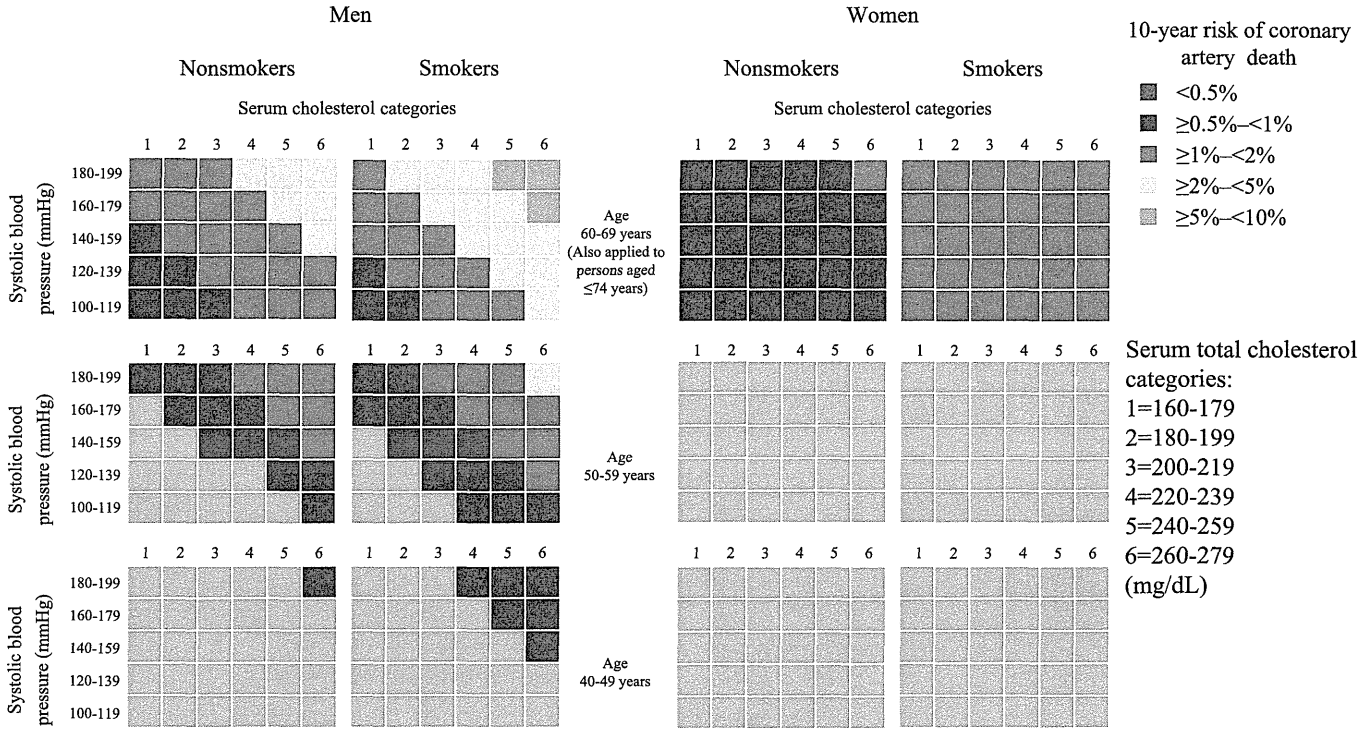
The 10-year absolute risk of CAD-related death should be determined based on the risk assessment chart provided in the NIPPON DATA80[11]. However, since this chart does not include hypo-HDL cholesterolemia, a family history of premature CAD or impaired glucose tolerance, the category should be raised if the patient meets one or more of these criteria (**Fig. 2**).

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

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

4. Management Targets for Dyslipidemic Patients

The management targets for dyslipidemic patients are presented by category in **Table 2**. For primary prevention, drug therapy should be considered after lifestyle factors have been improved for a certain



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

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

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

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

period and the response has been evaluated. For individuals in category I low absolute risk group), the management target for the LDL-C level is set at < 160 mg/dL. The target for individuals in category II is set at < 140 mg/dL, while that for individuals in category III (high absolute risk group) is set at < 120 mg/dL. It should be noted that achieving these targets is recommended but not obligatory. A meta-analysis of preventive clinical trials demonstrated that a 20%-30% reduction in the LDL-C level results in a decrease in the incidence of CAD of approximately 30%. Based on this finding, a 20%-30% decrease in

the LDL-C level can be considered a target. For secondary prevention, since the patient has already been diagnosed with CAD, the administration of drug therapy targeting an LDL-C level of <100 mg/dL is recommended in addition to lifestyle modification.

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

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

5. Treatment

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

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

6. High-Risk Conditions for CVD

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

7. Familial Hypercholesterolemia

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

8. Evaluation of CVD

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

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 1) published in Japanese in June 2012.

Acknowledgements

We are grateful to the following societies for their

collaboration and valuable contributions: Dr. Hidenori Arai (The Japan Geriatrics Society), Dr. Kiminori Hosoda (Japan Society for the Study of Obesity), Dr. Hiroyasu Iso (Japan Epidemiological Association), Dr. Atsunori Kashiwagi (Japan Diabetes Society), Dr. Masayasu Matsumoto (The Japan Stroke Society), Dr. Hiromi Rakugi (The Japanese Society of Hypertension), Dr. Tetsuo Shoji (Japanese Society of Nephrology) and Dr. Hiroaki Tanaka (Japanese Society of Physical Fitness and Sports Medicine). We also thank Dr. Shinji Koba, Dr. Manabu Minami, Dr. Tetsuro Miyazaki, Dr. Hirotoshi Ohmura, Dr. Mariko Harada-Shiba, Dr. Hideaki Shima, Dr. Daisuke Sugiyama, Dr. Minoru Takemoto and Dr. Kazuhisa Tsukamoto for supporting this work.

Disclosures

T. Teramoto: Astellas Pharma Inc., MSD K.K., Kowa Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., Pfizer Co., Ltd., Bayer Yakuhin Ltd., Kobayashi Pharmaceutical Co., Ltd., GlaxoSmithKline K.K., Shionogi & Co., Ltd.; J. Sasaki: MSD K.K., Daiichi-Sankyo Co., Ltd., Bayer Yakuhin Ltd.; S. Ishibashi: Kowa Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., MSD K.K.; S. Biro: none.; H. Daida: AstraZeneca K.K., MSD K.K, Mochida Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Pfizer Co., Ltd., Boston Scientific Japan K.K., Takeda Pharmaceutical Co., Ltd., Bayer Yakuhin Ltd., Mitsubishi Tanabe Pharma Corp., Dainippon Sumitomo Pharma Co., Ltd., Sanofi-Aventis K.K., Novartis Pharma K.K. Ltd., Shionogi & Co. Ltd.; S. Dohi: none.; G. Egusa: none.; T. Hiro: Kowa Pharmaceutical Co., Ltd.; K. Hirobe: none.; M. Iida: none.; S. Kihara: none.; M. Kinoshita: Daiichi-Sankyo Co., Ltd.; C. Maruyama: none.; T. Ohta: none.; T. Okamura: none.; S. Yamashita: MSD K.K., Bayer Yakuhin Ltd., Kowa Pharmaceutical Co., Ltd., Skylight Biotech Inc., Astellas Pharma Inc., Shionogi & Co., Ltd., Otsuka Pharmaceuticals Co., Ltd., Kissei Pharmaceuticals Co., Ltd.; M. Yokode: Otsuka Pharmaceuticals Co., Ltd., MSD K.K.; K. Yokote: MSD K.K., Ono Pharmaceutical Co., Ltd., Pfizer Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Novartis Pharma K.K., Daiichi-Sankyo Co., Ltd., Eli Lilly Japan K.K., Sanofi-Aventis K.K., Novo Nordisk Pharma Ltd., Dainippon Sumitomo Pharma Co., Ltd, Kyowa Hakko Kirin Co., Ltd., Shionogi & Co. Ltd.

References

1) Imano H, Noda H, Kitamura A, Sato S, Kiyama M, Sankai T, Ohira T, Nakamura M, Yamagishi K, Ikeda A, Shimamoto T, Iso H: Low-density lipoprotein cholesterol and risk of coronary heart disease among Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). Prev Med, 2011; 52: 381-386
2) Saito I, Folsom AR, Aono H, Ozawa H, Ikebe T, Yamashita T: Comparison of fatal coronary heart disese occurrence based on population surveys in Japan and the USA. Int J Epidemiol, 2000; 29: 837-844
3) Menotti A, Blackburn H, Kromhout D, Nissinen A, Fidanza F, Giampaoli S, Buzina R, Mohacek I, Nedeljkovic S, Aravanis C, Toshima H: Changes in population cholesterol levels and coronary heart disease deaths in seven countries, Eur Heart J, 1997; 18: 566-571
4) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using riskfactor categories. Circulation, 97: 1837-1847, 1998
5) Kitamura A, Iso H, Naito Y, Iida M, Konishi M, Folsom AR, Sato S, Kiyama M, Nakamura M, Sankai T: High-density lipoprotein cholesterol and premature coronary heart disease in urban Japanese men, Circulation, 1994; 89: 2533-2539
6) Matsuzaki M, Kita T, Mabuchi H, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, Itakura H; J-LIT Study Group: Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia: primary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT). Circ J, 2002; 66: 1087-1095
7) Mabuchi H, Kita T, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, Itakura H; J-LIT Study Group. Japan Lipid Intevention Trial: Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia and coronary heart disease: secondary prevention cohort study of the Japan Lipid Intervention Tr(la J-LIT). Circ J, 2002; 66: 1096-1100
8) Verschuren WM, Jacobs DR, Bloemberg BP, Bloemberg BPM, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Karvonen MJ, Nedelijković S, Nissinen A, Toshima H: Serum total cholesterol and long-term coronary heart disease mortality in different cultures: twenty five-year follow-up of the seven countries study. JAMA, 1995; 274: 131-136
9) Hirobe K, Terai T, Fujioka S, Goto K, Dohi S; 3M-Study Project Committee of the Japan Association of Occupational Physicians "San-yu-kai": Morbidity of Myocardial Infarction Multicenter Study in Japan (3M Study): study design and event rates for myocardial infarction and coronary death by age category in Japanese workers. Circ J, 2005; 69: 767-773
10) Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, Nakamura Y, Okayama A, Ueshima H; NIPPON DATA80 Research Group. The relationship

between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis, 2007; 190: 216-223
11) NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. Circ J, 2006; 70: 1249-1255
12) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA, 2001; 285: 2486-2497
13) Catapano AL,Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Perrone Filardi P, Riccardi G, Storey RF, Wood D; ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis, 2011; 217 Suppl 1: S1-44

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

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

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.*

Received: November 14, 2012
Accepted for publication: December 23, 2012

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.

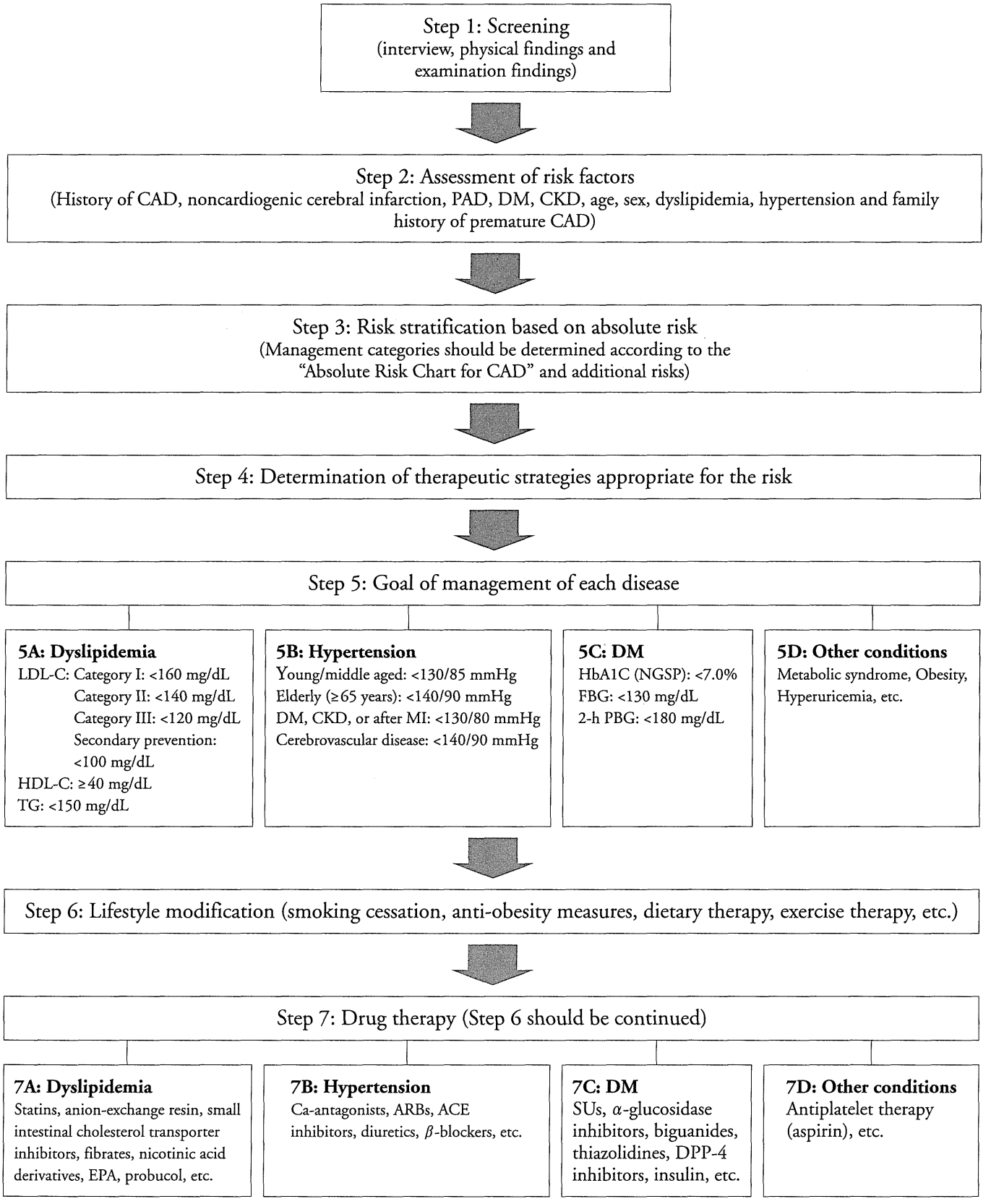


Fig. 1. Comprehensive Risk Management Chart for the Prevention of Cardiovascular Disease.

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/1.73m^2) = $194 \times Cre^{-1.094} \times age^{-0.287}$
Women: eGFR (mL/min/1.73m^2) = $194 \times Cre^{-1.094} \times age^{-0.287} \times 0.739$ ("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 (AI, 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.)

Table 3. Major Secondary Hyperlipidemia

- Hypothyroidism
- Nephrotic syndrome
- Renal failure/uremia
- Primary biliary cirrhosis
- Obstructive jaundice
- DM
- Cushing's syndrome
- Obesity
- Alcohol
- Autoimmune diseases (systemic lupus erythematosus, etc.)
- Drug-induced (diuretics, β-blockers, corticosteroids, estrogen, retinoic acid, cyclosporin, etc.)
- Pregnancy

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.

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

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 4. Patient Conditions Requiring Stricter Management in Secondary Prevention

- Acute coronary syndrome
- Smoking
- DM
- CKD
- Noncardiogenic cerebral infarction/PAD
- Metabolic syndrome
- More than one major risk factor

Table 5. Diabetic Patients at Higher Risk of Developing CAD

- Microangiopathy (retinopathy, nephropathy, etc.)
- Persistent poor glycemic control*
- Smoking
- Noncardiogenic cerebral infarction/PAD
- Metabolic syndrome
- More than one major risk factor

*HbA1c (NGSP) ≥8.4%

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 asymptomatically, 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

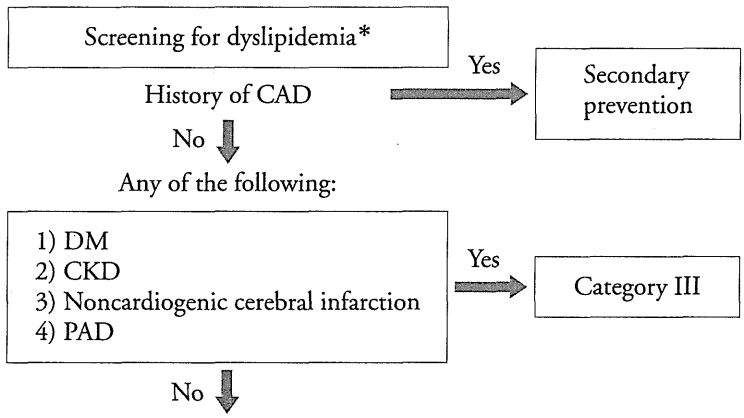
Step 5A: Management Targets for Dyslipidemia (Fasting Venous Blood)

- *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



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

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

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

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

Table 6. Lipid Management Targets for Patients with Different Risk Levels

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

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**).

In patients with secondary hyperlipidemia com-

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

Risk strata (risk factors other than blood pressure) \ Blood pressure classification	High-normal blood pressure 130-139/85-89 mmHg	Grade I hypertension 140-159/90-99 mmHg	Grade II hypertension 160-179/100-109 mmHg	Grade III hypertension ≥180≥110 mmHg
Risk stratum-1 (no other risk factors)	No additive risk	Low risk	Moderate risk	High risk
Risk stratus-2[a] (one to two risk factors (other than diabetes) or metabolic symdrome)[b]	Moderate risk[c]	Moderate risk	High risk	High risk
Risk stratum-3[a] (three or more risk factors, diabetes, CKD, target organ damage/cardiovascular disease)	High risk[c]	High risk	High risk	High risk

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^{-1} and/of 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)

plicating 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.

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

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[4, 5] and is associated with the development and/or progression of CKD[6, 7]. An elevated uric acid level reflects an increased frequency of metabolic syndrome[8]. 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 ≥8.0 mg/dL. Lifestyle modification is also the basis of treatment in such cases[9].

6. Therapy (Lifestyle Modification)

Step 6: Lifestyle Modification

• *Lifestyle modification is positioned as the foundation of prevention of CVD. All patients should be provided with adequate guidance regarding lifestyle modification.*

• *If a patient is monitored while only being encouraged to modify his/her lifestyle, he/she should desirably make regular hospital visits to maintain motivation and improve treatment adherence and effects.*

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 ≥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[10, 11].

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, nicotinic 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[12].

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 (**Table 4**).*
- *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[13], and the effectiveness of this medication in Japanese individuals was shown in the Japanese Antiplatelet Myocardial Infarction Study (JAMIS)[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[16], suggesting that administration without careful consideration should be avoided[17]. Among Japanese individuals, the J-PAD showed no inhibitory effects of low-dose aspirin on cardiovascular events in patients with type 2 DM[18], while a subanalysis demonstrated inhibition of cardiovascular events in elderly subjects ≥65 years of age and patients with moderate renal dysfunction[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[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[20, 21].

Footnotes

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

Acknowledgements

We are grateful to the following societies for their collaboration and valuable contributions: Dr. Hidenori Arai (The Japan Geriatrics Society), Dr. Kiminori Hosoda (Japan Society for the Study of Obesity), Dr. Hiroyasu Iso (Japan Epidemiological Association), Dr. Atsunori Kashiwagi (Japan Diabetes Society), Masayasu Matsumoto (The Japan Stroke Society), Dr. Hiromi Rakugi (The Japanese Society of Hypertension), Tetsuo Shoji (Japanese Society of Nephrology) and Hiroaki Tanaka (Japanese Society of Physical Fitness and Sports Medicine). We also thank Dr. Shinji Koba, Dr. Manabu Minami, Dr. Tetsuro Miyazaki, Dr. Hirotoshi Ohmura, Dr. Mariko Harada-Shiba, Dr. Hideaki Shima, Dr. Daisuke Sugiyama, Dr. Minoru Takemoto and Dr. Kazuhisa Tsukamoto for supporting this work.

References

1) The Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension (edit): Guidelines for the Management of Hypertension (JSH 2009). Life Science Publishing, 2009
2) The Japan Diabetes Society (edit): Evidence-based Practice Guideline for the Treatment of Diabetes in Japan. Nankodo, 2010
3) Japanese Society of Nephrology (edit): Evidence-based Practice Guideline for the Treatment of CKD. Tokyo Igakusha, 2009
4) Nakanishi N, Okamoto M, Yoshida H, et al: Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. Eur J Epidemiol, 18: 523-530, 2003
5) Mellen PB, Bleyer AJ, Erlinger TP, et al: Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. Hypertension, 48: 1037-1042, 2006
6) Weiner DE, Tighiouart H, Elsayed EF, et al: Uric acid and incident kidney disease in the community. J Am Soc Nephrol, 19: 1204-1211, 2008
7) Tomita M, Mizuno S, Yamanaka H, et al: Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. J Epidemiol, 10: 403-409, 2000
8) Onat A, Uyarel H, Hergen? G, et al: Serum uric acid is a determinant of metabolic syndrome in a population-based study. Am J Hypertens, 19: 1055-1062, 2006
9) Japanese Society of Gout and Nucleic Acid Metabolism Committee for the Revised Guideline for the Management of Hyperuricemia and Gout (edit): Guideline for the Management of Hyperuricemia and Gout (2nd edition). Medical Review, 2010
10) Jolliffe JA, Rees K, Taylor RS, et al: Exercise-based rehabilitation for coronary heart disease. Cochrane Database Syst Rev, CD001800, 2001
11) Taylor RS, Brown A, Ebrahim S, et al: Exercise based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med, 116: 682-692, 2004
12) Yokoyama M, Origasa H, Matsuzaki M, et al: Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet, 369: 1090-1098, 2007
13) Antithrombotic Trialists' Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ, 324: 71-86, 2002
14) Yasue H, Ogawa H, Tanaka H, et al: Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction. Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. Am J Cardiol, 83: 1308-1313, 1999
15) Ishikawa K (section leader); The Japanese Circulation Society, The Japanese Coronary Association, The Japanese Society of Intensive Care Medicine, et al: Guidelines for Secondary Prevention of Myocardial Infarction (JCS 2006). 2006
16) Baigent C, Blackwell L, Collins R, et al; Antithrombotic Trialists (ATT) Collaboration: Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet, 373: 1849-1860, 2009
17) Hori M (section leader); The Japanese Circulation Society, The Japanese Coronary Association, The Japanese Association for Thoracic Surgery, et al: Guidelines for Management of Anticoagulant and Antiplatelet Therapy in Cardiovascular Disease (JCS 2009). 2009
18) Ogawa H, Nakayama M, Morimoto T, et al: Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA, 300: 2134-2141, 2008
19) Shinohara Y, Ogawa A, Suzuki N, et al (edit): Japanese Guidelines for the Management of Stroke 2009. Kyowa Kikaku, 2009
20) Norgren L, Hiatt WR, Dormandy JA, et al: Inter-society consensus for the management of peripheral arterial disease (TASC II). Eur J Vasc Endovasc Surg, 33 (Suppl 1): S1-S75, 2007
21) Japanese College of Angiology (edit): Inter-society consensus for the management of PAD (TASC II). Medical Tribune, 2007

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

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

*Reference group

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