Committee Report 4

Absolute Risk of Cardiovascular Disease and Lipid Management Targets

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

Tamio Teramoto, Jun Sasaki, Shun Ishibashi, Sadatoshi Birou, Hiroyuki Daida, Seitaro Dohi, Genshi Egusa, Takafumi Hiro, Kazuhiko Hirobe, Mami Iida, Shinji Kihara, Makoto Kinoshita, Chizuko Maruyama, Takao Ohta, Tomonori Okamura, Shizuya Yamashita, Masayuki Yokode and Koutaro Yokote

Committee for Epidemiology and Clinical Management of Atherosclerosis

Traditionally, the relative risk has been primarily used to evaluate the strength of the associations between risk factors and cardiovascular disease (CVD) and the effects of treatment. In Western countries, scoring tables consisting of scores for each risk factor weighted according to their absolute risk and risk assessment charts in which squares at the points of intersection of the vertical and horizontal axes, each of which has a different risk factor at a different level, are expressed in different colors to represent the absolute risk have been developed to predict an individual's absolute risk in several guidelines. Typical examples are the U.S. Framingham risk score¹⁾ and the European SCORE risk chart²⁾. As the name implies, the Framingham risk score is a method for scoring sex (the weighting of each risk factor differs between men and women), age, total cholesterol (TC), the smoking status, high density lipoprotein cholesterol (HDL-C) and systolic blood pressure. The probability of developing coronary artery disease (CAD), coronary death and nonfatal myocardial infarction within 10 years is calculated from the sum of the scores. The SCORE is a risk assessment chart method used to calculate the probability of death due to all CVD, including stroke, within 10 years based on sex, age, TC, the smoking status and systolic blood pressure. Because the mortality of CVD differs between countries even at the same level of risk factors, the SCORE risk chart is classified into two types: one used in countries with low cardiovascular mortality (e.g., France and Italy) and the other used in countries with high mortality (e.g., the U.K. and Germany).

In Japan, where the size of the aging population is increasing, the concept of absolute risk is important for the management of risk factors for CVD in terms of determining the priority of treatment options and promoting efficient preventive strategies. In addition to the J-LIT chart for dyslipidemia³⁾, many risk assessment tools for predicting CVD based on cohort studies in the general population have recently been published in Japan⁴⁻⁹⁾. This chapter explains the background and rationale of classifying patients according to absolute risk and the management targets for dyslipidemia in each category.

1. Establishing the Absolute Risk

In this guideline, the NIPPON DATA80 risk chart⁵⁾ was used as source data to establish the absolute risk for the following reasons:

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

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

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

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

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

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

6) The measurement of TC was internationally standardized.

The limitations of the chart include:

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

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

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

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

With regard to the guidelines for primary prevention, it is difficult to perform a cohort study in a large population or urban area if accuracy of the end point is pursued. In particular, the majority of epidemiological studies in which the end point is the inci-

dence of CVD have been conducted in non-urban areas. For example, the pooled analysis of a cohort study called the JALS-ECC, in which the end point was myocardial infarction morbidity and information on the HDL-C levels was provided⁴⁾, included almost no urban areas. The crude incidence of myocardial infarction in the JALS-ECC was approximately 0.6 per 1,000 person-years, whereas that observed in the Suita study of a cohort of only urban dwellers was 1.4 per 1,000 person-years, a rate that is two-fold or more higher (no significant differences were observed in sex, age composition or the initial year of follow-up)¹⁰⁾. In this case, it cannot be determined which study is more representative of the Japanese population, and estimating the absolute risk based on the data obtained for only one area is not recommended.

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

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

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

Step 1: The applicable portion of the above figures should be used based on gender, age, the present smoking status, systolic blood pressure (mmHg) and the TC level (mg/dL).

Absolute risk $\geq 2\%$ → Category III

Absolute risk $< 2\%$ → To Step 2

Step 2: The presence of any of the following conditions: Hypo-HDL cholesterolemia (< 40 mg/dL), a family history of CAD and/or impaired glucose tolerance

Absolute risk $\geq 0.5\%$ $< 2\%$ + Yes → Category III

Absolute risk $\geq 0.5\%$ $< 2\%$ + No → Category II

Absolute risk $< 0.5\%$ + Yes → Category II

Absolute risk $< 0.5\%$ + No → Category I

Supplementary notes

(1) The TC category 160-179 mg/dL should be used in patients with a TC level of < 160 mg/dL.

(2) The TC category 260-279 mg/dL should be used in patients with a TC level of ≥ 280 mg/dL.

(3) The systolic blood pressure category of 100-119 mmHg should be used in patients with a systolic blood pressure of < 100 mmHg, while the systolic blood pressure category of 180-199 mmHg should be used in patients with a systolic blood pressure of ≥ 200 mmHg.

(4) These guidelines cannot be applied to persons 75 years of age or older. For patients < 40 years of age, the relative risk charts (Supplementary Table 1) should be used.

(5) Blood pressure should be managed according to the guidelines established by the Japanese Society of Hypertension, and diabetes mellitus should be managed according to the guidelines established by the Japan Diabetes Society.

(6) It is desirable to encourage smokers to stop smoking, irrespective of the level of absolute risk.

2. Categorical Classification Based on Absolute Risk

It is impossible to statistically determine the cut-off point for the absolute risk at which patients are at a high risk; the criteria must be determined based on clinical consensus or socially accepted ideas. The U.S.

NCEP ATP III¹¹⁾ defines a high risk as a $\geq 20\%$ risk of developing fatal CAD or nonfatal myocardial infarction within 10 years based on the Framingham risk score. However, because the incidence of CAD greatly differs between Japan and the U.S., it is not appropri-

ate to use this absolute risk criterion as a reference.

Meanwhile, the European guidelines using the SCORE risk chart¹²⁾ are similar to the NIPPON DATA in that they both use the end point of death. The European guidelines that are based on the SCORE risk chart define a high risk as a $\geq 5\%$ risk of cardiovascular disease death within 10 years. The chart for all CVD deaths in the NIPPON DATA80 employs almost the same end point as that used in the SCORE risk chart. However, strokes account for a high proportion of CVD in Japan, and similar to most cohort studies conducted in Japan, the NIPPON DATA80 shows no relationship between the TC level and stroke mortality. The ratio of stroke death to CAD death in Japan is approximately 2:1. The purpose of these guidelines is to promote the comprehensive prevention of CAD and provide lipid management goals for Japanese individuals. Therefore, in reference to these categories, these guidelines define Category I (low risk) as a $<0.5\%$ risk of CAD mortality, Category II (intermediate risk) as a $\geq 0.5\%$ to $<2\%$ risk of CAD mortality and Category III (high risk) as a $\geq 2\%$ risk of CAD mortality.

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

In the NIPPON DATA80 chart used in the assessment of absolute risk, sex, age, hypertension¹³⁾, smoking¹⁴⁾, DM (a random glucose level)¹⁵⁾ and TC¹⁶⁾ are

included in the criteria for absolute risk. With respect to DM, because the absolute risk greatly depends on the presence or absence of complications and severe patients tend to be managed at medical institutions and are less likely to participate in community-based cohort studies, this guideline considers DM separately and does not use the DM category (a random glucose level ≥ 200 mg/dL) included in the original NIPPON DATA80 chart. Although the guidelines used in Western countries define patients with DM as high-risk as secondary prevention patients (patients with a history of CAD), at present there is no clear evidence suggesting that patients with DM correspond to secondary prevention patients in Japan. Therefore, in the same way as patients with noncardiogenic cerebral infarction or PAD, those with DM (excluding impaired glucose tolerance) are assigned to Category III, regardless of other factors, in this guideline. Recently, evidence that CKD is an important risk factor for CVD among Japanese has been reported¹⁷⁻²¹⁾, and patients with CKD are also considered as being at high risk according to the SCORE chart. Therefore, these guidelines classify patients with CKD into Category III, regardless of other factors.

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

3. Patient Management Based on the Relative Risk

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

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

Therapeutic principle	Management category	Lipid management target (mg/dL)			
		LDL-C	HDL-C	TG	Non HDL-C
Primary prevention	Category I	< 160			< 190
Drug therapy should be considered after lifestyle modification	Category II	< 140			< 170
	Category III	< 120	≥ 40	< 150	< 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 charts (Supplementary Table 1) should be used and changes in the absolute risk should be monitored carefully while encouraging the patient to modify their lifestyle.
- These values should be considered as general goals, not mandatory goals.
- A 20%-30% reduction in the level of LDL-C is considered to be a prime target for pharmacological intervention.
- The management target for non HDL-C is the secondary target to be used after a patient with hypertriglyceridemia has achieved the management target for LDL-C. The non HDL-C level should be used if blood is collected after meals or if the TG level is ≥ 400 mg/dL.
- For patients in any category, the management goals should generally be achieved through lifestyle modification.
- For patients in category I, drug therapy should be considered if the LDL-C level is ≥ 180 mg/dL.

4. Management Targets for Dyslipidemia

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

patients are at very high risk for CAD.

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

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

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

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

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

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

Footnotes

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

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. Hirotohi Ohmura, Dr. Mariko Harada-Shiba, Dr. Hideaki Shima, Dr. Daisuke Sugiyama, Dr. Minoru Takemoto and Dr. Kazuhisa Tsukamoto for supporting this work.

References

- 1) D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB: General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*, 2008; 117: 743-753
- 2) Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM; SCORE project group: Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*, 2003; 24: 987-1003
- 3) 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
- 4) Tanabe N, Iso H, Okada K, Nakamura Y, Harada A, Ohashi Y, Ando T, Ueshima H; Japan Arteriosclerosis Longitudinal Study Group: Serum total and no high-density lipoprotein cholesterol and the risk prediction of cardiovascular events - the JALS-ECC -. *Circ J*, 2010; 74: 1346-1356
- 5) 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
- 6) Arima H, Yonemoto K, Doi Y, Ninomiya T, Hata J, Tanihara Y, Fukuhara M, Matsumura K, Iida M, Kiyohara Y: Development and validation of a cardiovascular risk prediction model for Japanese: the Hisayama study. *Hypertens Res*, 2009; 32: 1119-1122
- 7) Matsumoto M, Ishikawa S, Kayaba K, Gotoh T, Nago N, Tsutsumi A, Kajii E: Risk charts illustrating the 10-year risk of myocardial infarction among residents of Japanese rural communities: the JMS Cohort Study. *J Epidemiol*, 2009; 19: 94-100
- 8) Ishikawa S, Matsumoto M, Kayaba K, Gotoh T, Nago N, Tsutsumi A, Kajii E: Risk charts illustrating the 10-year risk of stroke among residents of Japanese rural communities: the JMS Cohort Study. *J Epidemiol*, 2009; 19: 101-106

- 9) Noda H, Iso H, Sairenchi T, Irie F, Fukasawa N, Toriyama Y, Ota H, Nose T: Prediction of stroke, coronary heart disease, cardiovascular disease, cancer, and total death based on results of annual health checkups. *Japanese Journal of Public Health*, 2006; 53: 265-276
- 10) Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, Okayama A: Low-density lipoprotein cholesterol and non-high density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: the Suita study. *Atherosclerosis*, 2009; 203: 587-592
- 11) 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
- 12) Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), 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 Committee for Practice Guidelines 2008-2010 and 2010-2012 Committees: 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-S44
- 13) Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H; NIPPON DATA80 Research Group: Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). *J Hypertens*, 2006; 24: 459-462
- 14) Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, Okamura T, Minowa M, Iimura O: Cigarette smoking as a risk factor for stroke death in Japan, NIPPON DATA80. *Stroke*, 2004; 35: 1836-1841
- 15) Kadowaki S, Okamura T, Hozawa A, Kadowaki T, Kadota A, Murakami Y, Nakamura K, Saitoh S, Nakamura Y, Hayakawa T, Kita Y, Okayama A, Ueshima H: Relationship of elevated casual blood glucose level with coronary heart disease, cardiovascular disease and all-cause mortality in a representative sample of the Japanese population. *NIPPON DATA80. Diabetologia*, 2008; 51: 575-582
- 16) 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
- 17) Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, Wakugawa Y, Hata J, Oishi Y, Shikata K, Yonemoto K, Hirakata H, Iida M: Chronic kidney disease and cardiovascular disease in general Japanese population: the Hisayama Study. *Kidney Int*, 2005; 68: 228-236
- 18) Ninomiya T, Kiyohara Y, Tokuda Y, Doi Y, Arima H, Harada A, Ohashi Y, Ueshima H: Impact of kidney disease and blood pressure on the development of cardiovascular disease: An overview from the Japan Arteriosclerosis Longitudinal Study. *Circulation*, 2008; 118: 2694-2701
- 19) Nakayama M, Metoki H, Terawaki H, Ohkubo T, Kikuya M, Sato T, Nakayama K, Asayama K, Inoue R, Hashimoto J, Totsune K, Hoshi H, Ito S, Imai Y: Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population-the Ohasama study. *Nephrol Dial Transplant*, 2007; 22: 1910-1915
- 20) Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Ohnishi H, Saitoh S, Sakata K, Okayama A, Ueshima H; NIPPON DATA90 Research Group: Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: Nippon Data 90. *Circ J*, 2006; 70: 954-959
- 21) Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, Higashiyama A, Kamide K, Kawanishi K, Okayama A, Kawano Y: Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: the Suita Study. *Stroke*, 2009; 40: 2674-2679
- 22) Fager G, Wiklund O: Cholesterol reduction and clinical benefit. Are there limits to our expectations? *Arterioscler Thromb Vasc Biol*, 1997; 17: 3527-3533
- 23) Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*, 2005 366: 1267-1278
- 24) 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 Intervention 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 Trial (J-LIT). *Circ J*, 2002; 66: 1096-1100
- 25) Sakamoto T, Kojima S, Ogawa H, Shimomura H, Kimura K, Ogata Y, Sakaino N, Kitagawa A; Multicenter Study for Aggressive Lipid-Lowering Strategy by HMG-CoA Reductase Inhibitors in Patients With Acute Myocardial Infarction Investigators: Effects of early statin treatment on symptomatic heart failure and ischemic events after acute myocardial infarction in Japanese. *Am J Cardiol*, 2006; 97: 1165-1171
- 26) Kitamura A, Noda H, Nakamura M, Kiyama M, Okada T, Imano H, Ohira T, Sato S, Yamagishi K, Iso H: Association between non-high-density lipoprotein cholesterol levels and the incidence of coronary heart disease among Japanese: the Circulatory Risk in Communities Study (CIRCS). *J Atheroscler Thromb*, 2011; 18: 454-463
- 27) Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Ono Y, Miyamoto Y, Yoshimasa Y, Okayama A: Triglycerides and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese

- cohort: the Suita study. *Atherosclerosis*, 2010; 209: 290-294
- 28) Noda H, Iso H, Irie F, Sairenchi T, Ohtaka E, Ohta H: Association between non-high-density lipoprotein cholesterol concentrations and mortality from coronary heart disease among Japanese men and women: the Ibaraki Prefectural Health Study. *J Atheroscler Thromb*, 2010; 17: 30-36
- 29) Sasaki J, Yokoyama M, Matsuzaki M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, Itakura H, Hishida H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Matsuzawa Y; JELIS Investigators: Relationship between coronary artery disease and non HDL-C, and effect of highly purified EPA on the risk of coronary artery disease in hypercholesterolemic patients treated with statins: sub-Analysis of the Japan EPA Lipid Intervention Study (JELIS). *J Atheroscler Thromb*, 2012; 19: 194-204
- 30) Shimano H, Arai H, Harada-Shiba M, Ueshima H, Ohta T, Yamashita S, Gotoda T, Kiyohara Y, Hayashi T, Kobayashi J, Shimamoto K, Bujo H, Ishibashi S, Shirai K, Oikawa S, Saito Y, Yamada N: Proposed guidelines for hypertriglyceridemia in Japan with non HDL-Cholesterol as the second target. *J Atheroscler Thromb*, 2008; 15: 116-121
- 31) Sugimoto K, Isobe K, Kawakami Y, Yamada N: The relationship between non HDL-Cholesterol and other lipid parameters in Japanese subjects. *J Atheroscler Thromb*, 2005; 12: 107-110

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

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

*Reference group

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

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

Start:				
Screening for dyslipidemia		Yes →	Secondary prevention	Target for LDL-C < 100 mg/dL
History of coronary artery disease (CAD)				
No ↓		Yes →	Category III	
Any of the following:				
1) DM 2) CKD 3) Noncardiogenic cerebral infarction 4) PAD		No ↓		
Baseline risk		Determined based on the number of risk factors		
Sex	Age	(1) Hypertension (2) Smoking (3) Hypo-HDL cholesterolemia (HDL-C < 40 mg/dL) (4) Family history of premature CAD (first-degree male relatives aged < 55 years or female relatives aged < 65 years) (5) Impaired glucose tolerance (excluding DM)	Absolute risk of CAD (%)	Category*
Men	40-49 years (Also applied to persons aged 30-39 years)	0	0.23	Category I
		1-2	0.32-0.55	Category II
		≥ 3	0.48-0.83	Category III
	50-59 years	0	0.63	Category II
		1	0.91-1.08	Category II
		≥ 2	1.55	Category III
Women	60-69 years (Also applied to persons aged ≤ 74 years)	0	1.78	Category II
		≥ 1	2.55-4.31	Category III
		0-1	0.10-0.20	Category I
	40-59 years	≥ 2	0.24	Category II
		0-1	0.87-1.83	Category III
		≥ 2	2.19	Category III

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

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

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

Management Category Target for the LDL-C level:

Category I < 160 mg/dL, Category II < 140 mg/dL, Category III < 120 mg/dL, Secondary prevention < 100 mg/dL