
Eiko Takahashi¹², Kengo Moriyama² and Minoru Yamakado¹³

Abstract

Objective The Japan Atherosclerosis Society (JAS) has recommended serum lipid management goals (SLMGs) based on the coronary heart disease (CHD) risk classification included in its 2007 guidelines for the diagnosis and prevention of atherosclerotic cardiovascular disease in the Japanese population (JAS GL 2007). The Japan Society of Ningen Dock created a database of subjects receiving annual health examinations. Using this database, we evaluated the lifestyles of patients with dyslipidemia by identifying risk factors for CHD development based on the JAS recommendations.

Methods A total of 223,407 adults (men: 138,435; women: 84,972) aged between 20 and 79 years were enrolled in the analysis. Those who were already being treated for dyslipidemia and had a history of CHD were excluded. CHD risk factors in the JAS GL 2007, such as an advanced age, hypertension, diabetes mellitus, smoking habits, a family history of coronary artery disease, and low high-density lipoprotein cholesterol levels, were used for the evaluation. The subjects were categorized into three groups (Categories I, II and III) according to the number of risk factors other than the low-density lipoprotein cholesterol (LDL-C) level. We evaluated the percentage of goals met during primary prevention in each group. The serum LDL-C levels were calculated using the Friedewald formula. The LDL-C levels were measured using a direct homogeneous assay if the triglyceride level was ≥400 mg/dL.

Results Overall, 72.9% of the subjects achieved their SLMGs. Most subjects (>90%) with no CHD risk factors other than the LDL-C level in Category I achieved their SLMGs, while less than half of the subjects in Category III achieved their goal.

Conclusion Smoking cessation and medication administration should be considered in patients in Categories II and III.

Key words: dyslipidemia, management goal, lifestyle

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Introduction

Dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease (1-3). The correlation between hypercholesterolemia and the risk of coronary heart disease (CHD) has also been demonstrated by the finding that decreased levels of serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) lead to a reduced risk of CHD (4-8). Therefore, treating patients with dyslipidemia by managing their serum lipid levels is very important for reducing the incidence of atherosclerotic events. In the United States, recent guidelines have recommended treatment goals for the serum lipid levels according to risk categories in which individual patients are classified (9-14). The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) collaborated to establish guidelines for the management of dyslipidemia with the aim of assisting

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physicians in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on the outcome, as well as the risk-benefit ratio of particular diagnostic or therapeutic strategies (15).

The Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and treatment of hyperlipidemia in Japanese adults were published in 1997 (16). The Japan Lipid Intervention Trial (J-LIT) (17) studied a cohort of >50,000 patients with hypercholesterolemia who were prescribed lipid-lowering therapy with simvastatin for the primary prevention of CHD. The J-LIT found the risk of CHD to be higher when the mean TC concentration was ≥240 mg/dL and the mean LDL-C concentration was ≥160 mg/dL (17, 18). The JAS then revised its guidelines in 2002 (19) and proposed strict regimens to achieve serum lipid management goals (SLMGs) in patients at high risk of CHD.

Despite the JAS recommendations, there is still a lack of consensus among physicians in Japan regarding the choice of first-line therapy in patients with hyperlipidemia. The JAS revised its guidelines again in 2007 (20). SLMGs were established for each risk group, and the LDL-C levels rather than the TC levels were used to evaluate the cholesterol levels and predict the risk of atherosclerotic disease. The JAS guidelines were promulgated in 2012 (21). Comparing the 2012 and 2007 JAS guidelines indicates that the new guidelines introduced the concept of “absolute risk” using CHD risk evaluation charts and emphasized the importance of comprehensive management of atherosclerotic disease by introducing chronic renal disease (CKD) as a high risk factor. In addition, familial hypercholesterolemia was specifically described in the guidelines. Moreover, the level of non-high-density cholesterol (HDL-C) was promoted for evaluating dyslipidemia.

Despite the use of various treatments, many patients have not achieved their lipid management goals. For example, the Japan Lipid Assessment Program (JLAP) (22) surveyed the status of lipid-lowering therapy and found poor lipid management in many patients (surveyed in 2003 based on the 2002 guidelines). We also surveyed SLMG achievement rates in 18,000 Japanese patients with dyslipidemia throughout the country (surveyed in 2009 based on the 2007 guidelines) (23). The results of both surveys showed that more than half of the patients in the primary prevention high-risk and secondary prevention groups did not achieve their SLMGs. Moreover, the lipid management status of subjects who do not receive pharmacotherapy remains unknown.

This study aimed to evaluate lifestyle factors and to determine the optimal therapeutic strategies for patients with dyslipidemia by identifying risk factors for CHD development based on the 2007 JAS recommendations (JAS GL 2007) (20).

### Materials and Methods

#### Study population

This multicenter, retrospective study was conducted using data for subjects undergoing annual health examinations at 21 Ningen Dock institutes located throughout Japan in 2008 and 2009 (24). The number of subjects was 286,246 (men: 178,377; women: 107,869) in 2009. Among the 286,246 participants, 223,407 adults (men: 138,435; women: 84,972) aged between 20 and 79 years were enrolled in the analysis. Those already under treatment for dyslipidemia or who had a history of CHD were excluded.

This study was designed in compliance with the ethics regulations outlined in the Declaration of Helsinki. Anonymized health records were used for the analysis, and each participant’s privacy was completely protected. Verbal consent was obtained from the subjects to use their anonymized health records for the analysis. This study was approved by the ethics committee of the Japan Society of Ningen Dock.

#### Methods

The subjects were assigned to a CHD risk category based on the JAS GL 2007. The CHD risk factors outlined in the JAS GL 2007 were as follows: an advanced age (≥45 years in men, ≥55 years in women), hypertension (under medication or a blood pressure of ≥140/90 mmHg), diabetes mellitus (including impaired glucose tolerance [under medication or a fasting plasma glucose level of ≥110 mg/dL]), smoking habits (current smoker), a family history of coronary artery disease and low HDL cholesterol (<40 mg/dL). For primary prevention, in order to prevent future CHD, the subjects were categorized into low-risk, intermediate-risk and high-risk groups (Categories I, II and III, respectively) depending on the number of risk factors other than the LDL-C level. The major coronary risk factors other than the LDL-C level confirmed to date include age, hypertension, diabetes mellitus (including impaired glucose tolerance), smoking habits and a low HDL-C level. A family history of CHD was not evaluated. Patients with diabetes or cerebral infarction were placed in Category III even if no other risk factors were present. Arteriosclerosis obliterans was not evaluated in this study. In Category I (the low-risk group), which included patients with no major coronary risk factors, the management goal was an LDL-C level of <160 mg/dL. The goal for Category II (the intermediate-risk group), which included patients with one to two major risk factors, was an LDL-C level of <140 mg/dL, while that for Category III (the high-risk group), which included patients with three or more major coronary risk factors as well as diabetes and/or cerebral infarction, was an LDL-C level of <120 mg/dL.

Anthropometric measurements and blood samples were obtained after overnight fasting. The serum LDL-C levels were calculated using the Friedewald formula (25): LDL-C = TC-HDL-C-TG/5. The LDL-C levels were measured using a
direct homogeneous assay if the TG level was 400 mg/dL or higher. All health examination institutes operated in coordination with a central clinical laboratory where the blood biochemistry tests were performed. The serum lipid levels were directly measured using visible absorption spectrophotometry or ultraviolet absorption spectrophotometry. The type of measuring kits used for blood biochemistry and the accuracy of the measurements in each central clinical laboratory were unknown. Since all health examination institutes were investigated and accepted as being superior by the Council for Quality Function, the accuracy of the measurements in each central clinical laboratory was inspected by a third-party organization.

The primary outcome was the percentage of subjects in each group who achieved their SLMG.

**Statistical analysis**

Continuous variables are expressed as the mean ± SD. Categorical variables are expressed as frequencies and percentages. The significance of pairwise comparisons was determined using the t-test or Chi-square test. The comparisons of mean values among groups were made using Scheffe’s multiple comparison tests. All p values were two-tailed, and p values of less than 0.05 were considered to be significant. The SAS software program version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for the statistical analyses.

**Results**

Table 1 shows the characteristics of the study subjects. The mean age was 49.8 years for men and 48.9 years for women. With the exception of the levels of TC and HDL-C, the clinical parameters in the men were greater than those observed in the women. The prevalence of every CHD risk factor was higher in the men than in the women.

Table 2 shows the lipid profiles and other examination data across the CHD risk categories. The mean HDL-C level was highest among the subjects in Category I and decreased from Category I to Category III in both men and women. In contrast, the remaining markers were lowest in Category I and increased from Category I to Category III in both sexes. All markers listed in the table were significantly different among the categories, with the exception of the TC levels in Categories II and III in the men.

Table 3 shows the distribution of the CHD risk factors and the SLMG achievement rates across the CHD risk categories. In Category II, the proportion of men with two risk factors was 42.0%, which was greater than that observed in the women. Although 68.0% of the men in Category III had three risk factors, 13.2% and 1.0% of the subjects in this group had four and five risk factors, respectively. Among the women in Category III, 50.7% had three risk factors, whereas only 2.2% had more than four risk factors. A comparison of the frequencies of CHD risk factors in Categories II and III revealed that, among men, an advanced age (≥45 years) was the most frequently observed factor (75.9% and 93.2% in Categories II and III, respectively) followed by smoking habits in Category II and hypertension in Category III. Among the women, an advanced age (≥55 years) was the most frequently observed factor, followed by hypertension in Categories II and III. In Category III, the frequency of diabetes in the women was higher than that observed in the men (51.7% vs. 37.3%). Overall, 72.9% of the subjects (68.5% of the men and 79.9% of the women) achieved their SLMGs. Most of the men (90.2%) in Category I achieved their goal, while only 43.4% of the men in Category III achieved their goal. Most of the women (93.8%) in Category I achieved their goal. In contrast, the women in Category III exhibited the lowest achievement rate (33.0%).

Figure shows the distribution of the LDL-C levels according to the CHD risk categories. The proportion and distribution of men in Categories II and III were almost identical. The rate of a high LDL-C level (≥180 mg/dL) was 3.8% overall and increased from Category I to Category III.

**Discussion**

Of the 286,246 subjects who visited 21 Ningen Dock institutes located throughout Japan in 2009, where data quality control was superior, 223,407 adults (men: 138,435; women: 84,972) were enrolled in the analysis. Patients who were al-
Table 2. Lipid Profile and Other Examination Data Across CHD Risk Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Category I</td>
<td>Category II</td>
</tr>
<tr>
<td></td>
<td>n=23,824</td>
<td>n=90,545</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>199.0 ± 31.7</td>
<td>205.7 ± 32.3 ++</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>118.5 ± 28.4</td>
<td>122.4 ± 29.6 ++</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>59.4 ± 13.0</td>
<td>58.6 ± 14.7 ++</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>106.6 ± 66.5</td>
<td>126.2 ± 89.9 ++</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 ± 2.9</td>
<td>23.4 ± 2.9 ++</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>82.0 ± 8.0</td>
<td>84.0 ± 8.0 ++</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>113.8 ± 10.7</td>
<td>119.1 ± 14.9 ++</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70.5 ± 8.3</td>
<td>74.7 ± 10.8 ++</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>93.7 ± 7.3</td>
<td>97.1 ± 8.7 ++</td>
</tr>
</tbody>
</table>

TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose
++ p<0.01, # p<0.05 (vs. category I), ## p<0.01, # p<0.05 (vs. category II), by Scheffe’s multiple comparison test

Table 3. Distribution of CHD Risk Factors and SLMG Achievement Rates

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Category I</td>
<td>Category II</td>
</tr>
<tr>
<td></td>
<td>n=23,824</td>
<td>n=90,545</td>
</tr>
<tr>
<td></td>
<td>20,238 (100%)</td>
<td>54 (0.2%)</td>
</tr>
<tr>
<td></td>
<td>1 -</td>
<td>52,541 (58.0%)</td>
</tr>
<tr>
<td>CHD risk</td>
<td>2 -</td>
<td>38,004 (42.0%)</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>16,371 (68.0%)</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>3,186 (13.2%)</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>235 (1.0%)</td>
</tr>
<tr>
<td>Advanced age</td>
<td>0 (0.0%)</td>
<td>68,761 (75.9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0.0%)</td>
<td>16,477 (18.2%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0 (0.0%)</td>
<td>32,181 (35.5%)</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>0 (0.0%)</td>
<td>4,753 (5.2%)</td>
</tr>
<tr>
<td>IGT</td>
<td>0 (0.0%)</td>
<td>6,377 (7.0%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0 (0.0%)</td>
<td>8,967 (37.3%)</td>
</tr>
</tbody>
</table>

SLMG: serum lipid management goal; CHD: coronary heart disease, HDL-C: high-density lipoprotein cholesterol; IGT: impaired glucose tolerance
*Major risk factors other than LDL-C: advanced age (≥45 years in men, ≥55 years in women), hypertension (under medication or blood pressure ≥140/90 mmHg), low HDL-C (<40 mg/dL), smoking, IGT (FPG 110 to ≤126 mg/dL) & diabetes (under medication or FPG ≥126 mg/dL)

Of the men, 65.4% were in Category II, 17.4% were in Category III and 17.2% were in Category I. Of the women, 57.6% were in Category I, 39.1% were in Category II and 3.3% were in Category III. An advanced age was the most frequently observed CHD risk factor, followed by hypertension, although smoking ranked above hypertension in men in Category II.

The SLMG achievement rate was >90% in Category I for ready being treated for dyslipidemia or had a history of CHD were excluded from the study. The mean subject age was 49.5 years; 65.9% of the men were ≥45 years of age and 29.6% of the women were ≥55 years of age. For both sexes, an advanced age (≥45 years in men, ≥55 years in women) was the most frequently observed CHD risk factor in addition to the LDL-C level, followed by smoking and hypertension.
The percentage of Japanese subjects who take dyslipidemia medications increases with age (23, 26). Moreover, it has been reported that the distribution of the LDL-C level is higher in men <50 years of age and higher in women >50 years of age (24, 27). Since the mean age of the subjects in this study (none of whom were taking medications) was younger than that of the typical patients who receive dyslipidemia medications, the LDL-C levels in the men in this study were higher than those observed in the women.

In a previous study, the proportion of subjects in the primary prevention group who were taking medications was 5% in Category I, 50-60% in Category II and 35-40% in Category III (22, 23, 28, 29). In the current study, the distribution of subjects in the primary prevention group was quite different: 32.6% in Category I, 55.4% in Category II and 12.0% in Category III. Overall, more subjects had a lower risk of CHD. In addition, the proportion of individuals with a smoking habit was higher among the subjects who were not receiving medications (32.6% in men and 8.2% in women) than among the subjects receiving dyslipidemia medications (24.2% in men and 4.4% in women) (23). The percentage of individuals with hypertension was higher among the subjects receiving dyslipidemia medications (55.8% in men and 41.8% in women) (23) than among the subjects who were not receiving medications (22.4% in men and 11.4% in women).

Our study findings indicated that 93.2% of the subjects in Category I who had not received medication achieved their SLMGs, suggesting that lifestyle modification is adequate to achieve treatment goals in most subjects without CHD risk factors. However, one-third of the subjects in Category II and more than half of the subjects in Category III failed to achieve their treatment goals, which reflects lower rates than those observed in the subjects taking dyslipidemia medications. Moreover, quitting smoking and/or starting medication therapy should be considered when patients try to modify their lifestyle habits but fail to achieve their treatment goals since smoking was found to be the primary CHD risk factor in the current study. Our findings also indicated that 3.8% of the subjects had an LDL-C level of ≥180 mg/dL, a level at which patients should immediately begin taking medication. All institutes have satisfied accreditation standards for quality evaluation for Ningen Dock and health screening institutes according to the Japan Society of Ningen Dock. Since most subjects in this study were given health guidance as well as an explanation of the results of their examination, the findings of this study may partly involve intervention. A total of 27.1% of the subjects (36.7% of the subjects with CHD risk factors) required medication. Since the majority of the JAS guidelines were revised in 2012, we intend to investigate the achievement rates of SLMGs in 2014.

In conclusion, most subjects without CHD risk factors other than the LDL-C level in Category I achieved their SLMGs. In contrast, smoking cessation and medication administration should be considered in patients in Categories II and III because the SLMG achievement rates are insufficient in these patients.
The authors state that they have no Conflict of Interest (COI).

References


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