Lower High-Density Lipoprotein Cholesterol is a Significant and Independent Risk for Coronary Artery Disease in Japanese Men

Hiroki Satoh1,2, Kazuo Tomita3, Satoshi Fujii4, Reiko Kishi2, and Hiroyuki Tsutsui1

1Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Hokkaido, Japan
2Department of Public Health, Hokkaido University Graduate School of Medicine, Hokkaido, Japan
3Health Management Center, NTT East Japan Sapporo Hospital, Hokkaido, Japan
4Department of Molecular and Cellular Pathobiology and Therapeutics, Nagoya City University Graduate School of Pharmaceutical Sciences, Aichi, Japan

Aim: Lower levels of high-density lipoprotein cholesterol (HDL-C) have been recognized as a risk factor for coronary artery disease (CAD), but the relationship between HDL-C values and the occurrence of CAD has not been fully established in the Japanese general population.

Methods: A cohort study of 5,371 Japanese men with 12 years of follow-up was conducted to identify risk factors for the occurrence of CAD.

Results: One hundred and twelve subjects had CAD (acute myocardial infarction in 67 patients and angina in 45 patients) during the follow-up period. Adjustment for variables including age, body mass index, smoking habit, alcohol intake, systolic blood pressure, low-density lipoprotein cholesterol, triglyceride, fasting plasma glucose, hypertension, diabetes mellitus and hyperlipidemia, adjusted hazard ratio (HR) of lower levels of HDL-C for the occurrence of CAD was 1.21 (95% confidence interval (CI): 1.11-1.33, p<0.001). Serum HDL-C concentration less than 51 mg/dL was a significant risk for CAD.

Conclusions: Low HDL-C was identified as a significant and independent risk for CAD in Japanese men using long-term follow-up data.


Key words; Coronary artery disease, High-density lipoprotein cholesterol, Primary prevention, Japanese population

Introduction

The plasma lipoprotein profile is a major risk factor for developing a risk of coronary disease (CAD)1,2. We demonstrated that fasting triglyceride values were significantly related with the occurrence of CAD in a 10-year cohort study3. A number of previous studies have shown that high total cholesterol, high low-density lipoprotein cholesterol (LDL-C), and low high-density lipoprotein cholesterol (HDL-C) are risk factors for CAD4-8. The Framingham Heart Study indicated that HDL-C was a more potent risk factor for CAD than LDL-C9. Analysis of the data from 4 large clinical studies in the United States demonstrated that 1 mg/dL increment in HDL-C was associated with a significant decrement of CAD risk by 2% in males and 3% in females10. Several epidemiological studies have indicated the inverse relations of HDL-C and CAD risk among Japanese subjects11-14. In Japanese general populations with higher HDL-C levels and a lower incidence of CAD than Western populations15,16, the effects and significance of HDL-C in the primary prevention of CAD have not been fully established.

Therefore, the purpose of the present study was to elucidate the relationship between HDL-C levels and the occurrence of CAD among the Japanese gen-
eral population during a long-term follow-up period up to 12 years.

**Methods**

**Study Subjects**

The study subjects included 5,745 Japanese men, 35 to 59 years old, employed in a company in Hokkaido, Japan, from 1995–2007. Twenty-eight subjects who had already been diagnosed as having CAD and 346 subjects who were lost during follow-up were excluded from the analysis. Thus, 5,371 subjects who did not have a history of CAD remained in the analysis. The study protocol was approved by the ethics committee of NTT East Japan Sapporo Hospital.

**Baseline Data Collection**

For each subject, body weight and height were measured in the morning in the fasting state. Body mass index (BMI) was calculated as body weight (kilograms) divided by squared height (meters squared). Smoking and alcohol intake were determined by interviews. Subjects who had never smoked and ex-smokers were classified as “nonsmokers”. Blood pressure was measured by a trained nurse using a standard mercury sphygmomanometer with the study subjects in the sitting position after at least a 5-minute rest. Blood samples were obtained from the antecubital vein in the morning after overnight fasting and serum samples were separated after centrifugation. Total cholesterol and LDL-C were measured using commercial enzymatic kits (Daiichi Pure Chemicals, Tokyo, Japan). HDL-C was measured after precipitation of apo B-containing lipoproteins with a commercial reagent containing phosphotungstate and magnesium chloride (Daiichi Pure Chemicals). Triglyceride was measured enzymatically (Kyowa Medex, Tokyo, Japan). Fasting plasma glucose was enzymatically determined by the hexokinase method (Shino-Test, Tokyo, Japan).

**Follow-up and Outcomes**

During the follow-up period of 12 years (mean ± SD: 11.6 ± 0.8 years), the occurrence of CAD was identified by the company’s health management center and was confirmed in the clinical records by the investigators. CAD was identified as the new onset of acute myocardial infarction and/or angina pectoris. The diagnostic criteria for CAD were based on the recommendations by the World Health Organization Expert Committee. Acute myocardial infarction was diagnosed by the presence of at least 2 of the following 3 criteria: (1) typical ischemic chest pain lasting 30 minutes or more, (2) electorocardiographic changes (i.e., ST segment elevation greater than 0.1 mV in at least 1 standard or 2 precordial leads, ST segment depression greater than 0.1 mV in at least 2 leads, abnormal Q wave, or T wave inversion in at least 2 leads), and (3) an increase of serum creatine kinase to 2-fold over the upper limit of the normal range. Angina pectoris was diagnosed by repeated episodes of chest pain during effort that usually disappeared rapidly after the cessation of effort or by the sublingual administration of nitroglycerin.

**Statistical Analysis**

The clinical and biochemical data of the study subjects are expressed as the mean ± SD, a median (and interquartile range) for variables with a skewed distribution and a percentage. Differences in variables between two groups were examined by Student’s unpaired t test for approximately normal distributed variables, or by the Wilcoxon rank-sum test for triglyceride, and by the χ²-test for the proportion of smoking and medical history. The data were compared among groups using analysis of variance (ANOVA), the Kruskal-Wallis test, or the χ²-test. Kaplan-Meier estimates, stratified according to the value of HDL-C, for the occurrence of CAD were determined and presented as events curve. The Cox proportional hazard model was used to examine the relationship between HDL-C values and CAD and to access the unadjusted and adjusted hazard ratio (HR) for CAD. HDL-C was indicated per additional 5 mg/dL decrease. The principle model included candidate variables for age (years), smoking (non and current smokers), alcohol intake (g/day), BMI (kg/m²), systolic blood pressure (mmHg), LDL-C (mg/dL), HDL-C (mg/dL), log triglyceride and fasting plasma glucose (mg/dL), hypertension, diabetes mellitus, and hyperlipidemia. A p value 0.05 was considered significant. All statistical analyses were performed using SPSS software (version 11.0).

**Results**

The baseline characteristics of the subjects with and without CAD are shown in Table 1. During the 12-year follow-up, 112 subjects had CAD; 67 subjects had acute myocardial infarction and 45 subjects had angina pectoris. Subjects with CAD had a significantly higher age, BMI, systolic blood pressure, total cholesterol, LDL-C, triglyceride, and fasting plasma glucose values and lower HDL-C values and alcohol intake. The prevalence of smoking, hypertension, and diabetes mellitus was higher in subjects with than without CAD.
Fig. 1 shows the distributions of baseline HDL-C values in subjects with and without CAD. Subjects with CAD were more likely to have lower HDL-C values than those without.

Using the Cox proportional hazard models, age, smoking, systolic blood pressure, LDL-C, and HDL-C were identified as significant and independent risk factors for the occurrence of CAD (Table 2). The HR of CAD adjusted for risk factors, with an one-year increase in age was 1.27 (95% confidence interval (CI): 1.22–1.33, \(p < 0.001\)), with smoking was 2.01 (95%CI: 1.25–3.22, \(p < 0.01\)), with a 10 mmHg increase in systolic blood pressure was 1.23 (95%CI: 1.12–1.35, \(p < 0.001\)), with a 10 mg/dL increase in LDL-C was 1.14 (95%CI: 1.08–1.21, \(p < 0.001\)), and with a 5 mg/dL decrease in HDL-C was 1.21 (95%CI: 1.11–1.33, \(p < 0.001\)).
1.14 (95%CI: 1.08–1.21, \( p < 0.001 \)), and with a 5 mg/dL decrease in HDL-C was 1.21 (95%CI: 1.11–1.33, \( p < 0.001 \)).

Table 3 shows the clinical characteristics, medical history, and laboratory data by baseline HDL-C quartiles ranging \( \geq 62 \), 51–61, 42–50, \( \leq 41 \) mg/dL. The prevalence of CAD was higher according to lower HDL-C quartiles. The proportion of smokers and a medical history of hypertension increased substantially and the subjects had significantly greater BMI, LDL-C, triglyceride, and fasting plasma glucose values according to lower HDL-C quartiles.

Fig. 2 shows cumulative CAD occurrence rates according to HDL-C quartiles ranging \( \geq 62 \), 51–61, 42–50, \( \leq 41 \) mg/dL. Kaplan-Meier survival analysis demonstrated that cumulative CAD occurrence rates were higher according to lower HDL quartiles during follow-up.

HRs for the occurrence for CAD were further assessed in HDL-C quartiles (Table 4). There was a negative relationship between quartile levels of HDL-C and the occurrence of CAD. Comparing the highest to the third high quartile level of HDL-C, the unadjusted HR was 3.80 (95%CI: 1.82–7.94, \( p < 0.001 \)). After adjusting for confounding variables, the adjusted HR was 2.57 (95%CI: 1.19–5.52, \( p < 0.02 \)).

Discussion

The relationship between HDL-C values and the occurrence of CAD has been poorly established in the general population despite the importance of this dis-
ease in public health. The present study demonstrates that serum HDL-C is inversely associated with the development of CAD and a serum HDL-C concentration level 51 mg/dL is a significant risk for CAD in Japanese men.

The incidence of CAD in our subjects without a prior history of CAD was 1.74 events per 1,000 person-years. Meanwhile, cumulative CAD occurrence profiles showed that the curves hit a plateau at around the 120th month (Fig. 2). Two possibilities may exist: First, CAD subjects during 12-year follow-up in the present study were 112 of 5,371 subjects and the occurrence rate of CAD was relatively small. Thus, the low morbidity of CAD in the present study might affect this phenomenon. Second, all of our subjects belonged to one company in Hokkaido. This company implemented a health program and encouraged exercise for all employees in 2006 and 2007 (the final two years of this study follow-up period). Conventional risk factors, such as total cholesterol, triglyceride, and HDL-C, were not investigated in these two years; however, encouraging exercise might have favorably affected the decrement of CAD occurrence in this period. Kubo M et al. reported that the age-adjusted incidence of CAD events per 1,000 person-years was 3.48 in the Hisayama study \(^{18}\) and the incidence rate of CAD in subjects younger than 60 years in this study was similar to that of our subjects. This value was much lower than the 4.3 reported by Western countries \(^{19,20}\). However, there is a serious concern that the incidence of CAD is increasing even in Japan due to westernization of the lifestyle because the most important risk factors for CAD, such as smoking, hypertension, and dyslipidemia are, also increasing \(^{21}\).

Prospective epidemiological studies have shown that serum HDL-C levels are inversely related to CAD \(^{22}\). A 1 mg/dL increase of HDL-C in Caucasian populations \(^{9}\) is associated with a 2 to 4% decrease of major cardiovascular events \(^{10}\); however, these studies were performed in Western countries and can not be directly applicable to the Japanese population, which has a higher HDL-C, higher prevalence of genetic cholesteryl ester transfer protein (CETP) deficiency \(^{15,23,24}\), and lower BMI, all of which are attributable to the lower incidence of CAD. Nevertheless, in agreement with previous studies from Western countries and Japan, the present study demonstrated that a 1 mg/dL increase of HDL-C was associated with a 5.1% reduction of CAD occurrence in the general population. These results suggest that serum HDL-C is more protective against the occurrence of CAD in Japanese than Caucasian populations.

The primary prevention cohort study of the Japan lipid intervention trial (J-LIT) study demonstrated that the coronary heart disease risk was significantly decreased to HDL-C \(\geq 45 \text{mg/dL}\) in men \(^{12,14}\); however, all subjects were receiving low-dose simvastatin therapy. Thus, these study subjects might have gained favorable pleiotrophic effects of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors \(^{25}\) and the results might not be applicable to the general population. Okamura T et al. indicated a positive but non-significant relationship between low HDL-C and all-cause or cardiovascular mortality; however, cardiovascular morbidity was not investigated in this study \(^{13}\). We examined the first occurrence of CAD in the general population and the prevalence of our subjects with hyperlipidemia therapy was only 0.7%, which differed from these previous epidemiological studies. Kitamura A et al. demonstrated that CAD was inversely related to HDL-C in urban middle-aged Japanese men in a prospective study \(^{11}\); however, this study was performed between 1979 and 1986 and 80% of the study subjects had total cholesterol values less than 200 mg/dL. Epidemiological studies have demonstrated that lifestyle changes have a great influence on the risk factors for atherosclerosis \(^{26}\). Arai et al. demonstrated that total cholesterol, triglyceride, and HDL-C levels increased from 1990 to 2000 in the Japanese Lipid Survey \(^{27}\). In fact, only 48.3% of study subjects had total cholesterol values less than 200 mg/dL in the present study. Thus, an epidemiological study examining the relationship between dyslipidemia and the occurrence of CAD is needed using a contemporary study cohort.

In the third Adult Treatment Panel of the National Cholesterol Education Program (NCEP ATP III), a low level of HDL-C is defined categorically

### Table 4. Hazard ratios for CAD occurrence according to baseline HDL-C quartiles

<table>
<thead>
<tr>
<th>HDL-C values (mg/dL)</th>
<th>≥62</th>
<th>51–61</th>
<th>42–50</th>
<th>≤41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.0</td>
<td>1.81</td>
<td>3.80</td>
<td>6.63</td>
</tr>
<tr>
<td>95%CI</td>
<td>-</td>
<td>0.79–4.14</td>
<td>1.82–7.94</td>
<td>3.27–13.4</td>
</tr>
<tr>
<td>p value</td>
<td>-</td>
<td>0.16</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.0</td>
<td>1.41</td>
<td>2.57</td>
<td>3.40</td>
</tr>
<tr>
<td>95%CI</td>
<td>-</td>
<td>0.61–3.25</td>
<td>1.19–5.52</td>
<td>1.59–7.29</td>
</tr>
<tr>
<td>p value</td>
<td>-</td>
<td>0.42</td>
<td>0.02</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval.
as 40 mg/dL\textsuperscript{28}. The present study demonstrated that HDL-C < 51 mg/dL was a significant risk for CAD (Table 4). This HDL-C value is much higher than the cut-off level of HDL-C in the diagnostic criteria for metabolic syndrome in the International Diabetes Federation (IDF) and NCEP ATPIII. These results may suggest that HDL-C has more significant impact in Japanese men than in Caucasian populations for the prevention of CAD.

There are several limitations that should be acknowledged in this study. First, our study subjects included only men whose age ranged from 35 to 59 years old. Thus, we need to be cautious when extending the present results to the general population. Second, the present study did not collect data on abdominal obesity and insulin resistance, now recognized as significant risk factors for the development of CAD; however, this study aimed to enroll many subjects from the general population and to perform long-term follow-up.

In conclusion, the present study demonstrated that lower HDL-C is an independent and significant risk for the occurrence of CAD among the Japanese male population.

References

Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation, 2003; 108: 2543-2549