LDL Cholesterol and the Development of Stroke Subtypes and Coronary Heart Disease in a General Japanese Population

The Hisayama Study

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Background and Purpose—Although the relation between serum LDL cholesterol level and coronary heart disease (CHD) is well established, its relation with stroke subtypes is less clear.

Methods—A total of 2351 inhabitants age ≥40 years in a Japanese community were followed up for 19 years.

Results—During follow-up, 271 subjects developed stroke and 144 developed CHD. Whereas the age- and sex-adjusted incidences of CHD significantly increased with increasing LDL cholesterol levels (P for trend <0.001), the associations between LDL cholesterol level and the incidences of ischemic or hemorrhagic stroke were not significant. The age- and sex-adjusted incidences of atherothrombotic infarctions (ATIs) and lacunar infarctions (LIs) significantly increased with increasing LDL cholesterol level (P for trend=0.03 for ATIs and =0.02 for LIs), but no such association was observed for cardioembolic infarction. After multivariate adjustment, the positive associations of LDL cholesterol level with the risks of ATI and CHD remained significant (P for trend=0.02 for ATIs and =0.03 for CHD), whereas the association with LIs was not significant. The risk of ATI significantly increased in the fourth quartile of LDL cholesterol compared with the first quartile (multivariate-adjusted hazard ratio=2.84; 95% CI, 1.17 to 6.93). The multivariate-adjusted risks for developing nonembolic infarction (ATIs and LIs) and CHD were significantly elevated in the groups with elevated LDL cholesterol values with and without the metabolic syndrome.

Conclusions—Our findings suggest that an elevated LDL cholesterol level is a significant risk factor for developing ATI as well as CHD, and these associations are independent of the metabolic syndrome. (Stroke. 2009;40:382-388.)

Key Words: epidemiology ■ cholesterol ■ lipoproteins ■ risk factors

Increased blood cholesterol levels are causally related to an increased risk of coronary heart disease (CHD).1 In contrast, the relation between total cholesterol levels and the risk of stroke remains unclear because of conflicting results reported in the literature.2,3 The inconsistent results may be due to several reasons. First, because stroke is a heterogeneous syndrome of different etiologic origins, lipid abnormalities may be important for some subtypes of stroke but not for others. An inverse association has been observed between total cholesterol and hemorrhagic stroke,2,4 and there is a positive association between total cholesterol and ischemic stroke.2,5 Furthermore, the association may be different for ischemic stroke subtypes.6 Second, lipoprotein subfractions are considered to exert varying influence on stroke risk.7 It is possible that the protective effect of HDL cholesterol against stroke weakens the positive association between total cholesterol and stroke in instances where lipoprotein subfractions are counted together. The association between cholesterol and stroke, therefore, needs to be discussed on the basis of stroke subtypes and lipoprotein subfractions.

Together with the results from prospective studies, the positive association between LDL cholesterol level and the risk of CHD has been confirmed by lipid-lowering randomized trials.8 On the other hand, whereas statins significantly reduced the risk of stroke,8 the risk reduction for stroke in trials in which subjects were treated with nonstatins was not significant,9 suggesting that statins involve mechanisms other than cholesterol lowering for the prevention of stroke. Therefore, the true association between LDL cholesterol and the risk of stroke remains unknown. The purpose of this study was to evaluate the association between LDL cholesterol...
level and the development of stroke by its subtypes as well as of CHD in a prospective study of a general Japanese population.

Subjects and Methods

Study Population

Since 1961, we have been conducting a long-term, prospective cohort study of cardiovascular disease (CVD) in the town of Hisayama, a suburb of Fukuoka city in southern Japan. In 1983, a screening survey for the present study was performed in the town. A total of 2548 residents age ≥40 years (80.7% of the total population of this age group) consented to participate in the examination. Of these, 197 subjects were excluded for the following reasons: past history of stroke or myocardial infarction (MI); n = 89), blood samples not being collected or collected after a meal (n = 86), and excessively high level of triglyceride (≥4.48 mmol/L) for which the Friede-wald formula loses its validity10 (n = 22). The remaining 2351 subjects (991 men, 1360 women) were included in this study.

Follow-Up Survey

This population was followed up prospectively for 19 years, from November 1983 through October 2002, by annual health examinations. For subjects who did not undergo regular examinations or who moved out of Hisayama, health status was checked yearly by mail or telephone. We also established a daily commuting system, which connected us with local physicians and the members of the Health and Welfare Office for the town, and through the system we gathered information on new events of CVD, including suspected cases. When stroke or CHD occurred or was suspected, physicians in the study team examined the subject and evaluated his/her detailed clinical information. The clinical diagnosis of stroke or CHD was based on the patient’s history, physical and neurologic examinations, and ancillary laboratory examinations. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 1 subject was lost to follow-up, 707 subjects died, and 555 subjects (78.5%) underwent autopsy examination.

Definition of Cardiovascular Events

The diagnosis and classification of stroke were determined on the basis of clinical information, including brain computed tomography and magnetic resonance imaging, cerebral angiography, echocardiography, carotid duplex imaging, or autopsy findings. In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficits persisting for ≥24 hours, and the stroke was then classified as either hemorrhagic or ischemic. Hemorrhagic stroke included cerebral hemorrhage and subarachnoid hemorrhage. Isch-emic stroke was further divided into 4 clinical categories: athero-thrombotic infarction (ATI), lacunar infarction (LI), cardioembolic infarction (CEI), and undetermined subtype of ischemic stroke (UND), based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke,11 as well as on the basis of the diagnostic criteria of the Trial of Org10172 in Acute Stroke Treatment (TOAST) Study12 and the Cerebral Embolism Task Force.13 Details of the diagnostic criteria for ischemic stroke subtypes have been described previously.14 In brief, ATI was diagnosed when the subjects had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size ≥1.5 cm on brain imaging or autopsy. LI was diagnosed as the presence of a relevant brainstem, basal ganglia, or subcortical hemispheric lesion with a diameter <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. The diagnosis of CEI was made on the basis of primary and secondary clinical features suggestive of CEI as reported by the Cerebral Embolism Task Force.13 The category of UND included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphologic information. We considered morphologic findings to be significant and used clinical features as reference information. Cases with cerebrovascular diseases with distinct pa-thology, such as collagen disease, hematologic disorder, trauma, chronic subdural hematoma, or moyamoya disease, were excluded from the evaluation.

During the follow-up period, we identified 271 first-ever stroke events. All of the stroke cases underwent morphologic evaluation that included brain imaging and autopsy; 269 subjects (99.3%) underwent brain imaging studies, and autopsies were performed on 128 subjects of 157 deceased stroke cases (81.5%), including 2 subjects who were not examined by brain imaging. When sufficient clinical and morphologic information was obtained, a diagnosis of cerebral infarction subtype was defined as “definite.” When the amount of either type of information was insufficient, the diagnosis level was defined as “probable.” On the basis of the aforementioned criteria, stroke cases were divided into 80 hemorrhagic strokes and 191 ischemic strokes (51 ATIs, 93 LIs, 46 CEIs, and 1 UND). Among 191 ischemic strokes, 182 were defined as definite and 9 as probable. In this study, we present the data regarding definite and probable stroke cases together, because these combined data were almost identical to those for definite cases only.

The criteria for the diagnosis of CHD included first-ever acute MI, silent MI, sudden cardiac death within 1 hour after the onset of acute illness, coronary artery angioplasty, and bypass grafting. The diag-nosis of MI was based on detailed clinical information and at least 2 of the following findings: typical clinical symptoms, ECG evidence of MI, elevated cardiac enzymes, or morphologic findings including echocardiographic, scintigraphic, or angiographic abnormalities compatible with myocardial injury. Silent MI was defined as myocardial scarring without any historical indication of clinical symptoms and/or abnormal cardiac enzyme changes.15 During the follow-up period, we identified 144 first-ever events of CHD.

Risk Factors

Blood samples were drawn after an overnight fast of at least 12 hours. All measurements were done within 24 hours after venipunc-ture in the central study laboratory (Japan Medical Laboratory Inc, Fukuoka, Japan), which participated in the Centers for Disease Control and Prevention Lipid Standardization Program. Total cho-lesterol and triglyceride levels were measured enzymatically. Mea-surement of HDL cholesterol was performed after precipitation of VLDL and LDL with dextran sulfate and magnesium. LDL choles-terol concentration was calculated with the Friedewald formula.10 Plasma glucose levels were determined by the glucose oxidase method. Sitting blood pressure (BP) was measured with a sphygmo-monometer 3 times at the right upper arm after at least 5 minutes of rest, and the mean of the 3 measurements was used in the analysis. Hypertension was defined as a BP ≥140/90 mm Hg and/or current treatment with antihypertensive agents. ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code 3-1), ST-segment depression (Minnesota codes 4-1,2,3), or atrial fibrillation (Minnesota code 8-3). Body height and weight were measured in light clothing without shoes, and body mass index (BMI; kg/m²) was calculated. Information on alcohol consumption, smoking habits, and physical activity during leisure time was obtained by the use of a questionnaire. Alcohol consumption and smoking habits were clas-sified as either current use or not. Those subjects who engaged in sports or other forms of exertion ≥3 times per week during their leisure time were designated the regular-exercise group. We defined the presence of the metabolic syndrome according to the National Cholesterol Education Program Expert Panel criteria16 with a minor modification. The presence of the metabolic syndrome was based on the existence of 3 or more of the following components: (1) BMI ≥25 kg/m² as a substitute for waist circumference17; (2) fasting triglyceride concentration ≥1.68 mmol/L; (3) HDL cholesterol concentration <1.03 mmol/L in men and <1.29 mmol/L in women; (4) BP ≥140/85 mm Hg or use of antihypertensive drugs; and (5) fasting plasma glucose value ≥6.1 mmol/L or current use of antidiabetic drugs.

Statistical Analysis

To analyze LDL cholesterol level as a categorical variable, we classified the subjects into 4 groups according to quartiles of LDL
cholesterol level: \( \geq 2.65, 2.66 \) to 3.24, 3.25 to 3.88, and \( \geq 3.89 \) mmol/L. Serum triglyceride levels were logarithmically transformed to improve the skewed distribution. Age- and sex-adjusted mean values of the possible risk factors were calculated by the ANCOVA method, and their trends across LDL cholesterol levels were tested by multiple-regression analysis. Frequencies of risk factors were adjusted for age and sex by the direct method and were examined for trends by the Cochran-Mantel-Haenszel test. The incidences of CVD were calculated by the person-year method and were adjusted for age and sex by the direct method according to the ANCOVA method. All statistical analyses were performed with the SAS program package.

### Results

The age- and sex-adjusted mean values or frequencies of risk factors for CVD are listed by quartiles of LDL cholesterol levels at baseline in Table 1. The frequencies of male sex, current drinking, current smoking, and regular exercise and the mean values of HDL cholesterol declined with increasing LDL cholesterol level, whereas mean values of age, total cholesterol, triglycerides, fasting blood glucose, systolic and diastolic BPs, BMI, and frequency of hypertension significantly increased with rising LDL cholesterol level. The frequency of ECG abnormalities was not different among serum LDL cholesterol levels.

Table 2 shows the age- and sex-adjusted incidences of CVD according to quartiles of LDL cholesterol levels. No significant associations were observed between LDL cholesterol levels and the incidences of stroke, whether ischemic or hemorrhagic. In regard to subtypes of ischemic stroke, the incidences of ATI and LI significantly increased with increasing LDL cholesterol level (\( P \) for trend=0.03 for ATI and=0.02 for LI), and there were significant differences between the first and fourth quartiles of LDL cholesterol for both subtypes (age- and sex-adjusted HR=2.31; 95% CI, 1.03 to 5.16; \( P=0.04 \) for ATI; age- and sex-adjusted HR=2.00; 95% CI, 1.05 to 3.80; \( P=0.03 \) for LI; Table 3). No such association was observed for CEI. The incidence of CHD also significantly increased with increasing LDL cholesterol level (\( P \) for trend <0.001), and compared with the first quartile, the incidence was significantly higher in the third (age- and sex-adjusted HR=1.77; 95% CI, 1.07 to 2.91; \( P=0.03 \); Table 3) and fourth (age- and sex-adjusted HR=2.00; 95% CI, 1.22 to 3.28; \( P=0.006 \)) quartiles.

As shown in Table 3, the positive associations between LDL cholesterol level and risk of ATI and CHD remained significant even after adjustment for age, sex, HDL cholesterol, triglycerides, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise (\( P \) for trend=0.02 for ATI and=0.03 for CHD). Compared with the first quartile, the risk of ATI was significantly high in the fourth quartile after adjustment for the aforementioned confounding factors (multivariate-adjusted HR=2.84; 95% CI, 1.17 to 6.93; \( P=0.02 \)). On the other hand, the negative association between LDL cholesterol and the risk of CEI appeared to be significant after multivariate adjustment (\( P \) for trend=0.03), and the risk of CEI was significantly lower in the fourth quartile than in the first quartile (multivariate-adjusted HR=0.34; 95% CI, 0.12 to 0.96; \( P=0.04 \)). A similar association was observed when LDL cholesterol was examined on a continuous scale.

Because not only LDL cholesterol but also other metabolic factors may be strong risk factors for CVD, we examined the combined as well as the separate effects of elevated LDL cholesterol level and the metabolic syndrome on the development of selected CVDs. As shown in the Figure, we...
estimated the HRs for the occurrence of nonembolic infarction, including ATI and LI, as well as of CHD, by dividing the subjects into 4 groups according to the presence or absence of high LDL cholesterol levels (the fourth quartile, ≥3.89 mmol/L for nonembolic infarction; the third and fourth quartiles, ≥3.25 mmol/L for CHD) and the metabolic syndrome after adjustments for age, sex, ECG abnormalities, current drinking, current smoking, and regular exercise. Compared with a reference group with neither high LDL cholesterol levels nor the metabolic syndrome, the risk of developing nonembolic infarction was significantly high in the group with high LDL cholesterol levels alone and in the group with both high LDL cholesterol levels and the metabolic syndrome, whereas it was marginally significant for the group with the metabolic syndrome alone. Similarly, the risk for the development of CHD was elevated in both the group with high LDL cholesterol without the metabolic syndrome and the group with high LDL cholesterol and the metabolic syndrome. The risk of CHD was also significant for the group with the metabolic syndrome alone.

**Discussion**

In a long-term, prospective study of a general Japanese population, we demonstrated positive and significant associations between serum LDL cholesterol level and risk for the development of ATI and CHD. These associations remained unchanged even after adjustment for other lipid fractions as well as other confounding factors, namely, age, sex, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. In addition, the impact of high LDL cholesterol on CVD appeared to be similar to that of the metabolic syndrome. On the other hand, the association between LDL cholesterol level and the risk of CEI was negative and significant after adjusting for the aforementioned risk factors. To our knowledge, this is the first prospective cohort study to investigate the association between LDL cholesterol and the development of subtypes of ischemic stroke.

Several prospective studies have investigated the association between LDL cholesterol and ischemic stroke, but the results were not unanimous. The Cardiovascular Health Study reported a positive association between LDL cholesterol and the risk of ischemic stroke, whereas the Atherosclerosis Risk in Communities Study and the Framingham Study found no clear associations. In the present analysis, LDL cholesterol level was not clearly associated with the risks of stroke and ischemic stroke, but these associations were heterogeneous across ischemic stroke subtypes. Because LI and CEI seem to have a less potent relation with elevated LDL cholesterol, inclusion of those subtypes may mask the positive association between LDL cholesterol and ATI.

This heterogeneity in the associations of LDL cholesterol level and ischemic stroke subtypes may be a reason for the controversial results obtained from previous studies that investigated the outcome of “total” ischemic stroke.
The atherogenesis of LDL cholesterol to large vessels, including coronary arteries and other peripheral arteries, is well known, and clinical studies have shown that an elevated LDL cholesterol level is also significantly related to the development of atherosclerotic lesions in extracranial or intracranial large vessels.23,24 Because ATI is caused by atherosclerotic lesions of those large vessels, the significant association between elevated LDL cholesterol level and the risk of ATI observed in the present analysis is compatible with the evidence of the atherogenic role of LDL cholesterol.

Table 3. Age-, Sex-, and Multivariate-Adjusted HRs and 95% CIs for the Development of CVD According to LDL Cholesterol Quartiles

<table>
<thead>
<tr>
<th>Quartile of LDL Cholesterol Levels, mmol/L</th>
<th>No. of Events</th>
<th>Age- and sex-adjusted HR (95% CI)</th>
<th>Multivariate-adjusted HR (95% CI)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.65 (n=586)</td>
<td>56</td>
<td>1.0</td>
<td>1.0</td>
<td>0.13</td>
</tr>
<tr>
<td>2.66 to 3.24 (n=591)</td>
<td>62</td>
<td>0.96 (0.66–1.37)</td>
<td>0.94 (0.64–1.38)</td>
<td>0.16</td>
</tr>
<tr>
<td>3.25 to 3.88 (n=585)</td>
<td>74</td>
<td>1.12 (0.84–1.69)</td>
<td>1.15 (0.79–1.67)</td>
<td>0.16</td>
</tr>
<tr>
<td>≥3.89 (n=589)</td>
<td>79</td>
<td>1.23 (0.86–1.75)</td>
<td>1.23 (0.84–1.81)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Multivariate adjustment was made for age, sex, HDL cholesterol, triglycerides, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. For the continuous scale, HR is given for each 1-mmol/L increase in LDL cholesterol.

P<0.05, †P<0.01 vs lowest quartile; ‡P<0.05, §P<0.01.

The atherogenesis of LDL cholesterol to large vessels, including coronary arteries and other peripheral arteries, is well known, and clinical studies have shown that an elevated LDL cholesterol level is also significantly related to the development of atherosclerotic lesions in extracranial or intracranial large vessels.23,24 Because ATI is caused by atherosclerotic lesions of those large vessels, the significant association between elevated LDL cholesterol level and the risk of ATI observed in the present analysis is compatible with the evidence of the atherogenic role of LDL cholesterol.
In our cohort, the association between LDL cholesterol and the risk of LI was no longer significant after multivariate adjustment, suggesting that elevated LDL cholesterol was not an independent risk factor for the development of LI. Our previous report showed that multiple risk factors were related to the occurrence of LI, and case-control studies on the relation between LDL cholesterol level and LI have reported varied associations. One study reported a significant association between elevated LDL cholesterol and the risk of LI, another study observed lower LDL cholesterol levels in LI cases, and another study found no significant association. Lacunar infarcts occur as a result of multiple mechanisms, such as (1) lipohyalinosis and/or fibrinoid necrosis, (2) microatheroma, (3) atherosclerosis of the basilar and middle cerebral artery stem or proximal division of large vessels, or (4) cardioembolic occlusion. Lipohyalinosis is a vasculopathy caused by hypertension, whereas large-vessel atherosclerosis is affected by risk factors including LDL cholesterol, but cardioembolism seems less related to elevated LDL cholesterol. These heterogeneous roles for LDL cholesterol in the multiple pathogenesis of LI occurrence might account for the weak association between LDL cholesterol and the risk of LI.

An inverse relation between LDL cholesterol level and the risk of CEI was observed in our earlier population in the 1960s, and the same association was found in the present analysis. One study reported a significant association between elevated LDL cholesterol and the risk of LI; another study observed lower LDL cholesterol levels in LI cases, and another study found no significant association. Lacunar infarcts occur as a result of multiple mechanisms, such as (1) lipohyalinosis and/or fibrinoid necrosis, (2) microatheroma, (3) atherosclerosis of the basilar and middle cerebral artery stem or proximal division of large vessels, or (4) cardioembolic occlusion. Lipohyalinosis is a vasculopathy caused by hypertension, whereas large-vessel atherosclerosis is affected by risk factors including LDL cholesterol, but cardioembolism seems less related to elevated LDL cholesterol. These heterogeneous roles for LDL cholesterol in the multiple pathogenesis of LI occurrence might account for the weak association between LDL cholesterol and the risk of LI.

The results of previous prospective studies of the association between LDL cholesterol and hemorrhagic stroke have been inconsistent; a significant inverse association was reported in women in the Framingham Study, whereas a nonsignificant association was observed in the Cardiovascular Health Study. Lipid-lowering trials recently conducted in Japan and a meta-analysis of >90,000 subjects enrolled in statin trials found no apparent increase in the risk of hemorrhagic stroke. A nonsignificant association between LDL cholesterol and the risk of hemorrhagic stroke observed in our data was in accord with the findings of a previous prospective study and intervention trials.

Several prospective studies conducted in Western countries have reported positive associations between LDL cholesterol and the risk of CHD. Among Japanese, no study has investigated the association between LDL cholesterol level and the risk of CHD, but several prospective studies have shown that total cholesterol is a strong risk factor for CHD. The findings obtained from the present analysis support the results from those prospective studies and, for the first time, have demonstrated a positive association between calculated LDL cholesterol and the risk of CHD in a general Japanese population.

The metabolic syndrome has been shown to be a clear risk factor for CVD, but LDL cholesterol level is not involved in the definition of the metabolic syndrome. In the present analysis, comparable and independent effects were observed for elevated LDL cholesterol and the metabolic syndrome on the risks of nonembolic infarction and CHD. The highest risk was observed for the subgroup with both an elevated LDL cholesterol value and the metabolic syndrome. Similar results were found in a prospective study of a Danish cohort. All of these results imply that management of LDL cholesterol as well as the metabolic syndrome is important for the prevention of ischemic stroke and CHD.

The strengths of our study include its longitudinal population-based study design, long duration of follow-up, almost perfect follow-up of subjects, sufficient number of cardiovascular events, and accuracy for diagnosis of CVD, including ischemic stroke subtypes. One limitation of our study is that our findings are based on a 1-time measurement of serum lipids. Subsequent use of cholesterol-lowering agents could have altered lipid levels in some participants; however, this source of variability could not account for the relation observed in the present study, because a random misclassification of such nature would tend to cause an underestimation of study findings and bias the results toward the null hypothesis. Therefore, the true association could be stronger than that observed in our study. Another limitation is that the value of LDL cholesterol was not directly assayed but was calculated by the Friedewald equation. This equation has been adopted in substantial epidemiologic and clinical studies of LDL cholesterol and CVD. It is unlikely that the bias of LDL cholesterol values that occurred through calculation, if any, would have strengthened the association between LDL cholesterol and ATI or CHD observed in the present analysis.

In conclusion, we have shown that elevated LDL cholesterol is a significant risk factor for developing ATI as well as CHD in a general Japanese population. Because LDL cholesterol level is independent of the metabolic syndrome for the development of CVD, lowering a patient’s LDL cholesterol level should be considered together with treatment of other metabolic disorders for the prevention of CVD.

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Disclosures
None.

References


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