Association between Lowering Low-Density Lipoprotein Cholesterol with Pravastatin and Primary Prevention of Cardiovascular Disease in Mild to Moderate Hypercholesterolemic Japanese

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Aims: To evaluate the relationship between low-density lipoprotein cholesterol (LDL-C) change and reduction of cardiovascular disease in the Management of Elevated cholesterol in the primary prevention Group of Adult Japanese (MEGA) study.

Methods: Patients in the diet plus pravastatin group were divided into tertiles by their on-treatment LDL-C level, and the hazard ratios (HRs) in each tertile were compared with the diet group at 5 years using the Cox proportional hazards model. In addition, the treatment groups were combined and divided into quintiles according to the on-treatment LDL-C level during follow-up, and the incidence of cardiovascular events was compared among the 5 groups.

Results: In the tertiles of the diet plus pravastatin group, HR was lowest in the second tertile against the diet group (HR 0.57, p=0.01) with on-treatment LDL-C range of 119.8–133.4 mg/dL. In the analysis of quintiles of the total population, a significant risk reduction of CVD was found in the fourth quintile (HR 0.48, p=0.0015) with an on-treatment LDL-C range of 120.9–133.3 mg/dL, and in the fifth quintile (HR 0.64, p=0.048) with an on-treatment LDL-C range of 56.7–120.8 mg/dL against tertile 1 with an on-treatment LDL-C range of 157.5–206.2 mg/dL.

Conclusions: The usual Japanese dose of pravastatin therapy is sufficient in this low-risk patient population to reduce cardiovascular risk, with an achieved LDL-C level ≤133.4 mg/dL. Further risk reduction was not found with an achieved LDL <120 mg/dL.


Key words: Cardiovascular disease, Clinical trials, LDL cholesterol, Pravastatin, Primary prevention

Introduction

The significant benefit of lowering low-density lipoprotein cholesterol (LDL-C) by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) for the primary and secondary prevention of cardiovascular disease (CVD) is well documented. In the 1980–90s, the landmark 4S study on secondary prevention and the West of Scotland Cardiovascular Prevention Study (WOSCOPS) on primary prevention revealed the beneficial effect of standard-dose statin therapy. Subsequently, a large number of trials with standard statin therapy and aggressive-dose statin therapy in the 1990–2000s provided further evidence of benefit. Meta-analysis of the 14 largest clinical trials, which analyzed 90,056 patients with statin treatment, demonstrated a 23% risk reduction of coronary events and a 17% reduction of stroke
events per 1 mmol/L reduction in LDL-C. Thus, the beneficial effect of statins on cardiovascular risk reduction is indisputable\textsuperscript{10}. Moreover, some recent clinical trials have indicated that aggressive lipid lowering, achieving an LDL-C level <70 mg/dL, provides a benefit in high-risk populations, such as patients with a history of cardiovascular disease. Based on this evidence, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines recommended an LDL-C goal <70 mg/dL in very high-risk populations\textsuperscript{11}; however it is not confirmed whether such a strict LDL-C goal is needed for a low-risk population, such as the Japanese.

The Management of Elevated cholesterol in the primary prevention Group of Adult Japanese (MEGA) Study conducted in Japan was the first study to evaluate the effect of pravastatin on CVD\textsuperscript{12,13}. Notably, the risk reductions achieved in MEGA were similar to those in Western studies in high-risk populations despite the lower approved dose of pravastatin (10–20 mg daily) used in the MEGA Study. The principal results of the MEGA Study, reported in The Lancet in 2006, showed that small to moderate changes in LDL-C significantly reduced the relative risk for CHD by 33\% (p=0.01) and CVD by 26\% (p=0.01) with diet plus pravastatin compared to diet alone. Surprisingly, this risk reduction was obtained by a small LDL-C reduction (0.7 mmol/L) compared to previous trials. The magnitude of the risk reduction was almost double the expected risk reduction by meta-analysis data\textsuperscript{10}.

Our aim in this analysis was to determine the relationship between LDL-C reduction and risk reduction of cardiovascular disease in the primary prevention setting in Japanese mild to moderate hypercholesterolemia.

**Methods**

**Study Procedure**

The details of the MEGA study have been described elsewhere\textsuperscript{12,13}. Briefly, 8,214 men and postmenopausal women aged 40–70 years with hypercholesterolemia, whose total cholesterol (TC) levels ranged 220–270 mg/dL, without a history of CHD and stroke, and who provided written informed consent were enrolled. The enrollment period was February 1994 to March 1999 and follow-up ended in March 2004.

Eligible patients were randomly assigned to the National Cholesterol Education Program (NCEP) step I diet\textsuperscript{14} alone (diet-alone group) or to the step I diet plus pravastatin (diet plus pravastatin group).

Major exclusion criteria included familial hypercholesterolemia, a history of CVD, a current diagnosis of malignancy, and secondary hyperlipidemia. The dose of pravastatin was 10–20 mg daily, the approved dose range in Japan. Patients in the diet-alone and diet plus pravastatin groups were counseled to follow the NCEP Step I diet throughout the study period. Treatment in the diet plus pravastatin group was initiated at pravastatin 10 mg/day. During follow-up, the dose of pravastatin could be adjusted by the treating physician up to 20 mg/day if the TC level did not decrease to 220 mg/dL or less, in compliance with the approved Japanese dose. Patients in each group exceeding TC 270 mg/dL, even after increasing the assigned treatment, could be switched to other aggressive treatments, including statin therapy. Although switching to other drugs was allowed in the study protocol, 66\% and 90\% of patients in the diet-alone and diet plus pravastatin group, respectively, completely adhered to the allocated treatment; only 2\% and 0.8\%, respectively, concomitantly took other statin drugs during the 5 years. Concomitant treatment for complications was not restricted in either group.

Patients were evaluated by their attending physicians at 1, 3, and 6 months after the start of follow-up, and every 6 months thereafter. Health checkups at each clinic visit included biochemical tests and assessment of patients’ compliance with dosing instructions. For each event, detailed information was obtained from physicians and evaluated by the Endpoint Committee under blinding according to the established criteria. Throughout the study period, TC, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and lipoprotein (a) [Lp(a)] levels were centrally measured at the same laboratory using methods standardized by the Centers for Disease Control and Prevention (CDC, Atlanta, GA). LDL-C level was estimated by the Friedewald formula\textsuperscript{15}. The follow-up period was initially scheduled for 5 years; however, based on the recommendation of the Data and Safety Monitoring Committee, the study was continued to increase the number of events, and thus, patients who provided written consent at 5 years to continue the study were followed until the end of March 2004.

The primary composite endpoint of the MEGA Study was the first occurrence of coronary heart disease (CHD), comprising fatal and non-fatal myocardial infarction, cardiac and sudden death, coronary revascularization procedure, and angina. Secondary endpoints included stroke, cerebral infarction (CI), intracranial hemorrhage, CHD + CI, CI + transient ischemic attack (TIA), all cardiovascular events (CVD), and total mortality. The present analysis primarily...
focused on the occurrence of CVD because there were sufficient events, but we also evaluated CHD and stroke.

Statistical Analyses

In this post-hoc analysis, patients in the diet plus pravastatin group were divided into tertiles by their on-treatment LDL-C level (mean level during the treatment period), and the hazard ratios (HRs) and 95% confidence interval (95%CI) in each tertile were estimated against the diet group using the Cox proportional hazards model at 5 years, adjusted by the baseline risk factors. The on-treatment lipid parameter was defined as the cumulative average LDL-C level during the period from the first month to the established evaluation point. When the LDL-C level was not measured at the scheduled point, the LDL-C level was imputed by a multiple regression model, the covariates of which were treatment arm, sex, age, baseline lipid values (TC, HDL-C, LDL-C, TG), diabetes mellitus, hypertension, treatment history of hyperlipidemia, BMI, cigarette smoking, alcohol drinking, and the latest LDL-C before the scheduled point. The risk factors were sex, age, baseline LDL-C level, baseline HDL-C level, diabetes, hypertension, and smoking habit. In addition, treatment groups were combined and divided into quintiles according to the on-treatment LDL-C level or LDL-C reduction rate from baseline during follow-up, and the incidence of cardiovascular events was compared among the 5 groups. Events that occurred within 6 months after starting follow-up were excluded in this analysis because these events might not have been associated with the treatment.

The statistical significance level was a two-sided p value of 5%. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA) software.

Results

A total of 7,581, 7,598, and 7,599 patients with a recorded baseline and the on-treatment LDL-C level of the 7,832 patients (primary analysis set in the main analysis\textsuperscript{13}) were analyzed for CVD, CHD, and stroke, respectively. The difference in the number of patients for each analysis was because we assessed only events that occurred from 6 months after follow-up began. The distribution of the baseline and on-treatment LDL-C level in the diet-alone and diet plus pravas-
The average baseline LDL-C level was 156 mg/dL in both treatment groups, which decreased to 151 mg/dL in the diet-alone group and to 127 mg/dL in the diet plus pravastatin group. The parameters in the tertiles of the diet plus pravastatin group and in the quintiles of all patients divided according to the on-treatment LDL-C level for CVD analysis are shown in Table 1A and 1B, respectively. Groups with low on-treatment LDL-C also had a low baseline LDL-C level in both tertile and quintile analyses. On the other hand, quintile analysis of the LDL-C reduction indicated that patients with a high baseline cholesterol had a much greater LDL-C reduction (Table 1C). The prevalence of pravastatin-treated patients was higher in groups with a low on-treatment LDL-C or greater LDL-C reduction than groups with a high on-treatment LDL-C level or smaller LDL-C reduction (Table 1C).

Regarding the incidence of CVD among tertiles in the diet plus pravastatin group, a significant risk reduction was observed in the second tertile with the lowest hazard ratio (0.57, \( p = 0.01 \)) among groups (Fig. 2a). The incidence of CHD was slightly decreased in relation to lowering on-treatment LDL-C, although this was not seen for stroke (Fig. 2b, 2c). A similar assessment was performed for the total patient group. The incidence of CVD was lowest in the fourth quintile (HR 0.48, 95%CI 0.31–0.76, \( p = 0.0015 \)), and in patients whose on-treatment LDL-C level ranged from 120.9 to 133.3 mg/dL. A significant risk reduction was also observed in the fifth quintile (HR 0.64, 95%CI 0.41–1.00, \( p = 0.048 \)), although the magnitude was smaller than in the fourth tertile (Fig. 3a). Similar tendencies were also found for CHD and stroke (Fig. 3b, 3c). The incidence of CHD and stroke was lowest in the fourth quintile, rather than in the fifth quintile with the lowest on-treatment LDL-C. Regarding risk reduction in relation to LDL-C reduction, a significant 45% risk reduction of CVD (HR 0.55, 95%CI 0.34–0.87) was found in the fifth quintile.

### Table 1. Parameters in each group

<table>
<thead>
<tr>
<th></th>
<th>On-treatment LDL level (range), mg/dL</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Event number, CVD (CHD, Stroke)/Patients</th>
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</thead>
<tbody>
<tr>
<td>Diet-alone group</td>
<td>151.7 (71.3–206.2)</td>
<td>155.7</td>
<td>133 (74, 53)/3,841</td>
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<tr>
<td>Diet plus pravastatin group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1 (T1)</td>
<td>142.0 (133.5–187.6)</td>
<td>167.1</td>
<td>29 (20, 6)/1,249</td>
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<tr>
<td>Tertile 2 (T2)</td>
<td>126.8 (119.8–133.4)</td>
<td>157.2</td>
<td>25 (15, 8)/1,245</td>
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<tr>
<td>Tertile 3 (T3)</td>
<td>111.8 (56.7–119.7)</td>
<td>144.1</td>
<td>34 (16, 16)/1,246</td>
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<thead>
<tr>
<th></th>
<th>On-treatment LDL level (range), mg/dL</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Event number, CVD (CHD, Stroke)/Patients</th>
<th>Ratio of statin treated patients (%)</th>
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<tr>
<td>Quintile 1 (Q1)</td>
<td>165.4 (157.5–206.2)</td>
<td>169.1</td>
<td>59 (34, 21)/1,514</td>
<td>31.3</td>
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<td>Quintile 2 (Q2)</td>
<td>150.8 (144.9–157.4)</td>
<td>159.5</td>
<td>39 (22, 15)/1,525</td>
<td>40.7</td>
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<tr>
<td>Quintile 3 (Q3)</td>
<td>139.2 (133.4–144.8)</td>
<td>156.2</td>
<td>47 (29, 16)/1,509</td>
<td>59.5</td>
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<tr>
<td>Quintile 4 (Q4)</td>
<td>127.6 (120.9–133.3)</td>
<td>153.0</td>
<td>31 (16, 12)/1,510</td>
<td>78.0</td>
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<tr>
<td>Quintile 5 (Q5)</td>
<td>112.6 (56.7–120.8)</td>
<td>141.9</td>
<td>45 (24, 19)/1,523</td>
<td>89.7</td>
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<tr>
<th></th>
<th>LDL reduction (range), %</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Event number, CVD (CHD, Stroke)/Patients</th>
<th>Ratio of statin treated patients (%)</th>
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<tbody>
<tr>
<td>Quintile 1 (Q1)</td>
<td>4.4 (−0.1–794.1)</td>
<td>145.2</td>
<td>45 (30, 14)/1,519</td>
<td>25.3</td>
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<td>Quintile 2 (Q2)</td>
<td>−3.6 (−6.7–−0.2)</td>
<td>156.4</td>
<td>59 (34, 24)/1,523</td>
<td>33.7</td>
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<tr>
<td>Quintile 3 (Q3)</td>
<td>−10.2 (−13.8–−6.8)</td>
<td>158.2</td>
<td>36 (19, 14)/1,505</td>
<td>57.3</td>
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<td>Quintile 4 (Q4)</td>
<td>−17.7 (−21.1–−13.9)</td>
<td>157.7</td>
<td>47 (24, 19)/1,511</td>
<td>85.9</td>
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<tr>
<td>Quintile 5 (Q5)</td>
<td>−26.0 (−59.8–−21.2)</td>
<td>162.2</td>
<td>34 (18, 12)/1,523</td>
<td>97.0</td>
</tr>
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</table>

On-treatment LDL levels are shown as the median and range in parentheses, and baseline LDL-C are shown as an average. Number of patients is shown only for CVD analysis. Data for CHD or stroke analysis were omitted because they were very similar to the CVD analysis.

The average baseline LDL-C level was 156 mg/dL in both treatment groups, which decreased to 151 mg/dL in the diet-alone group and to 127 mg/dL in the diet plus pravastatin group. The parameters in the tertiles of the diet plus pravastatin group and in the quintiles of all patients divided according to the on-treatment LDL-C level for CVD analysis are shown in Table 1A and 1B, respectively. Groups with low on-treatment LDL-C also had a low baseline LDL-C level in both tertile and quintile analyses. On the other hand, quintile analysis of the LDL-C reduction indicated that patients with a high baseline cholesterol had a much greater LDL-C reduction (Table 1C). The prevalence of pravastatin-treated patients was higher in groups with a low on-treatment LDL-C or greater LDL-C reduction than groups with a high on-treatment LDL-C level or smaller LDL-C reduction (Table 1C).
tile (less than −21.2% [average −26%]) (Fig. 4). A significant risk reduction was not found in the third and fourth quintiles. These results were not different from those adjusted by the continuous value of the HDL-C level instead of adjusting by the categorized value (data not shown), indicating that the HDL-C level does not impact the data interpretation.

**Discussion**

Since higher-dose statins were launched on the market and trial evidence was obtained, it has been accepted that lowering LDL-C further is associated with a greater reduction in cardiovascular risk. The Treatment to New Target (TNT) study\(^{16}\) demonstrated a significant 22% risk reduction with high-dose atorvastatin treatment (80 mg/day) compared to low-dose treatment (10 mg/day), achieving on-treatment LDL-C levels of 77 mg/dL and 101 mg/dL respectively. Direct comparison of a high-dose statin (80 mg atorvastatin) to usual-dose statin (simvastatin) treatment on cardiovascular disease risk reduction was made in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study of secondary prevention\(^{17}\). A larger risk reduction in CVD (13%) was obtained with high-dose statin treatment compared to the usual-dose statin. This also supported the hypothesis that a much lower LDL-C level induced a greater risk reduction. Moreover, studies with soft endpoints showed improved atherosclerosis by aggressively lowering LDL-C, again supporting the hypothesis of ‘the lower the better’ to reduce risk.
However, evidence supporting ‘the lower the better’ hypothesis came from studies with moderately-high to high-risk populations. In fact, most patients in these studies had a 10-year risk of CHD of more than 10%, based on the estimation of annual incidence. In contrast, in the MEGA study, the incidence of CHD was only 0.5% per year in the control group during the 5-year follow-up. It has not been clarified whether or not the findings from studies with moderately-high and high-risk patients can be extrapolated to a low-risk population, such as mild to moderate Japanese hypercholesterolemia, as studied in MEGA. The results of the present post-hoc analysis provide further information to answer this question. In this analysis, in patients taking pravastatin, the CVD incidence decreased in relation to the decrease in LDL-C; however, no further risk reduction was found below 120.8 mg/dL for the on-treatment LDL-C level. Although there was a lack of statistical power because of the small number of events, in the present analysis we did not find evidence to support the hypothesis of ‘the lower the better’ for CHD or stroke alone, which were components of our CVD endpoint. Similar results were found in an observational study that analyzed patients with mild to moderate hypercholesterolemia without a history of cardiovascular disease. Itakura et al.
al. demonstrated that coronary events were significantly higher in patients with an LDL-C of more than 140 mg/dL, and no significant difference was found for 100−139 mg/dL LDL-C.

The ATP III guidelines recommend an LDL-C goal of <130 mg/dL for a 10-year risk of <10% by Framingham risk scoring. The Japan Atherosclerosis Society (JAS) guideline for the diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese also recommends an LDL-C goal of <120 mg/dL or <140 mg/dL for patients with more than 3 risk factors or 1 to 2 risk factors for CVD, respectively, in patients without a history of CVD. Thus, for primary prevention in patients with some risk for CVD, the target of 120−140 mg/dL LDL-C in guidelines such as the ATP III and JAS is supported by the available evidence. The JAS guideline demonstrates that an LDL-C reduction of 20−30% is possible. In the present analysis, patients who achieved this 20−30% LDL-C reduction (primarily in the fifth quintile) had a significant CVD risk reduction, and the target LDL-C reduction of 20−30% recommended by the JAS guideline is appropriate for mild to moderate hypercholesterolemic Japanese.

An important limitation of this analysis was the narrow on-treatment LDL-C distribution. An LDL-C level less than 100 mg/dL was achieved in 5% of patients and an LDL-C reduction of more than 30% was achieved in 9.4% of patients, during 5-year follow-up. Thus, it is unclear whether a much greater

Fig. 4. Incidence of CVD, CHD, and stroke according to quintiles of LDL-C reduction in the total population. Bars express the 95% confidence interval (95%CI). Hazard ratio and 95% CI were estimated by the COX proportional hazard model against diet group, adjusted by sex, age, baseline LDL-C and HDL-C level, hypertension, diabetes, and smoking habit. The LDL-C level for each quintile was determined based on mean LDL-C reduction. The percentage of patients in each quintile of LDL concentration in the diet plus pravastatin group is indicated by a solid line, corresponding to the right vertical axis.
risk reduction for CVD could be obtained by more aggressive LDL-C reduction, because no data were obtained in this low-risk population.

**Conclusions**

The usual Japanese dose of pravastatin therapy is sufficient in this low-risk patient population to reduce cardiovascular risk, with an achieved LDL-C level <133.4 mg/dL. Further risk reduction was not found with an achieved LDL-C <120 mg/dL. A significant risk reduction was found in the group with an LDL-C reduction of 20–30%. These results support the JAS guideline recommendation for LDL-C treatment in Japanese.

**Acknowledgements**

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**References**

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