Appropriate Level of Low-Density Lipoprotein Cholesterol for Secondary Prevention of Coronary Artery Disease

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Aim: Current Japanese guidelines state the target level of low-density lipoprotein cholesterol (LDL-C) of <100 mg/dL for secondary prevention of coronary artery disease (CAD). However, this level was set considering the results of trials mainly conducted in Western countries. In addition, the effect of achieving target LDL-C on secondary prevention is unknown.

Methods: We examined the effects of achieving target LDL-C on clinical outcomes. Patients who underwent percutaneous coronary intervention at Juntendo University Hospital (Tokyo, Japan) from 2004 to 2010 and received follow-up coronary angiography (CAG) were analyzed. The study population was divided into two groups based on the follow-up LDL-C. The incidence of major adverse cardiovascular events within 3 years after the follow-up CAG was examined.

Results: A total of 1321 consecutive patients were enrolled. Sixty-three percent of the patients achieved the target LDL-C. The rate of 3-year events was lower in the group that achieved the target LDL-C (achieved group). The adjusted relative risk reduction in the achieved group was 26% (p = 0.02). In the sub-analysis among the four groups stratified by baseline LDL-C of 140 and follow-up LDL-C of 100, the adjusted hazard ratio for 3-year events was 1.84 (95% confidence interval: 1.10 – 3.24) in Group 3 (baseline <140, follow-up ≥100) and 2.05 (1.18 – 3.74) in Group 4 (baseline ≥140, follow-up ≥100) [Group 2 (baseline ≥140, follow-up <100) as reference].

Conclusions: Our data suggested that follow-up LDL-C <100 mg/dL was appropriate for secondary prevention of CAD in Japanese population.

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Key words: Low-density lipoprotein cholesterol, Secondary prevention, Coronary artery disease, Percutaneous coronary intervention

Introduction

Coronary artery disease (CAD) is a leading cause of death worldwide. Therefore, primary and secondary prevention of CAD is important. Treatment targets for secondary prevention have focused on traditional risk factors for CAD, such as diabetes mellitus, hypertension, and dyslipidemia. In particular, low-density lipoprotein cholesterol (LDL-C) was one of the most appropriate treatment targets for preventing future cardiovascular events. Recently, the American College of Cardiology and American Heart Association joint guidelines were updated, and they emphasized the importance of statin administration for secondary prevention of CAD, irrespective of the level of LDL-C, whereas the guidelines of the Japanese Atherosclerosis Society (JAS) and Japanese Circulation Society (JCS) state that the target level of LDL-C is <100 mg/dL for secondary prevention in patients with CAD. However, the target level was set considering the results of several large-scale clinical trials mainly conducted in Western countries.
addition, few studies have examined the effect of achieving target LDL-C on secondary prevention of CAD in clinical practice.

**Aim**

We aimed to examine whether a follow-up LDL-C value of \( \leq 100 \text{ mg/dL} \) was appropriate for secondary prevention of CAD in a clinical setting.

**Methods**

**Study Population**

We analyzed data from our database of PCI in Juntendo University Hospital (Tokyo, Japan). Consecutive patients who underwent PCI for the treatment of ACS or stable CAD between January 2004 and December 2010 were included in this study. Patients who did not undergo follow-up coronary angiography (CAG) were excluded from the study. Follow-up CAG was performed between 5 and 12 months after the index PCI. The study population was divided into two groups based on whether the follow-up LDL-C level was above or below 100 mg/dL. In addition, a subgroup analysis was performed in which the population was divided into four groups according to a baseline LDL-C level of 140 mg/dL and follow-up LDL-C level of 100 mg/dL.

**Measurement of Lipid Profiles**

Lipid profiles, including LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride, and total cholesterol, were measured the day when the index PCI was performed and follow-up lipid profiles were measured in the morning of the follow-up CAG. LDL-C was estimated using Friedewald equation if the triglyceride level was \( \geq 400 \text{ mg/dL} \). In cases with triglyceride level of \( \geq 400 \text{ mg/dL} \), direct LDL-C measurement was used.

**Clinical Outcomes**

The primary endpoint was a composite of all-cause mortality, non-fatal ACS, non-fatal stroke, and repeat revascularization. The primary endpoint was assessed at 3 years after the follow-up CAG. Information regarding outcomes was collected during clinical visits, via telephone interviews with the patients or from their referring physicians. Our institutional review board approved the protocol of this study, which was implemented in accordance with the principles established in the Declaration of Helsinki and our institutional ethics policy. In this study, all participants provided written informed consent regarding anonymized patients’ data to be made public.

**Definitions**

We defined ACS as unstable angina pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI), or STEMI. UAP was defined as angina at rest or in an accelerating pattern with negative cardiac biomarkers, with or without ECG changes indicative of myocardial ischemia (for example, ST segment depression or transient elevation or new T wave inversion). Myocardial infarction was defined as
Table 1. Patient characteristics

|                           | Follow-up LDL-C < 100 (N=829) | Follow-up LDL-C ≥ 100 (N=492) | \( \rho \) |
|---------------------------|-------------------------------|-------------------------------|-----------|
| Age, year                 | 65.1 ± 10.2                   | 64.8 ± 9.7                    | 0.7       |
| Male, n (%)               | 704 (84.7)                    | 399 (81.1)                    | 0.09      |
| BMI, kg/m²                | 24.4 ± 3.4                    | 24.4 ± 3.3                    | 0.9       |
| Hypertension, n (%)       | 593 (71.4)                    | 350 (71.1)                    | 0.9       |
| Diabetes mellitus, n (%)  | 354 (42.6)                    | 229 (46.5)                    | 0.2       |
| Dyslipidemia, n (%)       | 599 (72.1)                    | 373 (75.8)                    | 0.1       |
| Current smoking, n (%)    | 228 (27.4)                    | 124 (25.2)                    | 0.4       |
| Family history, n (%)     | 234 (28.2)                    | 140 (28.5)                    | 0.9       |
| LDL-C, mg/dL (baseline)   | 105.7 ± 32.4                  | 125.8 ± 31.5                  | <0.0001   |
| LDL-C, mg/dL (follow-up)  | 77.3 ± 15.0                   | 124.8 ± 48.4                  | <0.0001   |
| HDL-C, mg/dL              | 45.4 ± 12.3                   | 44.5 ± 12.0                   | 0.2       |
| TG, mg/dL                 | 137.3 ± 75.6                  | 143.0 ± 89.9                  | 0.2       |
| HbA1c (NGSP), %           | 6.3 ± 1.1                     | 6.5 ± 1.4                     | 0.01      |
| Hb, g/dL                  | 13.5 ± 1.6                    | 13.4 ± 1.7                    | 0.4       |
| LVEF, %                   | 61.9 ± 10.6                   | 62.5 ± 10.4                   | 0.3       |
| eGFR, mL/min/1.73 m²      | 67.2 ± 20.8                   | 67.7 ± 21.8                   | 0.6       |
| Acute coronary syndrome, n (%) | 257 (30.9)       | 116 (23.6)                    | 0.004     |
| Success rate, n (%)       | 830 (99.9)                    | 490 (99.6)                    | 0.3       |
| Type of procedure, n (%)  | 0.4                           |                               |           |
| POBA                      | 23 (2.77)                     | 8 (1.63)                      |           |
| BMS                       | 319 (38.39)                   | 194 (39.43)                   |           |
| DES                       | 779 (91.84)                   | 290 (58.94)                   |           |
| Medication                |                               |                               |           |
| Aspirin                   | 757 (91.9)                    | 469 (96.5)                    | 0.0009    |
| Statin                    | 550 (66.5)                    | 279 (57.2)                    | <0.0001   |
| ACEI                      | 98 (11.9)                     | 65 (13.4)                     | 0.4       |
| ARB                       | 334 (40.5)                    | 199 (41.0)                    | 0.9       |
| β-blocker                 | 411 (49.9)                    | 237 (48.8)                    | 0.7       |
| Calcium channel blocker   | 322 (39.1)                    | 204 (42.2)                    | 0.3       |
| Diseased vessel           |                               |                               | 0.002     |
| LAD                       | 393 (47.29)                   | 236 (47.97)                   |           |
| LCX                       | 150 (18.05)                   | 108 (21.95)                   |           |
| RCA                       | 251 (30.20)                   | 133 (27.03)                   |           |
| LMT                       | 30 (3.61)                     | 4 (0.81)                      |           |
| Others                    | 7 (0.84)                      | 11 (2.24)                     |           |
| MVD                       | 457 (56.0)                    | 268 (55.0)                    | 0.7       |
| QCA                       |                               |                               |           |
| Reference diameter, mm    | 2.83 ± 0.50                   | 2.81 ± 0.46                   | 0.6       |
| MLD (pre), mm             | 0.38 ± 0.35                   | 0.40 ± 0.32                   | 0.3       |
| MLD (post), mm            | 2.72 ± 0.50                   | 2.73 ± 0.48                   | 0.9       |
| Stent diameter, mm        | 2.99 ± 0.42                   | 2.97 ± 0.40                   | 0.3       |
| Stent length, mm          | 19.6 ± 5.8                    | 20.1 ± 6.7                    | 0.2       |

BMI; body mass index, LDL-C; low density lipoprotein cholesterol, HDL-C; high density lipoprotein cholesterol, TG; triglyceride, HbA1c; glycated hemoglobin, Hb; hemoglobin, LVEF; left ventricular ejection fraction, eGFR; estimated glomerular filtration rate, POBA; plain old balloon angioplasty, BMS; bare metal stents, DES; drug-eluting stents, ACEI; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, LAD; left anterior descending artery, LCX; left circumflex, RCA; right coronary artery, LMT; left main trunk, MVD; multivessel coronary artery disease, QCA; quantitative coronary angiography, MLD; minimum lumen diameter
rates were estimated by Kaplan–Meier methods and compared using the log-rank test between the groups. To identify whether follow-up LDL-C \(\leq 100\) mg/dL was associated with the primary endpoint, univariable Cox regression analysis was performed. The adjusted hazard ratio (HR) of follow-up LDL-C \(\leq 100\) mg/dL was analyzed by multivariable Cox regression analysis including age, gender, BMI, diabetes, hypertension, current smoking, and a presentation of ACS at the index PCI as confounding factors. Furthermore, Cox regression analysis for the primary endpoint was performed to identify an association between the primary endpoint and four subgroups stratified by the baseline LDL-C of 140 mg/dL and follow-up LDL-C of 100 mg/dL. HR and 95% confidence interval were also calculated. We set the day of follow-up CAG as the index day of the follow-up in the cumulative event rate calculation and Cox regression analyses. A \(p\) value \(\leq 0.05\) was considered to be statistically significant. All data were analyzed using JMP version 10.0 for Windows (SAS Institute, Cary, NC, USA).

**Results**

A total of 1321 consecutive patients who underwent PCI and follow-up CAG were enrolled in this study (Fig. 1). The median interval from the day of

Fig. 2. Event-free survival curves for the primary endpoint. Kaplan–Meier curves for the primary endpoint show that the group of patients with follow-up LDL-C \(\leq 100\) mg/dL had a lower incidence of clinical outcomes compared with other patients.
the measurement of baseline LDL-C to that of follow-up LDL-C was 232 days (interquartile range of between 189 and 252). The baseline characteristics are shown in Table 1. The percentage of patients who achieved the target LDL-C level of <100 mg/dL at follow-up was 62.8%. The group with follow-up LDL-C < 100 (achieved group) includes more patients with ACS. The glycated hemoglobin value was lower in this group. Baseline and follow-up LDL-C levels were 105.7 and 77.3 mg/dL in the achieved group and 125.8 and 124.8 mg/dL in the non-achieved group, respectively. Statin was prescribed to 66.5% of the patients in the achieved group, whereas the percentage was 57.2% in the non-achieved group (p < 0.0001) (Table 1).

Event-free survival curves for the primary endpoint are described in Fig. 2, which show a lower incidence of the events in the achieved group compared with that in the non-achieved group (p = 0.04). Univariable Cox regression analysis revealed that the achieved group was associated with a reduction in the primary endpoint, although the p value was not significant (p = 0.054). However, the adjusted relative risk reduction in the achieved group was 26% (p = 0.02). Advanced age and ACS at the index PCI were associated with an increase in the primary endpoint in the multivariable Cox regression analysis (Table 2). Regarding the association between statin administration at baseline and the change in the LDL-C value from baseline to follow-up, the interaction effect between the two variables on the primary endpoint was observed, although the p value was not statistically significant (p for interaction = 0.07). In the subgroup analysis among the four groups stratified by the baseline LDL-C of 140 mg/dL and follow-up LDL-C of 100 mg/dL (Fig. 3), the adjusted hazard ratio for the
There have been hitherto few available studies that have provided a rationale for the target LDL-C value \( \leq 100 \text{ mg/dL} \) for secondary prevention of CAD, particularly in Japan. The MUSASHI-AMI (MUlticenter Study for Aggressive lipid-lowering Strategy by HMG-CoA reductase Inhibitors in patients with Acute Myocardial Infarction) study was only a prospective clinical trial examining the effect of aggressive lipid-lowering therapy using statins on secondary prevention in patients with AMI\(^{16}\). The composite primary endpoint, including cardiovascular death, nonfatal AMI, recurrent symptomatic myocardial ischemia, heart failure, and nonfatal stroke, was less frequently observed in the statin-treated group with LDL-C reduction from 133 to 99.8 mg/dL 2 years after the treatment\(^{16}\), which was consistent with our results. However, no clinical practice-based data were available to determine the beneficial effect of the target LDL-C value \( \leq 100 \text{ mg/dL} \) on secondary cardiovascular events. In this regard, it is of significance that our results showed the beneficial effect of LDL-C \( \leq 100 \text{ mg/dL} \), that is recommended as the target value for secondary prevention of CAD, on the long-term cardiovascular events in the real-
of CAD in Japanese population.

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Disclosures

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The other authors report no conflicts.

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**Supplementary Table.** Univariable Cox regression analysis for the primary endpoint

|                                      | HR   | 95% CI     | p   |
|--------------------------------------|------|------------|-----|
| Follow-up LDL-C, 1 mg/dL increase    | 1.002| 0.99-1.005 | 0.5 |

LDL-C; low density lipoprotein cholesterol, HR; hazard ratio, CI; confidence interval