Comparison of the low-density lipoprotein cholesterol target value and the preventive effect of statins in elderly patients and younger patients

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Abstract

Objective To assess whether the low-density lipoprotein cholesterol (LDL-C) target value and preventive effect of statins are different between elderly and younger patients.

Methods We investigated 304 patients with previous percutaneous coronary intervention who underwent coronary angiography from January 2007 to December 2016 for examination of recurrent ischemia beyond the early restenosis. Patients were classified into two groups: age ≥ 75 years (elderly group: n = 140) and < 75 years (younger group: n = 164). Relationships between the achieved LDL-C level, incidence of late coronary events, and the effectiveness of statins were evaluated.

Results During follow-up, 179 patients underwent late coronary revascularization. Recurrent ischemia presenting as acute coronary syndrome (ACS) occurred in 83 cases. Kaplan-Meier curve analysis revealed that in the younger group, recurrent ACS was significantly lower in patients with LDL-C < 70 mg/dL than in those with LDL-C ranging from 70 to < 100 mg/dL (P = 0.035); however, there was no difference between these in the elderly group (P = 0.863). Instead, recurrent ACS was less frequent in patients with LDL-C ranging from 70 mg/dL to < 100 mg/dL in the elderly group (P = 0.033). Statin use was associated with decreased recurrent ACS (P = 0.005); moreover, only using statins was an independent predictor in the elderly group (HR: 0.375; P = 0.007).

Conclusions Strict control of LDL-C to < 70 mg/dL was effective for reducing the incidence of recurrent ACS in younger patients. However, LDL-C < 100 mg/dL might be sufficient as the target value of LDL-C-lowering therapy for secondary prevention of ischemic events in Japanese elderly patients.

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Keywords: Acute coronary syndrome; Late coronary event; Prevention

1 Introduction

Because of the large aging population, and because cardiovascular risk increases with age, the number of elderly patients with cardiac ischemia is increasing.¹ It has been reported that approximately 37% of patients admitted with acute myocardial infarction and 60% of patients dying from myocardial infarction are older than 75 years.² Therefore, it is important to consider how secondary prevention for elderly patients should be managed.

The effectiveness of low-density lipoprotein cholesterol (LDL-C)-lowering therapy with statins for primary and secondary prevention of atherosclerotic cardiovascular diseases has been established.³⁴ Aggressive LDL-C-lowering therapy with statins has been reported to induce significant regression of coronary plaque volume;⁵ the turning point of plaque regression was LDL-C < 70 mg/dL.⁶ In the Japanese guidelines for diagnosis and prevention of atherosclerotic cardiovascular diseases, an LDL-C target value of < 100 mg/dL is recommended for secondary prevention.⁷ The guidelines of the European Society of Cardiology also recommend controlling LDL-C to < 70 mg/dL as a treatment goal for patients at very high risk including secondary prevention.⁸ However, most randomized, controlled trials that have evaluated the relationship between lipid profile and cardiovascular outcome excluded elderly patients. Therefore, there is little information regarding the influence of statin therapy and the achieved LDL-C level on long-term cardiovascular events in secondary prevention of Japanese elderly patients.

In the present study, we assessed whether the target value of LDL-C and preventive effect of statins were different
between elderly patients and younger patients who underwent percutaneous coronary intervention (PCI) following recurrent cardiac ischemia after stabilization.

2 Methods

2.1 Study population

We retrospectively screened 384 patients with a history of PCI who underwent late coronary angiography (CAG) from January 2007 to December 2016 for the evaluation of recurrent cardiac ischemia after stabilization beyond the early phase of restenosis in our hospital. Stabilization was defined as survival without any subsequent coronary revascularization at follow-up CAG performed 6–12 months after the last PCI. Clinical rationales of suspected recurrent cardiac ischemia were new onset of chest pain in 373 patients; others were new electrocardiogram change or development of left ventricular asynergy. The following exclusion criteria were applied: (1) history of coronary artery bypass grafting (34 patients); (2) lack of follow-up CAG 6–12 months after PCI (29 patients); and (3) chronic total occlusion at the time of early follow-up CAG (17 patients). Because of retrospective design of this study, the patients without recurrent ischemia, including patients deceased by non-cardiac cause, others were new electrocardiogram change or development of left ventricular asynergy. The following exclusion criteria were applied: (1) history of coronary artery bypass grafting (34 patients); (2) lack of follow-up CAG 6–12 months after PCI (29 patients); and (3) chronic total occlusion at the time of early follow-up CAG (17 patients). Because of retrospective design of this study, the patients without recurrent ischemia, including patients deceased by non-cardiac cause, also excluded. As a result, 304 patients were eligible for this investigation. The index PCI period for these patients was from May 1988 to December 2014. Patients were classified into two groups according to age: older than 75 years (elderly group: n = 140; median age: 80 years) or younger than 75 years (younger group: n = 164; median age: 65 years).

The study protocol was approved by the Ethics Committee of Shimane University Hospital. Because of a retrospective study design, the requirement for informed patient consent was waived by the ethics committee. The study was conducted according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2 Study design and data collection

Late coronary revascularization was defined as that performed after the achievement of stabilization beyond the early phase of restenosis. Data regarding age, gender, risk factors for coronary artery disease, laboratory parameters and cardiovascular medications prescribed at the time of admission for late CAG were obtained from hospital records or by telephone contact (Smoking habit was confirmed by telephone interview in seven patients). Regarding laboratory measurements, the LDL-C concentration was calculated using Friedewald’s formula. Diabetic mellitus (medication-dependent status, systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg), dyslipidemia (medication-dependent status, LDL-C level ≥ 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) level < 40 mg/dL, and/or triglyceride level ≥ 150 mg/dL), chronic kidney disease (estimated glomerular filtration rate < 60 mL/min per 1.73 m²), and current smoking were examined as risk factors for atherosclerotic coronary artery disease. Similarly, CAG findings, late coronary events (including recurrent ischemia presenting as acute coronary syndrome [recurrent acute coronary syndrome (ACS)] and any late coronary revascularization), and in-hospital mortality rates were assessed. To evaluate the relationship between the achieved level of LDL-C and the incidence of late coronary events, patients were stratified into three subgroups according to the LDL-C value at the time of late CAG: those who achieved LDL-C < 70 mg/dL, those who achieved LDL-C 70 to < 100 mg/dL, and those who achieved LDL-C ≥ 100 mg/dL. Similarly, the incidence of late coronary events was compared between the patients who were and were not using statins. Moreover, predictors of recurrent ACS were examined on late CAG for the elderly group and younger group.

2.3 Statistical analysis

Continuous variables were expressed as mean ± SD and compared using Student’s t-test. Categorical variables were presented as percentages and compared using the chi-square test. Differences were considered statistically significant when \( P < 0.05 \). The cumulative incidence of late coronary events was analyzed using the Kaplan-Meier method; each group was compared using the log-rank test. The follow-up period comprised the day of the last PCI procedure until late CAG. The predictive value of recurrent ACS was verified using the univariate Cox proportional hazards model. A multivariate Cox proportional hazards model involving the forward selection method was used to assess the independent roles of these variables. Covariates that were statistically significant according to univariate analysis were included in the multivariate analysis. Hazard ratios (HR) and 95% confidence interval (CI) were reported. Statistical analyses were performed using the PASW Statistics version 17.0 software program (SPSS, Chicago, Illinois).

3 Results

3.1 Clinical characteristics and outcome

Clinical characteristics at the time of admission for late CAG are shown in Table 1. We evaluated 251 men and 53
women, with a mean age of 71.7 ± 10.1 years. Among these subjects, bare metal stents were implanted in 216 patients (71%) and drug-eluting stents were implanted in 102 patients (34%). In 40 patients (13%), both bare metal and drug-eluting stents were implanted. The average interval between the last PCI procedure and late CAG was 7.0 ± 4.4 years.

Risk factors more frequently found in the younger group than in the elderly group included male sex and dyslipidemia, whereas there was a higher incidence of chronic kidney disease in the elderly group. Because women were a quarter in the elderly group, furthermore, only one-tenth were women in younger group, that made it impossible to compare cardiac events between men and women. In terms of laboratory data, the elderly group showed significantly lower levels of total cholesterol, triglycerides, and non-high-density lipoprotein cholesterol (non-HDL-C) than the younger group. The value of LDL-C and the prevalence of diabetes mellitus were similar between the two groups. The proportion of patients who were prescribed statins and β-blockers was higher in the younger group than in the elderly group. The type and dose of statins varied (73 patients using atorvastatin 5–30 mg, 57 patients using pravastatin 5–10 mg, 41 patients using rosuvastatin 2.5–10 mg, 14 patients using pitavastatin 2–4 mg, 12 patients using fluvastatin 5–30 mg, and 12 patients using simvastatin 5–10 mg).

Clinical outcomes at the time of admission for late CAG are presented in Table 2. During the mean follow-up period of 7.0 years, 179 patients (59%) underwent any late coronary revascularization, including late target lesion revascularization (52 patients) and new lesion revascularization (127 patients). Clinical presentation of recurrent ACS and stable angina occurred in 83 cases and in 96 cases, respectively. The incidence of recurrent ACS and any late coronary revascularization was not different between the elderly group and younger group.

### 3.2 Relationship between the achieved level of LDL-C and the incidence of late coronary events

The probability of freedom from late coronary events stratified according to the value of LDL-C is shown in Figure 1. Kaplan-Meier curve analysis revealed that in the younger group, the incidence of recurrent ACS was significantly lower in patients with LDL-C < 70 mg/dL than in those with LDL-C 70 to <100 mg/dL (P = 0.035); however, there was no difference between these in the elderly group.

### Table 1. Clinical characteristics of patients at late coronary angiography.

|                   | Elderly group (n = 140) | Younger group (n = 164) | P  |
|-------------------|-------------------------|-------------------------|----|
| Interval from last PCI to late CAG, yrs | 7.1 ± 4.8 | 6.9 ± 4.1 | 0.685 |
| Age, yrs          | 80.4 ± 4.1             | 64.2 ± 7.5             | <0.001 |
| Male sex          | 105 (75%)              | 146 (89%)              | 0.001 |
| Hypertension      | 94 (67%)               | 108 (66%)              | 0.812 |
| Dyslipidemia      | 110 (79%)              | 152 (93%)              | <0.001 |
| Diabetes mellitus | 65 (46%)               | 86 (52%)               | 0.296 |
| Use of insulin    | 11 (8%)                | 12 (7%)                | 0.859 |
| Current smoker    | 25 (18%)               | 44 (27%)               | 0.063 |
| Chronic kidney disease | 62 (44%) | 42 (26%) | 0.001 |
| Hemodialysis      | 6 (4%)                 | 6 (4%)                 | 0.780 |
| Previous myocardial infarction | 60 (43%) | 83 (51%) | 0.177 |
| Use of drug eluting stent | 51 (36%) | 51 (31%) | 0.326 |
| Use of bare metal stent | 94 (67%) | 122 (74%) | 0.165 |
| Total cholesterol, mg/dL | 171.4 ± 33.2 | 180.9 ± 42.9 | 0.031 |
| LDL-C, mg/dL      | 98.9 ± 29.8            | 104.4 ± 38.3           | 0.164 |
| HDL-C, mg/dL      | 47.2 ± 13.3            | 46.0 ± 12.6            | 0.408 |
| Triglyceride, mg/dL | 126.5 ± 64.0   | 152.3 ± 86.9          | 0.003 |
| Non-HDL-C, mg/dL  | 124.2 ± 33.4           | 134.9 ± 41.9           | 0.014 |
| LDL-C/HDL-C ratio | 2.24 ± 0.88            | 2.43 ± 1.11            | 0.111 |
| HbA1c (NGSP, %)   | 6.53 ± 1.07            | 6.81 ± 1.52            | 0.062 |
| Creatinine, mg/dL | 1.23 ± 1.58            | 1.21 ± 1.72            | 0.908 |
| Use of statins    | 84 (60%)               | 125 (76%)              | 0.002 |
| Use of ACE-I or ARB | 74 (53%)          | 89 (54%)               | 0.806 |
| Use of β-blocker  | 32 (23%)               | 56 (34%)               | 0.031 |
| Use of antiplatelet drugs | 122 (87%) | 147 (90%) | 0.498 |

Data were presented as mean ± SD or n (%). The elderly group and younger group were defined as patients older than 75 years and those younger than 75 years, respectively. ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CAG: coronary angiography; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NGSP: National Glycohemoglobin Standardization Program; PCI: percutaneous coronary intervention.

### Table 2. Clinical outcomes of patients at late coronary angiography.

|                                | Elderly group (n = 140) | Younger group (n = 164) | P  |
|--------------------------------|-------------------------|-------------------------|----|
| Any late coronary revascularization | 84 (60%)               | 95 (58%)               | 0.714 |
| Late target lesion revascularization | 21 (15%)               | 31 (19%)               | 0.368 |
| New lesion revascularization     | 63 (45%)               | 64 (39%)               | 0.292 |
| Acute coronary syndrome          | 37 (26%)               | 46 (28%)               | 0.752 |
| Multi-vessel disease             | 69 (48%)               | 63 (38%)               | 0.081 |
| Chronic total occlusion          | 22 (16%)               | 24 (15%)               | 0.793 |
| Left main trunk disease          | 10 (7%)                | 4 (2%)                 | 0.051 |
| In hospital all cause mortality  | 1 (1%)                 | 3 (2%)                 | 0.373 |
| In hospital cardiac death        | 1 (1%)                 | 1 (1%)                 | 0.710 |

Data were presented as mean ± SD or n (%). The elderly group and younger group were defined as patients older than 75 years and those younger than 75 years, respectively.

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Figure 1. The probability of freedom from late coronary events stratified according to LDL-C. (A): Acute coronary syndrome in the elderly group; (B): acute coronary syndrome in the younger group; (C): any late coronary revascularization in the elderly group; and (D): any late coronary revascularization in the younger group. The elderly group and younger group were defined as patients older than 75 years and those younger than 75 years, respectively. LDL-C: low-density lipoprotein cholesterol; PCI: percutaneous coronary intervention.

Instead, recurrent ACS was less frequent in patients with LDL-C 70–100 mg/dL than in those with LDL-C ≥ 100 mg/dL in the elderly group (P = 0.033). In both the elderly and younger groups, late coronary revascularization subsequent to late CAG was significantly higher in patients with LDL-C ≥100 mg/dL than in those with LDL-C ranging from 70–100 mg/dL (P = 0.005 and P = 0.034, respectively). However, no such differences were noted between patients with LDL-C < 70 mg/dL and those with LDL-C ranging from 70 to < 100 mg/dL.

3.3 Incidence of late coronary events in patients using or not using statins

The probability of freedom from late coronary events in patients who were or were not using statins is shown in Figure 2. Kaplan-Meier curve analysis revealed that using statins was associated with a lower incidence of recurrent ACS in the elderly group and younger group (P = 0.005 and 0.010, respectively). In the younger group, any late coronary revascularization subsequent to late CAG decreased in patients using statins (P = 0.033); however, no such difference was noted in the elderly group.

Further stratification of patients using statins revealed that those with LDL-C < 100 mg/dL had a significantly lower incidence of any late coronary revascularization than those with LDL-C ≥ 100 mg/dL in the elderly group (P = 0.012), and a similar tendency was found in the younger group (P = 0.069) (Figure 3). However, the incidence of recurrent ACS was not different between patients with LDL-C ≥ 100 mg/dL and those with LDL-C < 100 mg/dL in the elderly group and younger group (P = 0.250 and 0.976, respectively).

3.4 Predictors of recurrent ischemia presenting as acute coronary syndrome

In the elderly group, a univariate Cox proportional
hazards analysis of the clinical characteristics demonstrated that total cholesterol, LDL-C, non-HDL-C, LDL-C/HDL-C ratio, statin use, and antiplatelet drug use were predictors of recurrent ACS. These significant variables were included in the multivariate Cox proportional hazards model to assess their independent roles. The multivariate analysis identified that only statin use (HR: 0.375; P = 0.007) was clarified as an independent predictor of recurrent ACS (Table 3). Conversely, in the younger group, LDL-C, HDL-C, non-HDL-C, LDL-C/HDL-C ratio, HbA1c, and statin use were predictors of recurrent ACS according to univariate analysis, and LDL-C/HDL-C ratio (HR: 1.404; P = 0.004) and HbA1c (HR: 1.204; P = 0.028) were independent predictors according to multivariate analysis (Table 4).

4 Discussion

The main findings of the present study are that the incidence of recurrent ischemia presenting as acute coronary syndrome was significantly lower in patients with LDL-C < 70 mg/dL than in those with LDL-C 70–100 mg/dL in the younger group; however, there was no difference between these in the elderly group. Any late coronary revascularization significantly increased in patients with LDL-C ≥ 100 mg/dL but not in those with LDL-C 70–100 mg/dL in the elderly group, similar to the younger group. Use of statins reduced the incidence of recurrent ischemia presenting as acute coronary syndrome in both the elderly and younger groups; however, the incidence of any late revascularization decreased only in the younger group.

It has been discussed whether there should be a target value of LDL-C. In the Japanese guidelines for diagnosis and prevention of atherosclerotic cardiovascular diseases,[7] the LDL-C target value of < 100 mg/dL is defined as a therapeutic goal for secondary prevention. The guidelines of the European Society of Cardiology also recommend...
controlling LDL-C to $< 70$ mg/dL as a treatment goal for patients at very high risk including secondary prevention.\[6\] However, these guidelines did not indicate an LDL-C target value for patients older than 75 years. Furthermore, the American College of Cardiology/American Heart Association 2013 guidelines advocated the abandonment of LDL-C targets and recommended moderate-intensity or high-intensity statin therapy on the basis of underlying risk categories.\[10\] In these guidelines, moderate-intensity statin therapy is recommended for patients with atherosclerotic cardiovascular disease beyond age 75 years, irrespective of LDL-C response. The turning point for plaque regression is LDL-C $< 70$ mg/dL for patients treated with aggressive LDL-C-lowering therapy using statins.\[6\] Moreover, in a meta-analysis of 8 randomized, controlled statin trials, patients who achieved very low LDL-C ($< 50$ mg/dL) were at a significantly lower risk for major cardiovascular events, even when compared with those who achieved LDL-C ranging from 75 to $< 100$ mg/dL.\[11\] Achieving sufficiently low levels of LDL-C seems to be beneficial for reducing cardiovascular events risk; however, there are few data regarding this for elderly patients.

In our study, younger patients with LDL-C $< 70$ mg/dL at late CAG were at lower risk for recurrent ACS compared with those with LDL-C $70–100$ mg/dL; however, a similar difference was found between elderly patients with LDL-C $70–100$ mg/dL and LDL-C $\geq 100$ mg/dL. It was reported that the association between LDL-C and relative risk of coronary heart disease was lower in elderly compared with middle-aged individuals.\[12\] In the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) which was the only prospective, randomized, controlled trial evaluating the effects of statin therapy on elderly patients older than 70 years, using pravastatin reduced the risk of coronary events in those 70–82 years of age.\[13\] However, results of a meta-analysis of 61 prospective studies revealed that total choles-

Figure 3. The probability of freedom from late coronary events divided by LDL-C $< 100$ mg/dL or $\geq 100$ mg/dL in patients using statins. (A): Acute coronary syndrome in the elderly group; (B): acute coronary syndrome in the younger group; (C): any late coronary revascularization in the elderly group; and (D): any late coronary revascularization in the younger group. The elderly group and younger group were defined as patients older than 75 years and those younger than 75 years, respectively. LDL-C: low-density lipoprotein cholesterol; PCI: percutaneous coronary intervention.
Table 3. Predictors of recurrent ischemia presenting as acute coronary syndrome in the elderly group (older than 75 years).

| Predictors                                      | Univariate analysis | Multivariate analysis |
|-------------------------------------------------|---------------------|-----------------------|
|                                                  | Hazard ratio (95% CI) | P value               | Hazard ratio (95% CI) | P value               |
| Age                                             | 1.002 (0.931–1.078)  | 0.952                 |                        |                      |
| Male sex                                         | 0.757 (0.356–1.606)  | 0.468                 |                        |                      |
| Hypertension                                     | 0.876 (0.449–1.709)  | 0.698                 |                        |                      |
| Dyslipidemia                                     | 1.160 (0.496–2.712)  | 0.732                 |                        |                      |
| Diabetes mellitus                                | 0.807 (0.413–1.576)  | 0.530                 |                        |                      |
| Use of insulin                                   | 0.368 (0.082–1.652)  | 0.192                 |                        |                      |
| Current smoker                                   | 1.326 (0.633–2.779)  | 0.455                 |                        |                      |
| Chronic kidney disease                           | 0.844 (0.434–1.642)  | 0.617                 |                        |                      |
| Hemodialysis                                     | 0.988 (0.134–7.299)  | 0.991                 |                        |                      |
| Total cholesterol                                | 1.013 (1.001–1.025)  | 0.027                 |                        |                      |
| LDL-C                                           | 1.016 (1.003–1.029)  | 0.014                 |                        |                      |
| HDL-C                                           | 0.987 (0.961–1.014)  | 0.353                 |                        |                      |
| Triglyceride                                     | 1.002 (0.997–1.007)  | 0.381                 |                        |                      |
| Non HDL-C                                        | 1.014 (1.003–1.025)  | 0.009                 |                        |                      |
| LDL-C/HDL-C ratio                                | 1.452 (1.077–1.957)  | 0.014                 |                        |                      |
| HbA1c (NGSP)                                     | 0.983 (0.702–1.375)  | 0.920                 |                        |                      |
| Creatinine                                       | 0.819 (0.479–1.401)  | 0.467                 |                        |                      |
| Use of statins                                   | 0.375 (0.183–0.768)  | 0.007                 | 0.375 (0.183–0.768)    | 0.007                 |
| Use of ACE-I or ARB                              | 1.359 (0.695–2.657)  | 0.370                 |                        |                      |
| Use of β-blocker                                 | 0.857 (0.373–1.970)  | 0.716                 |                        |                      |
| Use of antiplatelet drugs                        | 0.338 (0.151–0.757)  | 0.008                 |                        |                      |

ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NGSP: National Glycohemoglobin Standardization Program.

Table 4. Predictors of recurrent ischemia presenting as acute coronary syndrome in the younger group (younger than 75 years).

| Predictors                                      | Univariate analysis | Multivariate analysis |
|-------------------------------------------------|---------------------|-----------------------|
|                                                  | Hazard ratio (95% CI) | P                 | Hazard ratio (95% CI) | P                 |
| Age                                             | 0.970 (0.933–1.010)  | 0.137               |                        |                      |
| Male sex                                         | 0.991 (0.354–2.775)  | 0.986               |                        |                      |
| Hypertension                                     | 0.561 (0.313–1.009)  | 0.053               |                        |                      |
| Dyslipidemia                                     | 0.544 (0.193–1.533)  | 0.250               |                        |                      |
| Diabetes mellitus                                | 1.577 (0.849–2.929)  | 0.149               |                        |                      |
| Use of insulin                                   | 0.926 (0.331–2.591)  | 0.884               |                        |                      |
| Current smoker                                   | 1.425 (0.730–2.781)  | 0.299               |                        |                      |
| Chronic kidney disease                           | 0.794 (0.409–1.540)  | 0.494               |                        |                      |
| Hemodialysis                                     | 0.732 (0.177–3.029)  | 0.667               |                        |                      |
| Total cholesterol                                | 1.006 (1.000–1.013)  | 0.050               |                        |                      |
| LDL-C                                           | 1.009 (1.002–1.015)  | 0.010               |                        |                      |
| HDL-C                                           | 0.964 (0.938–0.991)  | 0.009               |                        |                      |
| Triglyceride                                     | 1.002 (0.999–1.005)  | 0.220               |                        |                      |
| Non HDL-C                                        | 1.009 (1.003–1.015)  | 0.004               |                        |                      |
| LDL-C/HDL-C ratio                                | 1.499 (1.202–1.870)  | < 0.001             | 1.404 (1.115–1.768)    | 0.004               |
| HbA1c (NGSP)                                     | 1.276 (1.092–1.491)  | 0.002               | 1.204 (1.020–1.420)    | 0.028               |
| Creatinine                                       | 0.955 (0.810–1.125)  | 0.582               |                        |                      |
| Use of statins                                   | 0.454 (0.244–0.844)  | 0.013               |                        |                      |
| Use of ACE-I or ARB                              | 0.648 (0.362–1.160)  | 0.144               |                        |                      |
| Use of β-blocker                                 | 1.111 (0.609–2.026)  | 0.732               |                        |                      |
| Use of antiplatelet drugs                        | 0.653 (0.314–1.359)  | 0.255               |                        |                      |

ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NGSP: National Glycohemoglobin Standardization Program.
inconsistent with Japanese guidelines, therefore, it might of LDL-C might not be as strong in elderly patients as in sufficient to only prescribe statins. Adequately reducing LDL-C, to prevent the progression of atherosclerosis, it is insufficient with LDL-C level with statin therapy in the range of LDL-C < 120 mg/dL was not significantly associated with cardiovascular outcomes of patients older than 80 years. Compared with younger patients, LDL-C might be poorly related to late coronary events in elderly patients. Because atherosclerosis is a multifactorial process, and because elderly patients often have multiple risk factors, the influence of LDL-C might not be as strong in elderly patients as in younger patients. Our results for the elderly group are not inconsistent with Japanese guidelines, therefore, it might be suggested that there is no need to reduce LDL-C to very low levels in many elderly patients.

Several studies have reported the effectiveness of statins for preventing cardiovascular events in elderly patients. In the present study, the lower incidence of recurrent ACS was found in patients using statins compared to those not using statins not only in the younger group but also in the elderly group; this was independent of LDL-C level at the time of admission for late CAG in patients using statins. Moreover, use of statins was an independent predictor of recurrent ACS in the elderly group. In the elderly group, using statins could not reduce any late coronary revascularization; however, in patients using statins, the incidence of any late coronary revascularization was lower in the LDL < 100 mg/dL group than in the LDL ≥ 100 mg/dL group. Beneficial cardiovascular effects of statins independent of LDL-C lowering, so-called pleiotropic effect, involve anti-inflammatory properties, improvement of endothelial dysfunction, increased nitric oxide bioavailability, anti-thrombotic effects, and stabilization of atherosclerotic plaques. There is a possibility that these pleiotropic effects are more useful for preventing recurrent ACS than stable angina. Insufficient control of LDL-C despite the use of statins is thought to be one of the reasons for this finding. To prevent the progression of atherosclerosis, it is insufficient to only prescribe statins. Adequately reducing LDL-C, at least to < 100 mg/dL, which is a therapeutic goal defined by the Japan Atherosclerosis Society Guidelines for secondary prevention, might be necessary for elderly patients.

4.1 Study limitations

This study was limited by its retrospective design and relatively small number of enrolled patients. Moreover, there might be some patients with premature death due to a cardiac event such as fetal ACS or sudden cardiac death, which we did not grasp. Such fatal events could be influenced by LDL-C levels. Therefore, the data was not enough to conclude that LDL-C < 100 mg/dL is suitable for the target value of Japanese elderly patients. To verify the present results, further prospective, multicenter, large-scale studies involving elderly patients are necessary. In addition, the indication for late coronary revascularization was determined by the attending cardiologist based on the results of CAG performed for recurrence of cardiac ischemia. Although the presence of significant stenotic lesions of the coronary artery was confirmed on CAG for all patients, some patients showed no evidence of myocardial ischemia on noninvasive functional tests, especially in emergency cases. Therefore, subsequent coronary intervention might be indispensable for some patients. However, all cases underwent late CAG evaluation due to any signs of recurrent cardiac ischemia and clinically driven subsequent coronary intervention. Furthermore, the proportion of subjects using statins was relatively low. Approximately half of all patients were prescribed a moderate-intensity statin and the remaining half were prescribed a low-intensity statin; no patients were treated with high-intensity statin. For these reasons, the average LDL-C was > 100 mg/dL; therefore, this therapy was insufficient for secondary prevention. In the present study, most patients were treated by family physicians. More than half of all patients had undergone PCI more than 10 years previously. In approximately 2000, only one-quarter of patients 65 years or older were prescribed statins at discharge after myocardial infarction. Therefore, some patients may have been prescribed previous medicines without sufficient recognition of the importance of prescribing LDL-C-lowering therapy and statins. Finally, adherence to medication use and modification of prescribed medicines were unknown factors. Because the follow-up period in this study was considerably long, treatment strategies targeting specific risk factors may have been altered during the course of the study by family physicians, meaning that the control of risk factors may have changed during the follow-up period. Especially, patients are unlikely to be treated with statins before 2000; a period of non-statin treatment could have significantly influenced the results in some patients.

4.2 Conclusions

Strict control of LDL-C to < 70 mg/dL was effective for
reducing the incidence of recurrent ACS in younger patients. However, LDL-C < 100 mg/dL might be sufficient as the target value of LDL-C-lowering therapy for secondary prevention of ischemic events in Japanese elderly patients. Using statins reduced the incidence of recurrent ACS in elderly patients similar to younger patients.

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