Small Dense Low-Density Lipoprotein Cholesterol and Cardiovascular Risk in Statin-Treated Patients with Coronary Artery Disease

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Aim: We investigated the relationship between small dense low-density cholesterol (sdLDL-C) and risk of major adverse cardiovascular events (MACE) in patients treated with high- or low-dose statin therapy.

Methods: This was a prospective case-cohort study within the Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) study, a randomized trial of high- or low-dose (4 or 1 mg/d pitavastatin, respectively) statin therapy, in patients with stable coronary artery disease (CAD). Serum sdLDL-C was determined using an automated homogenous assay at baseline (randomization after a rule-in period, >1 month with 1 mg/d pitavastatin) and 6 months after randomization, in 497 MACE cases, and 1543 participants randomly selected from the REAL-CAD study population.

Results: High-dose pitavastatin reduced sdLDL-C by 20% than low-dose pitavastatin (p for interaction < 0.001). Among patients receiving low-dose pitavastatin, baseline sdLDL-C demonstrated higher MACE risk independent of LDL-C (hazard ratio [95% confidence interval], 4th versus 1st quartile, 1.67 [1.04–2.68]; p for trend = 0.034). High-dose (versus low-dose) pitavastatin reduced MACE risk by 46% in patients in the highest baseline sdLDL-C quartile (>34.3 mg/dL; 0.54 [0.36–0.81]; p = 0.003), but increased relative risk by 40% in patients with 1st quartile (≤19.5 mg/dL; 1.40 [0.94–2.09]; p = 0.099) and did not alter risk in those in 2nd and 3rd quartiles (p for interaction = 0.002).
Conclusions: These findings associate sdLDL-C and cardiovascular risk, independent of LDL-C, in statin-treated CAD patients. Notably, high-dose statin therapy reduces this risk in those with the highest baseline sdLDL-C.

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Key words: Small dense LDL cholesterol, Coronary artery disease, Statin therapy, Secondary prevention

Abbreviations: CAD, coronary artery disease; CI, confidence intervals; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; non-HDL-C, non-high-density lipoprotein cholesterol; REAL-CAD, Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy with Pitavastatin in Coronary Artery Disease; sdLDL-C, small dense low-density lipoprotein cholesterol; TRL-C, triglyceride-rich lipoprotein cholesterol.

Introduction

Low-density lipoprotein cholesterol (LDL-C) is a primary risk factor for cardiovascular disease and lowering LDL-C levels with medications, such as statins, has proved effective for primary and secondary prevention. However, even when LDL-C levels drop to optimal levels, the risk of cardiovascular events exists, and an additional option may be necessary to reduce these events. Small dense LDL-C (sdLDL-C) levels may partly account for this residual risk. Because sdLDL particles contain less cholesterol and are smaller, increased sdLDL-C levels represent an increase in numbers of atherogenic LDL particles, which LDL-C levels may not reflect. These particles are considered more atherogenic than large buoyant LDL particles due to their lower binding affinity for LDL receptors, increased penetration into the arterial wall, longer plasma residence time, and greater susceptibility to oxidation. There have been demonstrations in recent large cohort studies using a simple homogeneous sdLDL-C assay of the interrelationship between higher sdLDL-C level and cardiovascular risk regardless of LDL-C level. Recently, the prospective Framingham Offspring Study documented that sdLDL-C may be the best measure of cardiovascular risk in atherogenic lipid markers, including LDL triglycerides, large buoyant LDL-C, triglyceride-rich lipoprotein cholesterol (TRL-C), remnant lipoprotein particle cholesterol, and lipoprotein (a). Thus, optimizing sdLDL-C may reduce cardiovascular risk. The statin therapy lowered the levels of LDL-C as well as sdLDL-C, primarily by enhancing apolipoprotein B catabolism. However, the role of sdLDL-C level in the prognosis of statin-treated patients remains undefined.

The Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) study is currently the largest randomized trial. It compared high- and low-dose pitavastatin therapy in patients with stable coronary artery disease and used a study design similar to the previously reported Treating to New Targets study. The REAL-CAD study demonstrated that, compared with low-dose, high-dose pitavastatin, safely reduced the risk of major adverse cardiovascular events (MACE) by 19% in Japanese patients with stable CAD, who commonly receive low-intensity statin therapy.

Aim

In this prospective case-cohort study, within the REAL-CAD study, we investigated the relationship between sdLDL-C level determined by a simple homogeneous assay and subsequent MACE in statin-treated patients with stable CAD. We evaluated
whether more intensive statin therapy attenuates this risk.

**Methods**

**Study Participants and Case-Cohort Design**

The REAL-CAD study is a prospective, multicenter, randomized trial that compared the efficacies of high- and low-dose (4 and 1 mg/d pitavastatin, respectively) statin therapy for secondary prevention 13,054 Japanese patients with stable CAD. The patients achieved LDL-C levels <120 mg/dL during a run-in period of >1 month with 1 mg/d of pitavastatin\(^22, 23\). This study was a prospective case-cohort study within the REAL-CAD study. MACE was the study's primary endpoint, comprising nonfatal myocardial infarction, cardiovascular death, unstable angina, and nonfatal ischemic stroke, requiring emergency hospitalization. Importantly, for the REAL-CAD study, fasting serum samples were obtained at baseline (randomization) after at least a 1-month run-in period on 1 mg/d pitavastatin and 6 months after randomization on 1 mg/d or 4 mg/d pitavastatin.

There were 11,887 participants with baseline blood samples in the full analysis population of the REAL-CAD study. We conducted a case-cohort analysis based on 582 cases who developed MACE during a median follow-up period of 3.9 years and a random cohort sample of 1,745 participants (three times the number of MACE cases). After excluding 202 participants with insufficient serum samples, the random cohort comprised 1,543 patients (high-dose, \(n=767\); low-dose, \(n=776\)). Similarly, exclusion of 85 MACE cases with insufficient serum samples resulted in 497 cases (high-dose, \(n=218\); low-dose, \(n=279\)). Of these, 68 MACE cases were duplicated in the random cohort. A case-cohort data set comprising 1,972 participants was created (Supplementary Fig. 1).

Ethics approval for the REAL-CAD study was granted by the Public Health Research Foundation ethics review committee and by ethics committees at all participating sites. All participants provided written informed consent. The study complied with the Declaration of Helsinki. The ethics committee of Fujita Health University also approved the present case-cohort study.

**Laboratory Analysis**

Fasting serum samples for sdLDL-C measurement were collected at baseline and 6 months after randomization. They were stored at \(-70^\circ\text{C}\) or colder. Serum sdLDL-C level was directly measured on a LABOSPECT 006 automated chemistry analyzer using a homogenous assay (sdLDL-EX “SEIKEN;” Denka Seiken, Tokyo, Japan)\(^26\). The central laboratory measured serum triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) levels. Serum LDL-C was calculated with the Friedewald formula\(^27\) unless the triglyceride level was \(\geq 400 \text{mg/dL}\), when LDL-C was directly measured by a homogenous assay. Non-HDL-C was defined as total cholesterol minus HDL-C. TRL-C level was defined as the difference between non-HDL-C and LDL-C. These calculated TRL-C levels have been reported to closely approximate triglyceride levels\(^28, 29\).

**Statistical Analysis**

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc). The random cohort's differences in the mean (standard deviation) or median (interquartile range) in high- and low-dose groups were tested by Wilcoxon rank-sum test. Similarly, the frequency of risk factors in the two groups was tested by Fisher's exact or Chi-square test. Trends in the mean (standard deviation) or median (interquartile range) and frequency of risk factors across quartiles of sdLDL-C levels at baseline were tested by the Jonckheere–Terpstra test and Cochran–Mantel–Haenszel correlation test, respectively. The association between sdLDL-C and other lipid markers was assessed using Spearman's rank correlation coefficient. Absolute and relative changes from baseline to 6 months after randomization in sdLDL-C, LDL-C, triglycerides, and percentage of sdLDL-C in LDL-C were tested with Wilcoxon signed-rank test, compared with Wilcoxon rank-sum test between treatment groups, and tested by an analysis of covariance (ANCOVA) with individual baseline covariate between treatment groups.

The subjects were categorized into quartiles for each baseline lipid marker according to the distribution in the random cohort. Hazard ratios (HR) and 95% confidence intervals (CI) of MACE concerning quartiles were calculated using Cox proportional hazard models with Barlow's methods\(^30\) to account for the case-cohort design. Multivariable models accounted for the following covariates: Model 1 was adjusted for standard risk factors (i.e., age \(\geq 65\) and \(<65\) years), male sex, body mass index, systolic blood pressure, heart rate, hypertension, diabetes mellitus, smoking status [current versus not current], myocardial infarction history, percutaneous coronary intervention history, coronary artery bypass grafting history, atrial fibrillation, heart failure, malignant disease, and peripheral artery disease), creatinine-based estimated glomerular filtration rate (eGFR), hemoglobin
A1c, high-sensitivity C-reactive protein (hsCRP), and HDL-C at baseline. Model 2 was adjusted for model 1 variables and LDL-C at baseline. Model 3 was adjusted for model 1 variables and triglycerides at baseline. Model 4 was adjusted for model 1 variables and TRL-C at baseline. Similarly, the subjects were categorized into quartiles for sdLDL-C level after 6 months and absolute and relative changes from baseline to 6 months in sdLDL-C level according to the distribution in the random cohort. The HR and Barlow’s 95% CI of MACE regarding quartiles were calculated for sdLDL-C level in the random cohort. The HR and baseline to 6 months in sdLDL-C level according to 6 months. Participants with MACE before 6 months were excluded from these analyses.

The intersetation (high- versus low-dose pitavastatin) differences in endpoint in subgroups, according to quartile of serum sdLDL-C at baseline, were examined with the weighted Kaplan–Meier method and compared with Barlow’s log-rank test. The weights were the inverse of patients’ sampling probability of this case-cohort design. The interaction of statin intensity (high- versus low-dose pitavastatin) by subgroup according to the quartile of serum sdLDL-C, LDL-C, triglycerides, TRL-C, non-HDL-C, and HDL-C levels at baseline, were examined separately in the same model with the interaction term. Multivariable models were created adjusting for standard risk factors, eGFR, hemoglobin A1c, hsCRP, triglycerides, and HDL-C at 6 months. Participants with MACE before 6 months were excluded from these analyses.

The interaction term. Multivariable models were created adjusting for established risk factors, eGFR, hemoglobin A1c, hsCRP, triglycerides, and HDL-C at baseline was significantly associated with risk of subsequent MACE (HR quartile 4 vs. 1, 1.76; 95% CI, 1.15–2.71; p for trend = 0.009) after adjustment for standard risk factors, eGFR, hemoglobin A1c, hsCRP, and HDL-C at baseline (Table 3). These associations remained significant even after additional adjustment for LDL-C level (HR quartile 4 vs. 1, 1.67; 95% CI, 1.04–2.68; p for trend = 0.034), triglyceride level (HR quartile 4 vs. 1, 1.78; 95% CI, 1.06–2.97; p for trend = 0.024) or TRL-C level (HR quartile 4 vs. 1, 1.82; 95% CI, 1.09–3.05; p for trend = 0.019). In the high-dose group, the sdLDL-C level at baseline was more strongly correlated with baseline TRL-C (r = 0.63, p < 0.001), triglyceride (r = 0.61, p < 0.001), and non-HDL-C (r = 0.71, p < 0.001) levels compared with baseline LDL-C (r = 0.33, p < 0.001) and HDL-C (r = –0.13, p < 0.001) levels. TRL-C level at baseline was strongly correlated with triglyceride level (r = 0.94, p < 0.001).

**Changes in Lipid Markers in High- and Low-dose Groups**

In the random cohort, mean sdLDL-C levels at baseline were 28.5 and 27.4 mg/dL in the high- and low-dose groups, respectively (Fig. 1A). The sdLDL-C level in the high-dose group decreased by 9.9% (p < 0.001) at 6 months when compared with the value at baseline, whereas in the low-dose group, an increase by 10% at 6 months was noted (p < 0.001). The high-dose pitavastatin significantly reduced sdLDL-C levels by 20% (p for interaction < 0.001) than low-dose pitavastatin.

Similar to sdLDL-C, the high-dose pitavastatin reduced LDL-C levels by 19% (p for interaction < 0.001; Fig. 1B) and triglycerides by 7.5% (p for interaction = 0.02; Fig. 1C). The percentage of sdLDL-C in LDL-C in the high- and low-dose statin groups increased at 6 months (p = 0.02 and p = 0.004, respectively) when compared with baseline (Fig. 1D). There was no significant change in the percentage of sdLDL-C in LDL-C with high-dose (versus low-dose) statin treatment.

**Changes in sdLDL-C in Subgroups According to sdLDL-C Quartile at Baseline**

In all baseline sdLDL-C quartile, high-dose pitavastatin significantly reduced sdLDL-C levels further than low-dose pitavastatin (all, p for interaction < 0.001; Table 2). Both absolute and relative changes in sdLDL-C from baseline to 6 months were associated with increased baseline sdLDL-C quartiles (p for trend < 0.001).

**MACE Risk and Lipid Markers**

In the low-dose statin group, the sdLDL-C level at baseline was significantly associated with risk of subsequent MACE (HR quartile 4 vs. 1, 1.75; 95% CI, 1.10–2.76; p for trend = 0.009) after adjustment for standard risk factors, eGFR, hemoglobin A1c, hsCRP, and HDL-C at baseline (Table 3). These associations remained significant even after additional adjustment for LDL-C level (HR quartile 4 vs. 1, 1.67; 95% CI, 1.04–2.68; p for trend = 0.034), triglyceride level (HR quartile 4 vs. 1, 1.78; 95% CI, 1.06–2.97; p for trend = 0.024) or TRL-C level (HR quartile 4 vs. 1, 1.82; 95% CI, 1.09–3.05; p for trend = 0.019). In the high-dose group, the sdLDL-C
Table 1. Patient characteristics at baseline in high- and low-dose groups among random cohort population

|                           | High-dose (n = 767) | Low-dose (n = 776) | p-value |
|---------------------------|---------------------|--------------------|---------|
| Age, y                    | 68.5 (8.4)          | 68.0 (8.4)         | 0.29    |
| Male, n (%)               | 649 (84.6)          | 631 (83.1)         | 0.08    |
| Body mass index, kg/m²    | 24.8 (3.3)          | 24.7 (3.4)         | 0.55    |
| Systolic blood pressure, mmHg | 128 (16.3)     | 128 (16.3)         | 0.82    |
| Diastolic blood pressure, mmHg | 72.7 (10.7)   | 72.8 (10.7)        | 0.53    |
| Heart rate, bpm           | 69.8 (11.2)         | 69.6 (11.8)        | 0.79    |
| Left ventricular ejection fraction, % | 60.0 (12.4) | 60.5 (12.0) | 0.77 |
| **Cardiovascular history**|                     |                    |         |
| Myocardial infarction, n (%) | 372 (48.5)  | 388 (50.0)         | 0.84    |
| Percutaneous coronary intervention, n (%) | 633 (82.5)  | 639 (82.3)         | 1.00    |
| Coronary artery bypass grafting, n (%) | 92 (12.0)   | 106 (13.7)         | 0.62    |
| Congestive heart failure, n (%) | 41 (5.3)     | 42 (5.4)           | 0.61    |
| Atrial fibrillation, n (%) | 48 (6.3)          | 47 (6.1)           | 0.99    |
| Ischemic stroke, n (%)    | 56 (7.3)           | 63 (8.1)           | 0.59    |
| Hemorrhagic stroke, n (%) | 12 (1.6)           | 11 (1.4)           | 0.81    |
| Peripheral artery disease, n (%) | 46 (6.0)    | 67 (8.6)           | 0.08    |
| Current smoking, n (%)    | 122 (15.9)         | 113 (14.6)         | 0.76    |
| Diabetes mellitus, n (%)  | 320 (41.7)         | 313 (40.3)         | 0.58    |
| Hypertension, n (%)       | 585 (76.3)         | 587 (75.6)         | 0.96    |
| Family history of coronary artery disease, n (%) | 130 (16.9) | 148 (19.1) | 0.66 |
| History of malignant disease, n (%) | 42 (5.5)    | 40 (5.7)           | 0.96    |
| **Blood examinations**    |                     |                    |         |
| Total cholesterol, mg/dL  | 166 (23.1)         | 166 (25.1)         | 0.50    |
| LDL-C, mg/dL              | 87.8 (18.0)        | 88.0 (18.9)        | 0.91    |
| HDL-C, mg/dL              | 49.6 (12.3)        | 51.6 (13.1)        | 0.01    |
| Triglycerides, mg/dL, median | 125 (92, 180)    | 120 (87, 168)      | 0.04    |
| sdLDL-C, mg/dL           | 28.5 (12.3)        | 27.4 (11.4)        | 0.09    |
| TRL-C, mg/dL, median      | 25.0 (18.6, 36.0)  | 24.0 (17.4, 33.6)  | 0.04    |
| hsCRP, mg/L, median       | 0.53 (0.25, 1.19)  | 0.52 (0.23, 1.19)  | 0.51    |
| Glucose, mg/dL            | 127 (41.7)         | 125 (43.0)         | 0.21    |
| Hemoglobin A1c, %         | 5.91 (0.93)        | 5.87 (0.87)        | 0.42    |
| eGFR, mL/min/1.73 m²      | 66.0 (16.2)        | 66.5 (30.2)        | 0.61    |
| **Chronic kidney disease, n (%)** | 58 (7.6)    | 61 (7.9)           | 0.93    |
| Stage 1                   | 412 (53.7)         | 428 (55.2)         |         |
| Stage 2                   | 275 (35.9)         | 269 (34.7)         |         |
| Stage 3                   | 10 (1.3)           | 9 (1.2)            |         |
| Stage 4                   | 0 (0)              | 0 (0)              |         |
| Medications, n (%)        |                     |                    |         |
| Aspirin                   | 664 (86.6)         | 660 (85.1)         | 0.68    |
| Thienopyridine            | 342 (44.6)         | 338 (43.6)         | 0.74    |
| Dual antiplatelet therapy | 316 (41.2)         | 320 (41.2)         | 0.75    |
| β-blocker                 | 284 (37.0)         | 297 (38.3)         | 0.60    |
| ACEI and/or ARB           | 479 (62.5)         | 496 (63.9)         | 0.50    |

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol; TRL-C, triglyceride-rich lipoprotein cholesterol. Data are n (%), mean (standard deviation) or median (interquartile range).
Table 2. Changes in sdLDL-C from baseline to 6 months in high- and low-dose groups according to baseline sdLDL-C quartiles

| Baseline sdLDL-C quartiles | High-dose | Low-dose | p-value |
|----------------------------|-----------|----------|---------|
| 1st (≤19.5 mg/dL)          |           |          |         |
| Baseline, mg/dL            | 15.2 (3.1)| 15.3 (2.8)| 0.84    |
| 6 months, mg/dL            | 16.2 (6.5)| 19.5 (7.2)| <0.001  |
| Absolute change, mg/dL, median | −0.30 (−3.3, 3.7) | 3.4 (−0.25, 6.8) | <0.001 |
| Relative change, %, median | −2.1 (−21.3, 22.4) | 20.3 (−2.0, 48.6) | <0.001 |
| 2nd (>19.5 to 25.7 mg/dL)  |           |          |         |
| Baseline, mg/dL            | 22.7 (1.8)| 22.7 (1.8)| 0.94    |
| 6 months, mg/dL            | 19.8 (5.9)** | 25.6 (8.5)** | <0.001 |
| Absolute change, mg/dL, median | −3.1 (−7.2, 0.50) | 2.2 (−2.5, 6.3) | <0.001 |
| Relative change, %, median | −14.6 (−31.5, 2.6) | 9.1 (−10.7, 26.5) | <0.001 |
| 3rd (>25.7 to 34.3 mg/dL)  |           |          |         |
| Baseline, mg/dL            | 29.6 (2.5)| 29.8 (2.5)| 0.74    |
| 6 months, mg/dL            | 25.1 (8.6)** | 30.3 (9.7) | <0.001 |
| Absolute change, mg/dL, median | −6.1 (−9.9, −0.50) | −0.60 (−5.1, 4.9) | <0.001 |
| Relative change, %, median | −20.7 (−33.0, −1.8) | −1.8 (−16.9, 16.5) | <0.001 |
| 4th (>34.3 mg/dL)          |           |          |         |
| Baseline, mg/dL            | 45.0 (9.8)| 43.9 (8.3)| 0.43    |
| 6 months, mg/dL            | 34.7 (12.0)** | 41.3 (12.5)** | <0.001 |
| Absolute change, mg/dL, median | −11.2 (−16.2, −3.6) | −2.8 (−9.75, 2.95) | <0.001 |
| Relative change, %, median | −25.2 (−37.5, −8.8) | −6.2 (−21.4, 6.7) | <0.001 |

Abbreviations: sdLDL-C, small dense low-density lipoprotein cholesterol. Absolute and relative changes in sdLDL-C level were defined as (sdLDL-C level at 6 months – at baseline) and (absolute change / baseline) ×100, respectively. Data are mean (standard deviation) for sdLDL-C at baseline and 6 months, and are median (interquartile range) for absolute and relative changes in sdLDL-C. **p<0.001 vs. baseline.
Risk of MACE according to baseline sdLDL-C quartiles in low- (A) and high-dose groups (B) adjusted for model 1 variables and triglycerides. Model 4 was adjusted for model 1 variables and TRL-C.

| A. Low-dose group | Unadjusted | Model 1 | Model 2 (Model 1 + LDL-C) | Model 3 (Model 1 + triglycerides) | Model 4 (Model 1 + TRL-C) |
|-------------------|------------|---------|--------------------------|-----------------------------------|--------------------------|
| sdLDL-C, mg/dL    |            |         |                          |                                   |                          |
| 1st quartile ≤ 19.5 | 1.00       | 1.00    | 1.00                     | 1.00                              | 1.00                     |
| 2nd quartile > 19.5 to 25.7 | 1.29 (0.87, 1.93) | 1.21 (0.76, 1.94) | 1.18 (0.73, 1.91) | 1.22 (0.75, 1.96) | 1.22 (0.76, 1.98) |
| 3rd quartile > 25.7 to 34.3 | 1.34 (0.90, 1.98) | 1.40 (0.88, 2.24) | 1.34 (0.81, 2.19) | 1.41 (0.87, 2.28) | 1.43 (0.88, 2.31) |
| 4th quartile ≥ 34.3 | 1.61 (1.09, 2.37) | 1.76 (1.15, 2.71) | 1.67 (1.04, 2.68) | 1.78 (1.06, 2.97) | 1.82 (1.09, 3.05) |
| p for trend        | 0.020      | 0.009   | 0.034                    | 0.024                             | 0.019                    |

| B. High-dose group | Unadjusted | Model 1 | Model 2 (Model 1 + LDL-C) | Model 3 (Model 1 + triglycerides) | Model 4 (Model 1 + TRL-C) |
|-------------------|------------|---------|--------------------------|-----------------------------------|--------------------------|
| sdLDL-C, mg/dL    |            |         |                          |                                   |                          |
| 1st quartile ≤ 19.5 | 1.00       | 1.00    | 1.00                     | 1.00                              | 1.00                     |
| 2nd quartile > 19.5 to 25.7 | 0.67 (0.41, 1.01) | 0.68 (0.41, 1.13) | 0.64 (0.38, 1.09) | 0.68 (0.41, 1.13) | 0.68 (0.41, 1.13) |
| 3rd quartile > 25.7 to 34.3 | 0.69 (0.46, 1.06) | 0.87 (0.54, 1.41) | 0.80 (0.49, 1.33) | 0.88 (0.53, 1.46) | 0.87 (0.51, 1.48) |
| 4th quartile ≥ 34.3 | 0.62 (0.41, 0.95) | 0.71 (0.43, 1.17) | 0.64 (0.37, 1.11) | 0.72 (0.40, 1.31) | 0.71 (0.38, 1.33) |
| p for trend        | 0.042      | 0.325   | 0.201                    | 0.466                             | 0.455                    |

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; sdLDL-C, small dense low-density lipoprotein cholesterol; TRL-C, triglyceride-rich lipoprotein cholesterol.

Data are hazard ratio (95% confidence interval). Model 1 was adjusted for standard risk factors (i.e., age [≥ 65 and < 65 years], male sex, body mass index, systolic blood pressure, heart rate, hypertension, diabetes mellitus, smoking status [current versus not current], myocardial infarction history, percutaneous coronary intervention history, coronary artery bypass grafting history, atrial fibrillation, heart failure, malignant disease, and peripheral artery disease), eGFR, hemoglobin A1c, hsCRP, and HDL-C at baseline. On the other hand, the level of sdLDL-C at 6 months and absolute and relative changes from baseline to 6 months in sdLDL-C level were not significantly associated with the risk of MACE among all study patients (Supplementary Table 3).

MACE Risk and Treatment Groups According to Quartile of Baseline Lipid Markers

If the findings for low-dose statin therapy were compared to high-dose statin therapy, the latter significantly reduced absolute risk in 5-year cumulative incidence by 4.9% and relative risk by 46% (p = 0.003) in patients with 4th quartile (> 34.3 mg/dL) sdLDL-C levels at baseline. However, it increased absolute risk in 5-year cumulative incidence by 2.1% and relative risk by 40% (p = 0.009) in patients with 1st quartile (≤ 19.5 mg/dL) sdLDL-C levels at baseline and did not alter the MACE risk in patients with 2nd and 3rd quartile of sdLDL-C levels at baseline (Fig. 2). The treatment interaction by sdLDL-C level at baseline was significant (p for interaction = 0.002; Fig. 3A), but that by LDL-C (Fig. 3B) or HDL-C (Fig. 3C) at baseline was not statistically significant. Similar to sdLDL-C, TRL-C (p for interaction = 0.013) and triglycerides (p for interaction = 0.014) had a statistically significant effect.
Fig. 2. Cumulative incidence of MACE stratified by treatment groups in subgroups according to baseline sdLDL-C quartile Numbers at risk of respective groups are described at the bottom of the figure.

Fig. 3. Risk of MACE and treatment groups by subgroups according to baseline lipid marker quartile

| Event | Hazard ratio Estimate | 95% CI | p for interaction |
|-------|-----------------------|--------|------------------|
| A     | 0.79 (0.65, 0.97)     | -      | -                |
| B     | 1.40 (0.94, 2.09)     | 0.002  | 0.009            |
| C     | 0.91 (0.61, 1.34)     | -      | -                |
| D     | 0.67 (0.45, 1.00)     | -      | -                |
| E     | 0.77 (0.50, 1.19)     | -      | -                |
| F     | 0.86 (0.53, 1.44)     | -      | -                |

1 adjusted for standard risk factors (i.e., age [≥ 65 and < 65 years], male sex, body mass index, systolic blood pressure, heart rate, hypertension, diabetes mellitus, smoking status [current versus not current], myocardial infarction history, percutaneous coronary intervention history, coronary artery bypass grafting history, atrial fibrillation, heart failure, malignant disease, and peripheral artery disease), eGFR, hemoglobin A1c, hsCRP, HDL-C, and triglycerides at baseline. 2 adjusted for standard risk factors, eGFR, hemoglobin A1c, hsCRP, LDL-C, and triglycerides at baseline. 3 adjusted for standard risk factors, eGFR, hemoglobin A1c, hsCRP, LDL-C, and HDL-C at baseline. 4 adjusted for standard risk factors, eGFR, hemoglobin A1c, hsCRP, and HDL-C at baseline.
in patients with 4th quartile levels at baseline. The effect with non-HDL-C (p for interaction = 0.139) was not statistically significant at baseline (Fig. 3). In addition, considering the covariate imbalance (HDL-C [p = 0.01], triglycerides [p = 0.04], and TRL-C levels [p = 0.04]) at baseline between the low- and high-dose groups, we assessed effects of high-dose statin therapy on baseline lipid markers by multivariate analyses. However, after multivariable adjustment for standard risk factors, eGFR, hemoglobin A1c, hsCRP, LDL-C, HDL-C, and triglycerides (excluding the subgroup classifier variable), identical results were obtained observed as in univariate analyses (Fig. 3).

Discussion

The present case-cohort study obtained the following main findings. First, high-dose statin therapy (4 mg/d pitavastatin) reduced sdLDL-C levels by 20% than low-dose statin therapy (1 mg/d). Second, among patients receiving low-dose statin therapy, the higher sdLDL-C level was associated with an increased risk of MACE independent of LDL-C level. Finally, compared with low-dose statin therapy, high-dose statin therapy caused a greater reduction of MACE risk in patients with the highest sdLDL-C level at baseline. Our findings support evidence from observational studies suggesting that sdLDL-C is a risk factor for cardiovascular disease.

Among patients targeted for secondary prevention, the prognostic role of the sdLDL-C level was less investigated than patients targeted for primary prevention. A recent prospective cohort study of 4,148 Chinese patients with stable CAD (mean age 60 years, 63.8% baseline statin use) showed a significant association between sdLDL-C level determined using a simple homogeneous assay and risk of MACE regardless of LDL-C level, for secondary prevention. However, the prognostic role of the sdLDL-C level has not been fully evaluated in statin-treated patients. Thus, we demonstrated the association between sdLDL-C level and risk of MACE, independent of LDL-C level, in statin-treated patients with stable CAD. Furthermore, we found novel evidence for a greater cardiovascular benefit from more intensive statin therapy in patients with stable CAD who had higher sdLDL-C levels. Thus, sdLDL-C may aid clinical decisions regarding whether to implement more intensive statin therapy or not. In fact, Japanese treatment guidelines recommend a therapeutic target of LDL-C < 100 mg/dL for secondary prevention. However, the present study suggests that it is clinically important to implement more intensive statin therapy in patients with higher sdLDL-C levels for secondary prevention, even when LDL-C levels drop to optimal levels (<100 mg/dL). Compared with low-dose, high-dose pitavastatin, patients in the lowest (≤ 19.5 mg/dL) baseline sdLDL-C quartile tended to increase MACE risk. Thus, intensive statin therapy may not be necessary to the lowest sdLDL-C subgroup. Moreover, these findings support the hypothesis that intensive lipid-lowering medication in patients with higher sdLDL-C levels effectively reduces cardiovascular risk. Further studies are warranted to determine whether the combination of statins with ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors may lead to additional benefits based on baseline sdLDL-C level.

On the analysis of sdLDL-C level at 6 months and absolute and relative changes from baseline to 6 months in sdLDL-C level, all these variables were not significantly associated with subsequent MACE risk. In the present study, there was no placebo arm and all study patients achieved LDL-C levels < 120 mg/dL with 1 mg/d pitavastatin for at least 1 month before randomization. Also, statin intensity in the high-dose statin group (4 mg/d pitavastatin) is generally considered moderate-intensity statin therapy. Furthermore, in the present study, high-dose statin therapy’s effect on sdLDL-C levels was evaluated at 6 months. However, this period might be too short to determine the high-dose statin therapy effect on sdLDL-C levels. These factors may make it difficult to evaluate these variables’ prognostic ability for MACE risk.

In the high-dose statin group, the sdLDL-C level at baseline was inversely associated with subsequent cardiovascular risk in the univariate Cox proportional hazard model with Barlow’s methods. Regarding the baseline characteristics of the random cohort, eGFR increased significantly with a higher sdLDL-C at baseline. Conversely, age and frequency of atrial fibrillation decreased significantly with higher sdLDL-C levels at baseline, possibly because of statin-treated patients. These confounding factors may lead to the inverse association of sdLDL-C level with cardiovascular risk in the high-dose group. This could be why there was no significant association between the sdLDL-C level at baseline and cardiovascular risk in the multivariable model. Additionally, LDL-C was an established risk factor1-4). However, the present study did not show a significant association between LDL-C level and MASE risk because of statin-treated patients.

Previous studies have suggested that sdLDL-C lowering effects of statin treatment may be due to the decrease in the LDL-C level rather than their effects.
on LDL particle size\textsuperscript{19,21}. In the present study, although the high-dose statin therapy reduced sdLDL-C level by 20\%, when compared with low-dose statin therapy, it brought about no change in the percentage of sdLDL-C in LDL-C from baseline to 6 months. Thus, high-dose statin therapy may not have any additional effect on LDL particle size compared with low-dose statin therapy. While lower triglyceride levels are generally expected to increase the size of LDL particles\textsuperscript{19,21}, the mild (but significant) reduction in triglycerides (8 mg/dL) by high-dose compared with low-dose pitavastatin in the present study might be insufficient to bring about this effect. In phase 2 trials, in the case of subjects with residual dyslipidemia (high triglycerides and non-HDL-C levels) on background statin therapy, a novel selective peroxisome proliferator-activated receptor alpha modulator—pemafibrate—shifted the distribution of LDL particle size to larger LDL particles, with a 20\% reduction in sdLDL-C level\textsuperscript{17,33}. Whether the combination of statins with pemafibrate may lead to additional benefits, based on baseline sdLDL-C levels, requires further research.

There are some limitations to our study. The study population enrolled only Japanese statin-treated patients with stable CAD. Therefore, our results may not generally apply to other populations. Also, there was no placebo arm, and all patients were treated with 1 mg/d pitavastatin for at least 1 month before randomization, which has known effects on lipid markers such as sdLDL-C level. Furthermore, the high-dose statin group (4 mg/d pitavastatin) is generally considered moderate-intensity statin therapy\textsuperscript{22,23}. This may have attenuated the changes in these lipid markers. In addition, high-intensity statin therapy (e.g., 80 mg/d atorvastatin) is not covered by Japanese national health insurance and is thus seldom used\textsuperscript{22,23}.

**Conclusion**

The sdLDL-C level, determined using a simple homogeneous assay, was associated with cardiovascular risk independent of LDL-C in statin-treated CAD patients. Notably, high-dose statin therapy reduced this risk in those with the highest baseline sdLDL-C level. Thus, sdLDL-C can be a useful risk marker and a predictive marker for the therapeutic benefit of intensive statin therapy. The present results provide the rationale for future studies of intensive lipid-lowering medication for secondary prevention, based on baseline sdLDL-C level.

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**Conflicts of Interest**

Dr J. Ishii received research grant from Sysmex Corp. and LSI Medience Corp., and honoraria from Siemens Healthineers Japan, and LSI Medience Corp.

Dr Kashiwabara reports no conflicts.

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Supplementary Fig. 1. Case-cohort design within REAL-CAD study

Abbreviations: MACE, major adverse cardiovascular events; REAL-CAD, Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease.
## Supplementary Table 1. Patient characteristics according to baseline sdLDL-C quartiles in random cohort population

| sdLDL-C quartile | 1st (n = 386) | 2nd (n = 398) | 3rd (n = 374) | 4th (n = 385) | p for trend |
|------------------|---------------|---------------|---------------|---------------|------------|
| sdLDL-C range, mg/dL | ≤ 19.5 | > 19.5 to 25.7 | > 25.7 to 34.3 | > 34.3 | 0.09 |
| **High-dose statin group, n (%)** | 175 (45.3) | 206 (51.8) | 183 (48.9) | 203 (52.7) | 0.09 |
| Age, y | 70.0 (7.6) | 69.2 (8.2) | 67.6 (8.4) | 66.2 (8.0) | < 0.01 |
| Male, n (%) | 304 (78.8) | 333 (83.7) | 317 (84.8) | 326 (84.7) | 0.03 |
| Body mass index, kg/m² | 24.0 (3.41) | 24.5 (3.23) | 24.7 (3.21) | 25.7 (3.33) | < 0.01 |
| Systolic blood pressure, mmHg | 128 (17.5) | 126 (17.4) | 127 (15.9) | 128 (14.1) | 0.09 |
| Diastolic blood pressure, mmHg | 71.9 (10.9) | 71.1 (10.8) | 72.9 (10.4) | 75.0 (10.3) | < 0.01 |
| Heart rate, bpm | 69.7 (11.6) | 69.5 (11.6) | 69.1 (11.4) | 70.3 (11.2) | 0.05 |
| Left ventricular ejection fraction, % | 60.1 (12.7) | 60.0 (12.3) | 61.1 (12.0) | 59.9 (11.9) | 0.94 |
| **Cardiovascular history** | | | | | |
| Myocardial infarction, n (%) | 196 (50.8) | 187 (47.0) | 196 (52.4) | 181 (47.0) | 0.64 |
| Percutaneous coronary intervention, n (%) | 318 (82.4) | 324 (81.4) | 313 (83.7) | 317 (82.3) | 0.73 |
| Coronary artery bypass grafting, n (%) | 63 (16.3) | 41 (10.3) | 42 (11.2) | 52 (13.5) | 0.34 |
| Congestive heart failure, n (%) | 16 (4.1) | 27 (6.8) | 16 (4.3) | 24 (6.2) | 0.46 |
| Atrial fibrillation, n (%) | 32 (8.3) | 23 (5.8) | 23 (6.1) | 17 (4.4) | 0.04 |
| Ischemic stroke, n (%) | 42 (10.9) | 32 (8.0) | 27 (7.2) | 20 (5.2) | 0.80 |
| Hemorrhagic stroke, n (%) | 8 (2.1) | 6 (1.5) | 7 (1.9) | 2 (0.5) | 0.75 |
| Peripheral artery disease, n (%) | 30 (7.8) | 30 (7.5) | 23 (6.1) | 30 (7.8) | 0.83 |
| Current smoking, n (%) | 45 (11.7) | 63 (15.8) | 54 (14.4) | 73 (19.0) | 0.01 |
| Diabetes mellitus, n (%) | 171 (44.3) | 168 (42.2) | 131 (35.0) | 163 (42.3) | 0.25 |
| Hypertension, n (%) | 291 (75.4) | 303 (76.1) | 281 (75.1) | 287 (77.1) | 0.60 |
| Family history of coronary artery disease, n (%) | 70 (18.1) | 67 (16.8) | 66 (17.4) | 76 (19.7) | 0.47 |
| History of malignant disease, n (%) | 31 (8.0) | 23 (5.8) | 17 (4.5) | 11 (2.9) | < 0.01 |
| **Blood examinations** | | | | | |
| Total cholesterol, mg/dL | 147 (19.0) | 162 (20.2) | 172 (19.5) | 183 (21.7) | < 0.01 |
| LDL-C, mg/dL | 76.1 (14.0) | 87.3 (16.5) | 92.6 (18.0) | 93.7 (19.6) | < 0.01 |
| HDL-C, mg/dL | 52.1 (12.9) | 51.5 (12.6) | 51.0 (13.7) | 47.8 (11.4) | < 0.01 |
| Triglycerides, mg/dL, median | 89.0 (66.114) | 108.5 (86.140) | 130 (100.171) | 192 (147.260) | < 0.01 |
| TRL-C, mg/dL, median | 17.8 (13.2, 22.8) | 21.8 (17.4, 28.0) | 26.0 (20.4, 34.2) | 38.2 (29.4, 51.4) | < 0.01 |
| hsCRP, mg/L, median | 0.49 (0.18, 1.32) | 0.50 (0.22, 1.22) | 0.54 (0.26, 0.98) | 0.56 (0.30, 1.21) | 0.03 |
| Glucose, mg/dL | 125 (44.8) | 122 (37.1) | 124 (39.6) | 131 (46.9) | 0.06 |
| Hemoglobin A1c, % | 5.82 (0.84) | 5.85 (0.78) | 5.86 (0.93) | 6.03 (1.02) | < 0.01 |
| eGFR, mL/min/1.73m² | 63.5 (16.7) | 66.7 (39.2) | 66.7 (16.0) | 68.1 (15.2) | < 0.01 |
| **Chronic kidney disease, n (%)** | | | | | |
| Stage 1 | 25 (6.5) | 29 (7.3) | 32 (8.6) | 33 (8.6) | < 0.01 |
| Stage 2 | 193 (50.0) | 215 (54.0) | 206 (55.1) | 226 (58.7) | < 0.01 |
| Stage 3 | 156 (40.4) | 145 (36.4) | 126 (33.7) | 117 (30.4) | < 0.01 |
| Stage 4 | 9 (2.3) | 6 (1.5) | 2 (0.5) | 2 (0.5) | < 0.01 |
| Stage 5 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | < 0.01 |
| **Medications, n (%)** | | | | | |
| Aspirin | 327 (84.7) | 336 (84.4) | 328 (87.7) | 333 (86.5) | 0.23 |
| Thienopyridine | 166 (43.0) | 171 (43.0) | 163 (43.6) | 180 (46.8) | 0.31 |
| Dual antiplatelet therapy | 156 (40.4) | 159 (39.9) | 153 (40.9) | 168 (43.6) | 0.36 |
| β-blocker | 131 (33.9) | 159 (39.9) | 138 (36.9) | 153 (39.7) | 0.21 |
| ACEI and/or ARB | 254 (65.8) | 252 (63.3) | 222 (59.4) | 247 (64.2) | 0.34 |

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol; TRL-C, triglyceride-rich lipoprotein cholesterol.

Data are n (%), mean (standard deviation) or median (interquartile range).
## Supplementary Table 2. Risk of MACE according to baseline lipid marker quartiles in low- and high-dose groups

|                | Unadjusted | Adjusted          |
|----------------|------------|-------------------|
| **A. LDL-C, mg/dL** |            |                   |
| **Low-dose group** |            |                   |
| 1st quartile ≤ 75.2 | 1.00       | 1.00              |
| 2nd quartile >75.2 to 88.0 | 0.99 (0.68, 1.47) | 1.23 (0.78, 1.93) |
| 3rd quartile > 88.0 to 101.4 | 1.04 (0.71, 1.52) | 1.26 (0.80, 1.98) |
| 4th quartile 4 > 101.4 | 1.13 (0.78, 1.65) | 1.46 (0.90, 2.38) |
| p for trend         | 0.501      | 0.131             |
| **High-dose group** |            |                   |
| 1st quartile ≤ 75.2 | 1.00       | 1.00              |
| 2nd quartile >75.2 to 88.0 | 0.78 (0.51, 1.19) | 0.64 (0.39, 1.05) |
| 3rd quartile > 88.0 to 101.4 | 1.00 (0.66, 1.51) | 0.96 (0.60, 1.55) |
| 4th quartile 4 > 101.4 | 0.84 (0.55, 1.27) | 0.85 (0.52, 1.39) |
| p for trend         | 0.671      | 0.928             |
| **B. Triglycerides, mg/dL** |            |                   |
| **Low-dose group** |            |                   |
| 1st quartile ≤ 90.0 | 1.00       | 1.00              |
| 2nd quartile >90.0 to 124 | 1.40 (0.95, 2.04) | 1.30 (0.81, 2.05) |
| 3rd quartile > 124 to 175 | 1.47 (1.00, 2.18) | 1.32 (0.84, 2.13) |
| 4th quartile >175 | 1.59 (1.06, 2.37) | 1.55 (0.93, 2.58) |
| p for trend         | 0.024      | 0.091             |
| **High-dose group** |            |                   |
| 1st quartile ≤ 90.0 | 1.00       | 1.00              |
| 2nd quartile >90.0 to 124 | 0.75 (0.49, 1.15) | 0.73 (0.43, 1.23) |
| 3rd quartile > 124 to 175 | 1.02 (0.68, 1.54) | 0.94 (0.56, 1.58) |
| 4th quartile >175 | 0.68 (0.45, 1.05) | 0.64 (0.38, 1.08) |
| p for trend         | 0.229      | 0.205             |
| **C. TRL-C, mg/dL** |            |                   |
| **Low-dose group** |            |                   |
| 1st quartile ≤ 18.0 | 1.00       | 1.00              |
| 2nd quartile >18.1 to 24.8 | 1.41 (0.96, 2.07) | 1.31 (0.83, 2.07) |
| 3rd quartile > 24.8 to 35.0 | 1.49 (1.00, 2.20) | 1.34 (0.84, 2.15) |
| 4th quartile >35.0 | 1.61 (1.09, 2.39) | 1.57 (0.95, 2.59) |
| p for trend         | 0.019      | 0.088             |
| **High-dose group** |            |                   |
| 1st quartile ≤ 18.0 | 1.00       | 1.00              |
| 2nd quartile >18.1 to 24.8 | 0.74 (0.49, 1.13) | 0.73 (0.43, 1.23) |
| 3rd quartile > 24.8 to 35.0 | 1.00 (0.67, 1.51) | 0.93 (0.55, 1.57) |
| 4th quartile >35.0 | 0.68 (0.44, 1.04) | 0.65 (0.39, 1.09) |
| p for trend         | 0.214      | 0.210             |

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; TRL-C, triglyceride-rich lipoprotein cholesterol.

Data are hazard ratio (95% confidence interval). Multivariable model was adjusted for standard risk factors (i.e., age [≥ 65 and <65 years], male sex, body mass index, systolic blood pressure, heart rate, hypertension, diabetes mellitus, smoking status [current versus not current], myocardial infarction history, percutaneous coronary intervention history, coronary artery bypass grafting history, atrial fibrillation, heart failure, malignant disease, and peripheral artery disease), eGFR, hemoglobin A1c, hsCRP, and HDL-C at baseline.
Supplementary Table 3. Risk of MACE according to quartiles of sdLDL-C at 6 months and absolute and relative changes from baseline to 6 months in all patients

|                      | Unadjusted | Adjusted   |
|----------------------|------------|------------|
| **A. sdLDL-C at 6 months, mg/dL** |            |            |
| 1st quartile ≤ 17.6  | 1.00       | 1.00       |
| 2nd quartile > 17.6 to 23.8 | 1.11 (0.83, 1.50) | 1.30 (0.91, 1.85) |
| 3rd quartile > 23.8 to 32.5 | 1.11 (0.83, 1.50) | 1.30 (0.91, 1.86) |
| 4th quartile > 32.5  | 0.90 (0.67, 1.23) | 0.93 (0.62, 1.41) |
| p for trend          | 0.541      | 0.758      |
| **B. Absolute change from baseline to 6 months in sdLDL-C level, mg/dL** |            |            |
| 1st quartile ≤ -6.9  | 1.00       | 1.00       |
| 2nd quartile > -6.9 to -1.7 | 0.90 (0.66, 1.24) | 0.94 (0.65, 1.34) |
| 3rd quartile > -1.7 to 3.5 | 0.95 (0.70, 1.30) | 0.97 (0.69, 1.38) |
| 4th quartile > 3.5   | 0.90 (0.66, 1.23) | 0.88 (0.61, 1.27) |
| p for trend          | 0.599      | 0.549      |
| **C. Relative change from baseline to 6 months in sdLDL-C level, %** |            |            |
| 1st quartile ≤ -25.2 | 1.00       | 1.00       |
| 2nd quartile > -25.2 to -7.1 | 0.80 (0.52, 1.25) | 0.73 (0.44, 1.20) |
| 3rd quartile > -7.1 to 15.7 | 1.05 (0.66, 1.66) | 0.86 (0.50, 1.50) |
| 4th quartile > 15.7  | 0.98 (0.58, 1.65) | 0.88 (0.47, 1.65) |
| p for trend          | 0.800      | 0.829      |

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular events; sdLDL-C, small dense low-density lipoprotein cholesterol.

Absolute and relative changes in sdLDL-C level were defined as (sdLDL-C value at 6 months – at baseline) and (absolute change / baseline) × 100, respectively. Data are hazard ratio (95% confidence interval). Multivariable model was adjusted for standard risk factors (i.e., age ≥ 65 and < 65 years), male sex, body mass index, systolic blood pressure, heart rate, hypertension, diabetes mellitus, smoking status [current versus not current], myocardial infarction history, percutaneous coronary intervention history, coronary artery bypass grafting history, atrial fibrillation, heart failure, malignant disease, and peripheral artery disease), eGFR, hemoglobin A1c, hsCRP, triglycerides, and HDL-C at 6 months.