Small dense low-density lipoprotein cholesterol is a promising biomarker for secondary prevention in older men with stable coronary artery disease

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Aim: The study objective was to investigate whether small dense low-density lipoprotein cholesterol (sdLDL-C) is superior to low-density lipoprotein cholesterol (LDL-C) and other biomarkers to predict future cardiovascular events (CE) in secondary prevention.

Methods: sdLDL-C measured by a homogeneous assay, remnant lipoprotein cholesterol, LDL particle diameter and other biomarkers were compared in 345 men aged ≥65 years with stable coronary artery disease. Baseline LDL-C was 100.5±30.1 mg/dL. CE including cardiovascular death, onset of acute coronary syndrome, need for arterial revascularization, hospitalization for heart failure, surgery procedure for cardiovascular disease and hospitalization for stroke were monitored for 5 years.

Results: CE occurred in 96 patients during the study period. LDL-C, sdLDL-C non-high-density lipoprotein cholesterol, apolipoprotein B, remnant lipoprotein cholesterol, glucose, glycated hemoglobin and brain natriuretic peptide were significantly higher; LDL particle diameter and apolipoprotein A-1 were significantly lower in patients with than in those without CE. Age-adjusted Cox regression analysis showed that sdLDL-C per 10 mg/dL, but not LDL-C, was significantly associated with CE (HR 1.206, 95% CI 1.006–1.446). A significant association of sdLDL-C and incident CE was observed in statin users (HR 1.252, 95% CI 1.017–1.540), diabetes patients (HR 1.219, 95% CI 1.018–1.460), patients without diabetes (HR 1.257, 95% CI 1.019–1.551) and patients with hypertriglyceridemia (HR 1.376, 95% CI 1.070–1.770).

Conclusions: sdLDL-C was the most effective predictor of residual risk of future CE in stable coronary artery disease patients using statins and in high-risk coronary artery disease patients with diabetes or hypertriglyceridemia. Geriatr Gerontol Int 2018; 18: 965–972.

Keywords: coronary artery disease, diabetes mellitus, secondary prevention small dense low-density lipoprotein, statins.

Introduction

Low-density lipoprotein cholesterol (LDL-C) is currently considered as the most important target for reducing cardiovascular risk. LDL includes fractions of large buoyant and small dense particles.1 Small dense LDL (sdLDL) particles are thought to be more atherogenic than large buoyant LDL (dbLDL) because of higher penetration of the arterial wall, lower binding affinity for the LDL receptor, prolonged plasma half-life, and lower resistance to oxidative stress.1–3 Increased sdLDL cholesterol (sdLDL-C) represents an increase in the number of atherogenic LDL particles, because sdLDL particles are smaller and contain less cholesterol.

The HDL Atherosclerosis Treatment Study reported a positive association of the plasma concentration of sdLDL particles and progression of coronary artery stenosis that was confirmed by gradient gel electrophoresis, vertical auto profile ultracentrifugation, nuclear magnetic
resonance spectroscopy and ion mobility. In our cross-sectional studies, heparin magnesium precipitation was used to show that high sdLDL-C, not high lbLDL-C, concentration was closely associated with the angiographic and/or clinical severity of coronary artery disease (CAD) independent of classical coronary risk factors. Our previous cohort study found that increased sdLDL-C and the sdLDL-C/LDL-C ratio were significantly associated with an elevated risk of cardiovascular events (CE) in patients with stable CAD, and prospective population-based cohort studies in Japan and the USA reported that increased sdLDL-C was significantly associated with the incidence of CAD independent of LDL-C.

A meta-analysis of 61 prospective cohort studies showed that age substantially attenuated the positive relationship between total cholesterol and CAD mortality. The INTERHEART study, a worldwide case-control study including more than 25,000 participants, found a significant decline in the odds ratio of myocardial infarction for each change of one standard deviation in total cholesterol, LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (ApoB) increasing age. The association of sdLDL-C with the risk of CE recurrence in older patients with CAD has not been compared with that of LDL-C. The study aim was to determine whether sdLDL-C is a better predictor than LDL-C and/or other lipid biomarkers of future CE in older patients with stable CAD.

Methods

Study patients

The present observational cohort study included of 345 consecutive male patients aged 65 years with angiographically confirmed CAD at Showa University Hospital, Tokyo, Japan, between September 2003 and December 2011. At the time the study began enrolling patients, aggressive lipid-lowering treatment was not common in patients with CAD. Significant CAD was defined as a ≥50% narrowing of the diameter of one or more coronary artery branch on an arteriogram and/or a prior history of percutaneous coronary intervention (PCI) and/or coronary artery bypass surgery. The peripheral artery disease was defined as the Ankle Brachial Index of <0.90 using an oscillometric device (Form/ABI, Colin Company, Komaki, Japan) and/or a history of endovascular treatment. Patients with acute coronary syndrome (ACS), nephrotic syndrome, renal dysfunction (serum creatinine >1.5 mg/dL), severe hepatic disease, infectious disease, currently treated for malignancy, receiving hemodialysis, taking drugs for thyroid dysfunction or with any other serious condition were excluded. Patients who could not be followed for 3 months after coronary angiography were also excluded.

The institutional review board of Showa University approved the study protocol, which was registered at UMIN-CTR (UMIN000027504). The investigation conformed to the ethical principles of the Declaration of Helsinki, and informed consent was obtained from all participants.

Baseline evaluation

Fasting blood samples were obtained by venipuncture immediate before cardiac catheterization. The LDL particle diameter (LDL-PD) and serum lipid biomarkers, except sdLDL-C, were assayed within 3 days of sampling; unused samples were stored at −80°C. Of the 345 participants, 245 men had a past history of myocardial infarction, 272 had previously undergone PCI and/or coronary artery bypass surgery, 234 were taking lipid-lowering drugs, and 102 men experienced coronary revascularization because of coronary angiography findings. Hypertension was determined by the medical history or by a blood pressure >140 mmHg systolic or 90 mmHg diastolic. Diabetes mellitus was defined as a fasting serum glucose value >126 mg/dL, glycated hemoglobin (Hb) A1c values estimated by (1.019 × HbA1c [Japan Diabetes Society] + 0.3) >6.5% and/or the current use of medication for diabetes. Dyslipidemia was defined as the current use of lipid-lowering medications and/or meeting the criteria of the Japan Atherosclerosis Society for fasting serum lipid levels; that is, LDL-C ≥140 mg/dL, HDL-C <40 mg/dL or triglyceride ≥150 mg/dL. A serum creatinine-based estimate of glomerular filtration rate (eGFR) was calculated as follows: glomerular filtration rate = 194 × creatinine−1.094 × age−0.287 (×0.793 for women). Body mass index was calculated as weight (kilograms) divided by height (meters) squared. Patients with a reported smoking habit of at least one cigarette per day on admission were classified as current smokers.

Definition of CE

In-hospital medical records were evaluated 60 months after the baseline blood screening. The end-points were: (i) the onset date of the first CE; (ii) the date of death; and (iii) the date of the patient’s last visit to Showa University Hospital. CE were defined as death caused by cardiovascular disease (CVD), onset of ACS, need for coronary or other arterial revascularization including restenosis after PCI; hospitalization for heart failure; surgery for any CVD; and hospitalization for ischemic or hemorrhagic stroke. Coronary revascularization within 3 months was not considered a CE, because at that time, unexpected and scheduled coronary revascularization could not be distinguished.
**Lipoprotein and brain natriuretic peptide assays and inflammatory markers**

Total cholesterol, triglycerides, HDL-C, HbA1c, apolipoproteins and lipoprotein(a) were assayed by standard laboratory procedures. Remnant lipoproteins (RLP) were isolated from serum by immunoaffinity mixed gels containing anti-apolipoprotein A1 (ApoA1) and anti-ApoB100 monoclonal antibodies (Japan Immunoresearch Laboratories, Takasaki, Japan). The cholesterol concentrations of the unbound fraction were measured as RLP-C. Serum LDL-C was determined by a direct homogenous assay using detergents (LDL-EX; Denka Seiken, Tokyo, Japan). Serum samples were kept frozen at −80°C until used for a direct homogenous assay for sdLDL-C, as previously described. The LDL-C and sdLDL-C assay kits were provided by Denka Seiken. LbLDL-C was estimated by subtracting the sdLDL-C concentration from the LDL-C concentration. The sdLDL-C/LDL-C ratio was also calculated from direct measurements. LbLDL-C values estimated by this method have previously been correlated with values determined by ultracentrifugation. Non-HDL-C was estimated by subtracting the HDL-C concentration from the total cholesterol concentration, and peak LDL-PD was determined by 2–16% non-denatured polyacrylamide gel electrophoresis, as described by Nichols et al. High-sensitivity C-reactive protein was assayed by the Dade Behring BN method. Plasma brain natriuretic peptide was measured by radioimmunoassay.

**Statistical analysis**

Statistical analysis was performed using the IBM SPSS Statistics for Macintosh, Version 23.0. (IBM Corp. Armonk, NY, USA). The baseline characteristics of patients with or without CE during follow up were compared using Wilcoxon tests, because most of the variables did not have a Gaussian distribution. Categorical variables were compared by χ²-tests. Although this was a case–control study, cumulative incidence was estimated by the Kaplan–Meier method in patients stratified by the median sdLDL-C level. The date of the baseline lipid measurements was set as the landmark point from which cardiovascular outcomes were evaluated. Clinical data obtained from patients who were lost to follow up were censored, and were used for the period for which follow up was available. Age-adjusted Cox regression analysis of the patient variables was used to calculate hazard ratios (HR) with corresponding 95% confidence intervals (CI) of the risk of future CE. Variables that differed significantly in patients with and without CE were included in a multivariate analysis. All statistical analyses were two-tailed, and P < 0.05 was considered statistically significant.

**Results**

**Baseline characteristics and CE**

The 5-, 3- and 1-year follow-up rates were 75.5%, 84.8% and 94.6%, respectively, and first-time CE were observed in 96 (27.8%) of the 345 patients (Table 1). A total of 11 patients died of CVD, (1 of acute myocardial infarction, 6 of heart failure and 4 of unknown cause). A total of 85 patients (24.6%) were hospitalized with non-fatal CVD, 11 (3.2%) with ACS and 11 (3.2%) with congestive heart failure and 14 (4.05%) with ischemic stroke. A total of 46 patients (13.3%) underwent revascularization and three (0.9%) received endovascular treatment. No patients were hospitalized with hemorrhagic stroke. Comparison of the baseline characteristics of patients with and without CE (Table 1) showed a significantly higher prevalence of diabetes and peripheral artery disease, greater need for coronary revascularization at baseline, and fewer statin uses among those who experienced a CE. A comparison of laboratory findings (Table 2) found that the mean LDL-C was approximately 100 mg/dL, which was lower than that in a previously studied cohort. The sdLDL-C in patients treated with statins were significantly lower than those not treated with statins (26.1 ± 11.5 vs 31.5 ± 14.2, P = 0.003). LDL-C, sdLDL-C, non-HDL-C, LDL/HDL-C ratio, ApoB, RLP-C, glucose, HbA1c and BNP were significantly higher, and LDL-PD and ApoA-1 were significantly lower in patients with CE. The differences in LbLDL-C, HDL-C, eGFR and high-sensitivity C-reactive protein in the two groups were not significant.

**Correlation of LDL-C and SdLDL-C, and patient characteristics**

The Spearman rank-order correlation of LDL-C and sdLDL-C, and patient characteristics are shown in the Table S2. Although sdLDL-C is a part of LDL-C, sdLDL-C had stronger correlations with biomarkers of atherogenic dyslipidemia, such as triglycerides and RLP-C, than LDL-C.

**Kaplan–Meier event-free survival analysis and Cox regression analysis**

The Kaplan–Meier event-free survival curves among patients above or below the median levels for sdLDL-C in patients, diabetic patients and patients treated with statins are shown in Figure 1. A total of 16 patients who died of causes other than CVD and without experiencing any non-fatal CE were treated as censored cases. Patients with sdLDL-C ≥25 mg/dL had a significantly increased risk for CE (log–rank 6.155, P = 0.003). Similar results were observed in diabetic patients and patients treated with statins at baseline.
log–rank 6.492, \( P = 0.011 \) and log–rank 4.193, \( P = 0.041 \), respectively). Age-adjusted Cox regression analysis (Table 3) showed that increases in LDL-C, sdLDL-C, non-HDL-C, LDL-C/HDL-C, ApoB, glucose, HbA1c and BNP, and decreases in LDL-PD and ApoA1 were significantly associated with an increased risk of CE; RLP-C was not. Multivariate analysis showed that decreased LDL-PD and increased HbA1c were significantly associated with the occurrence of CE independent of LDL-C and sdLDL-C, which is evidence in support of sdLDL as atherogenic LDL particles. The measurement of LDL-PD by gradient gel electrophoresis requires a separation time of >24 h, which makes it unsuitable for use in clinical practice. The direct homogenous assay for sdLDL-C does not require any pretreatment and can be carried out with the

**Discussion**

To the best of our knowledge, this is the first study to report that elevated sdLDL-C (determined by an automated homogenous assay) was independently associated with CE recurrence in elderly patients with stable CAD. These results are consistent with our previous results obtained in 190 patients with stable CAD using precipitation assay of sdLDL-C concentration.  To the best of our knowledge, this is the first study to report that elevated sdLDL-C (determined by an automated homogenous assay) was independently associated with CE recurrence in elderly patients with stable CAD. These results are consistent with our previous results obtained in 190 patients with stable CAD using precipitation assay of sdLDL-C concentration. In the present study, Cox’s proportional hazard analysis failed to find an association of increased sdLDL-C with the risk of CE. In the present study, multivariate Cox regression analysis showed that decreased LDL-PD was significantly associated with the occurrence of CE independent of LDL-C and sdLDL-C, which is evidence in support of sdLDL as atherogenic LDL particles. The measurement of LDL-PD by gradient gel electrophoresis requires a separation time of >24 h, which makes it unsuitable for use in clinical practice. The direct homogenous assay for sdLDL-C does not require any pretreatment and can be carried out with the
chemistry auto analyzers routinely used in clinical laboratories. The study found a significant association between sdLDL-C and the occurrence of CE in the entire study population, and in high-risk subpopulations including diabetes patients and those with hypertriglyceridemia. The results confirm that sdLDL-C, compared with LDL-C, was a more important biomarker for secondary prevention.

**Table 2** Laboratory findings in patients with and without cardiovascular events

|                  | Whole (n = 345) | CE (n = 96) | non-CE (n = 249) | P |
|------------------|-----------------|-------------|------------------|---|
| LDL-C (mg/dL)    | 100.5 ± 30.1    | 107.3 ± 30.0| 97.9 ± 29.7      | 0.008 |
| sdLDL-C (mg/dL)  | 28.2 ± 12.9     | 31.8 ± 15.1 | 26.9 ± 11.7      | 0.008 |
| lbLDL-C (mg/dL)  | 72.2 ± 24.2     | 75.5 ± 25.3 | 71.0 ± 23.7      | 0.171 |
| LDL-PD (Å)       | 256.2 ± 4.5     | 255.3 ± 4.9 | 256.5 ± 4.2      | 0.032 |
| Non-HDL-C (mg/dL)| 128.7 ± 34.0    | 137.7 ± 35.3| 125.3 ± 32.9     | 0.003 |
| Triglycerides (mg/dL) | 123.1 ± 70.5 | 133.7 ± 87.6 | 119.0 ± 62.5 | 0.195 |
| HDL-C (mg/dL)    | 46.6 ± 14.4     | 44.1 ± 12.7 | 47.5 ± 15.0      | 0.060 |
| LDL-C/HDL-C      | 2.4 ± 1.0       | 2.6 ± 1.0   | 2.3 ± 1.0        | 0.001 |
| sdLDL-C/LDL-C    | 0.28 ± 0.10     | 0.30 ± 0.12 | 0.28 ± 0.96      | 0.15  |
| ApoA1 (mg/dL)    | 124.9 ± 25.8    | 119.2 ± 23.1| 127.0 ± 26.5     | 0.013 |
| ApoB (mg/dL)     | 85.8 ± 21.0     | 91.0 ± 20.3 | 83.9 ± 21.1      | 0.004 |
| Lipoprotein(a) (mg/dL) | 22.8 ± 24.7 | 25.0 ± 25.2 | 22.0 ± 24.5      | 0.296 |
| RLP-C (mg/dL)    | 4.4 ± 3.0       | 4.8 ± 3.3   | 4.3 ± 2.9        | 0.04  |
| Glucose (mg/dL)  | 114.1 ± 35.5    | 121.3 ± 45.6| 111.3 ± 30.5     | 0.038 |
| HbA1c (%)        | 6.3 ± 1.1       | 6.7 ± 1.5   | 6.1 ± 0.88       | <0.001|
| eGFR (mL/min/1.73 m²) | 62.4 ± 18.1 | 62.6 ± 20.4 | 62.3 ± 17.2      | 0.479 |
| BNP (pg/mL)      | 105.1 ± 170.7   | 149.0 ± 254.0| 87.7 ± 119.5    | 0.021 |
| hsCRP (mg/dL)    | 0.40 ± 1.0      | 0.52 ± 1.4  | 0.35 ± 0.81      | 0.347 |

ApoA1, apolipoprotein A-1; ApoB, apolipoprotein B; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; lbLDL-C, large buoyant low-density lipoprotein; LDL-PD, low-density lipoprotein particle diameter; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol.

**Figure 1** The Kaplan–Meier event-free survival of patients stratified by the median small dense low-density lipoprotein cholesterol (sdLDL-C) concentration (25 mg/dL). (a) All patients, (b) patients treated with statins and (c) diabetes patients. CE, cardiovascular events.
A meta-analysis of eight randomized controlled statin trials found that on-treatment levels of non-HDL-C were more strongly associated with the risk of major CE than the levels of LDL-C and ApoB among statin-treated patients. A study of recent ACS patients treated with statins reported that fasting triglycerides at the initial randomization predicted short- and long-term risk of major CE. Both publications suggest that the cholesterol content of triglyceride-rich lipoproteins poses a residual risk in patients receiving effective statin therapy. A correlation of RLP-C and sdLDL has also been shown, and Kugiyama et al. showed that patients in the highest RLP-C tertile (>5.1 mg/dL) in a group of 135 CAD patients had a higher incidence of CAD events than those in the lowest tertile (≤3.3 mg/dL), even though their LDL-C levels were <100 mg/dL. In a later study of 190 patients treated with statins after ACS, they found that a high RLP-C (≥5.4 mg/dL) was a significant risk of secondary events independent of conventional risk factors (HR 2.94, 95% CI 1.40–6.18; P < 0.01). This study, which compared LDL-C, sdLDL-C, RLP-C, non-HDL-C and ApoB in patients with stable CAD, found that only sdLDL-C was independently associated with CE in patients treated with statins. A recent study of the LDL-C reduction achieved by statins with or without ezetimibe in patients with ACS found a greater reduction of sdLDL-C in patients with coronary plaque regression (measured by ultrasound) than in those with plaque progression. The evidence from a variety of sources thus supports sdLDL-C as a promising biomarker of residual risk in patients currently treated with statins.

The Japanese Elderly Diabetes Intervention Trial found a positive association of LDL-C with incident coronary events. Both HbA1c and non-HDL-C were positively associated with stroke. Cox regression analysis found that in the present study, LDL-C, sdLDL-C, ApoB and HbA1c were significantly associated with CE in diabetes patients, and the HR for sdLDL-C was slightly higher than that for LDL-C and ApoB. However, the association between these lipid biomarkers and CE was no longer significant in the multivariate analysis. Future studies in large populations are required to investigate lipid biomarkers in diabetes patients with CAD. In contrast, the association of increased sdLDL-C and non-HDL-C, and decreased in LDL-PD with CE in patients without diabetes are in agreement with results of the Multi-Ethnic Study of Atherosclerosis. That study reported significant associations of sdLDL-C and incident CAD in patients with normal fasting glucose, but not in those with impaired fasting glucose or diabetes mellitus.

The present study had several limitations including a small sample size and low follow-up rate. Second, the CE included those related to unstable plaque, as well as revascularization for restenosis after PCI, atherogenic cardiovascular diseases and ischemic heart failure requiring hospitalization. It remains unclear whether elevated sdLDL-C is related to ischemic heart failure. In addition, hospitalization for heart failure might be due to non-atherosclerotic disease, although all patients in the present study had coronary atherosclerosis. Third, the effects of lipid-lowering therapy and target levels of sdLDL-C could not be investigated. Fourth, lipid-lowering treatment was not evaluated during follow up. Fifth, left ventricular ejection fraction, frailty, malnutrition and anemia were not captured in the analysis. Future prospective studies should thus be carried out to evaluate these issues in larger samples.
Table 4  Univariate age-adjusted hazard ratios (95% confidence interval) for occurrence of major cardiovascular events in patient subpopulations

|                        | Statin users (n = 208) | Hypertriglyceridemia (n = 80) | Diabetes (n = 115) | Non-diabetes (n = 230) |
|------------------------|------------------------|------------------------------|-------------------|-----------------------|
| LDL-C per 10 mg/dL     | 1.062 (0.957–1.177)    | 1.089 (0.977–1.214)          | 1.103 (1.006–1.208)* | 1.078 (0.985–1.180)   |
| sdLDL-C per 10 mg/dL   | 1.252 (1.017–1.540)*   | 1.376 (1.070–1.770)*         | 1.219 (1.018–1.460)* | 1.257 (1.019–1.551)*  |
| sdLDL-C/LDL-C          | 6.111 (0.531–70.294)   | 5.453 (0.294–101.292)        | 3.455 (0.299–39.923) | 5.888 (0.394–88.098)  |
| LDL-PD/ldLDL-C         | 0.956 (0.901–1.015)    | 0.966 (0.884–1.056)          | 0.960 (0.897–1.028) | 0.934 (0.883–0.989)*  |
| Triglycerides per 10 mg/dL | 1.016 (0.893–1.156) | 1.037 (0.913–1.176)          | 1.088 (0.968–1.223) | 1.058 (0.943–1.186)   |
| TC per 10 mg/dL        | 1.043 (0.958–1.136)    | 1.060 (0.968–1.162)          | 1.047 (0.972–1.128) | 1.058 (0.977–1.146)   |
| HDL-C per 10 mg/dL     | 0.932 (0.745–1.167)    | 0.877 (0.635–1.211)          | 0.895 (0.733–1.093) | 0.842 (0.667–1.063)   |
| Non-HDL-C per 10 mg/dL | 1.060 (0.971–1.0157)  | 1.088 (0.987–1.200)          | 1.079 (0.996–1.169) | 1.082 (1.001–1.170)*  |
| LDL-C/HDL-C            | 1.281 (0.909–1.805)    | 1.222 (0.860–1.737)          | 1.394 (1.018–1.910)* | 1.325 (1.037–1.692)*  |
| ApoA1 per 10 mg/dL     | 0.919 (0.813–1.039)    | 0.886 (0.763–1.028)          | 0.894 (0.788–1.015) | 0.907 (0.807–1.018)   |
| ApoB per 10 mg/dL      | 1.079 (0.933–1.247)    | 1.104 (0.935–1.305)          | 1.157 (1.011–1.324)* | 1.126 (0.993–1.277)   |
| Lipoprotein(a)         | 1.004 (0.995–1.013)    | 1.023 (1.008–1.039)**        | 1.012 (1.000–1.025) | 1.004 (0.994–1.015)   |
| RLP-C                  | 0.999 (0.899–1.111)    | 1.005 (0.918–1.110)          | 1.000 (0.936–1.068) | 1.089 (0.940–1.261)   |
| Glucose                | 1.005 (0.997–1.013)    | 1.000 (0.991–1.009)          | 1.002 (0.996–1.008) | 0.995 (0.975–1.015)   |
| HbA1c                  | 1.574 (1.264–1.960)*** | 1.186 (0.916–1.534)          | 1.304 (1.088–1.563)** | 1.157 (0.654–2.046)  |
| eGFR                   | 0.999 (0.981–1.018)    | 0.984 (0.962–1.007)          | 1.003 (0.988–1.018) | 1.007 (0.989–1.025)   |
| hsCRP                  | 0.424 (0.113–1.588)    | 0.892 (0.418–1.904)          | 0.949 (0.635–1.408) | 1.202 (1.016–1.422)*  |
| BNP                    | 1.001 (0.999–1.003)    | 1.001 (0.999–1.003)          | 1.001 (1.000–1.002)** | 1.001 (0.999–1.003)   |

*P < 0.05, **P < 0.01, ***P < 0.001. ApoA1, apolipoprotein A-1; ApoB, apolipoprotein B; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; ldLDL-C, large buoyant low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDL-PD, low-density lipoprotein particle diameter; RLP-C, remnant lipoprotein cholesterol; sdLDL-C, small dense low-density lipoprotein cholesterol; TC, total cholesterol.

In conclusion, in older patients with stable CAD, elevated sdLDL-C levels measured by an automated homogenous assay were strongly associated with CE recurrence independent of LDL-C. Second, decreased LDL-PD was significantly associated with incident CE independent of LDL-C and sdLDL-C. Third, of all the lipid biomarkers, only sdLDL-C was independently associated with CE among patients treated with statins. Fourth, a significant association of sdLDL-C and incident CE was consistently observed in all patient sub-populations, including those with diabetes and hypertriglyceridemia, which are well-known high-risk populations. The results showed sdLDL-C to be a more effective secondary prevention biomarker than LDL-C to predict future CE. A large cohort study is required to determine the appropriate target level of sdLDL-C.

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Disclosure statement

Yasuki Ito is an employee of Denka Seiken. The other authors declare no conflict of interest.
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Supporting information

Additional supporting information may be found in the online version of this article at the publisher’s website: .

Table S1 Cardiovascular events

Table S2 Spearman’s correlation of low-density lipoprotein cholesterol or small dense low-density lipoprotein cholesterol and patient characteristics.