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Effects of Increasing Particle Size of Low-Density Lipoprotein on Restenosis After Coronary Stent Implantation

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Background Small dense low-density lipoprotein (LDL) has emerged as an important risk factor in coronary atherosclerosis and vascular inflammation, which is related to neointimal hyperplasia. Therefore, the aim of the present study was to investigate whether changes in LDL particle size are related to in-stent restenosis (ISR).
Methods and Results The LDL subfraction and lipid profiles were measured in 274 patients (412 stents) at both baseline and follow-up coronary angiography (CAG). The incidence of ISR (80 lesions, 19.4%) was lower in the patients with increased LDL particle size than in those with no change or decrease (14.2% vs 25.8%, p=0.004). Logistic multivariate analysis revealed that stent length (≥24 mm) (odds ratio (OR) =1.913, p=0.027), post minimal luminal diameter (>3 mm) (OR =0.528, p=0.028), acute coronary syndrome (OR =2.294, p=0.005), decrease in high-density lipoprotein-cholesterol (OR =1.028, p=0.047) and increase in LDL particle size (OR =0.528, p=0.031) were independent predictors for ISR.
Conclusions In the present study, an increase in the LDL particle size between baseline and follow-up CAG was associated with reduced incidence of ISR. Therefore, modification of LDL particle size may have a beneficial effect on the risk of ISR. (*Circ J* 2008; **72:** 1059 – 1064)

Key Words: Coronary stent; Restenosis; Small dense low-density lipoprotein

Although coronary stent implantation reduces the restenosis rate compared with that for balloon angioplasty, in-stent restenosis (ISR) remains a serious problem[1] Previous studies have shown that neointimal proliferation plays the most important role in restenosis after stent implantation[2,3] Neointimal hyperplasia is related to insulin resistance and endothelial dysfunction, both of which decrease nitric oxide and increase the migration and proliferation of vascular smooth muscle cells[4] thus interfering with the attenuation of binding of inflammatory cells to the vascular wall[4–7]

Among the fractions of low-density lipoprotein (LDL) particles, small dense LDL (sd-LDL) is particularly important in the development of endothelial dysfunction and atherosclerosis[8–10] Several large prospective studies showed that coronary artery disease (CAD) risk increased significantly when sd-LDL was the predominant LDL subclass[8,11,12] Previous angiographic clinical trials have also indicated that benefit was related to a decrease in sd-LDL particles[13,14]

Although sd-LDL is known to induce the formation of vulnerable plaques, resulting in acute coronary events, the precise relationship between the size of a lipoprotein molecule and ISR after stent implantation remains unclear. Therefore, we investigated whether a change in LDL particle size influences ISR following implantation.

Method

Subjects

This study enrolled 274 consecutive patients who underwent coronary angiography (CAG) at Yongdong Severance Hospital, Yonsei University, Seoul, South Korea, from October 2003 through November 2006, after excluding patients with chronic renal failure, hepatic failure, apparent thyroid disease, infectious or inflammatory disease, or malignancy.

The diagnosis of hypertension was based on a known history and systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg. The diagnosis of diabetes mellitus was based on a fasting serum glucose level >126 mg/dl or a history of treatment with either oral hypoglycemic agents or insulin. Height and weight were recorded in all subjects, and body mass index was calculated as weight (kg)/height^2 (m^2).

The diagnosis of acute coronary syndrome (ACS) was divided into ST-segment elevation myocardial infarction (MI), non-ST-segment elevation MI and unstable angina based on the patient's resting ECG, cardiac enzyme levels and clinical symptoms. Significant CAD on CAG was defined as stenosis ≥50% of the luminal diameter in ≥1 branch of the coronary arteries. Study subjects were divided into 2 groups: Group 1 comprised patients with an increase in the LDL particle size between baseline and follow-up CAG

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Table 1 Baseline Characteristics of the Patients

	Increase in LDL particle size (n=151)	*No change or decrease in LDL particle size (n=121)*	*p value*
Age (years)	*59.8±10.3*	*60.4±9.7*	*0.596*
Male (%)	*89 (58.9%)*	*62 (61.2%)*	*0.711*
BMI (kg/m²)	*25.3±2.6*	*25.5±3.2*	*0.626*
DM (%)	*37 (24.5%)*	*29 (24.0%)*	*0.918*
Hypertension (%)	*96 (63.6%)*	*74 (61.2%)*	*0.682*
Smoking (%)	*72 (45.0%)*	*55 (45.5%)*	*0.773*
ACS (%)	*65 (43.0%)*	*43 (35.5%)*	*0.208*
Mutivessel disease (%)	*107 (70.9%)*	*77 (63.6%)*	*0.206*
hs-CRP (mg/L)	*3.9±8.8*	*7.7±22.7*	*0.098*
Statins (%)	*128 (84.8%)*	*97 (80.2%)*	*0.318*
Fibrates (%)	*33 (21.8%)*	*7 (3.8%)*	*<0.001*

Values are n (%) or mean±SD.
LDL, low-density lipoprotein; BMI, body mass index; DM, diabetes mellitus; ACS, acute coronary syndrome; hs-CRP, high-sensitivity C-reactive protein.

and Group 2 was the patients with no change or a decrease in the LDL particle size.

This study was approved beforehand by the institutional ethics committee and written informed consent was given by all subjects.

Percutaneous Coronary Intervention (PCI)

All patients were treated with aspirin (200 mg), clopidogrel (75 mg) or ticlopidine (500 mg), and intravenous heparin 100 IU/kg prior to PCI, which was considered to be successful if quantitative CAG (QCA) estimated residual stenosis as <30% and Thrombolysis In Myocardial Infarction 3 flow was observed after stent implantation.

QCA

QCA was performed using an off-line system (CMS, Medis Medical Imaging System, Nuenen, The Netherlands) by a single individual who was unaware of the patient's treatment assignment. The minimal luminal diameter (MLD) of the treated coronary segments, the reference diameter, the percent diameter stenosis and the lesion length on the baseline angiogram were determined in the view that demonstrated the lesion to be the most severe and not foreshortened. Baseline and follow-up angiograms were evaluated in the same view. We defined ISR as a diameter stenosis ≥50% at the time of follow-up CAG at 6–9 months.

Lipoprotein and Metabolic Parameter Analysis

Fasting blood samples were obtained by venipuncture on both the day of the PCI and the day of follow-up CAG. Total cholesterol (TC), high-density lipoprotein (HDL)-cholesterol, and LDL-cholesterol were measured by direct enzymatic methods (Daiichi, Tokyo, Japan). Triglycerides (TG) were measured using glycerophosphate oxidase with glycerol blanking method (Asan, Seoul, Korea). The fasting serum insulin level was measured with an immunoradiometric assay and a gamma counter (Hewlett-Packard, Palo Alto, CA, USA).

LDL subclass analysis was performed electrophoretically using high-resolution 3% polyacrylamide gel tubes and the Lipoprint LDL System (Quantimetrix), according to the manufacturer's instructions.[15] This method does not measure the LDL particle size directly, but estimates it by comparing particle electrophoretic mobility with their known sizes. We used very-LDL as the starting reference point [retention factor (R_f)=0.0], whereas HDL migrates to the front (R_f=1.0). Because the R_f value obtained by this method correlates well with the peak LDL size obtained by ultracentrifugation, LDL peak particle sizes (PPS) could be derived from a previous report.[16] The mean LDL particle size is expressed as the weighted average of the PPS of all LDL subfractions:

$$\text{Mean particle size (nm)} = \sum(\text{LDL}i/\sum\text{LDL}i)\times\text{size}i$$

where LDL*i* is the area of the LDL bands relative to LDL-cholesterol and Size*i* is the PPS of the LDL band (in nm). Mean LDL particle size was calculated by Quantimetrix software (Lipoware-Research version). The fraction of sd-LDL (subtypes 3–7 of LDL) was measured as follows:

$$\text{sd-LDL fraction (\%)} = \frac{\text{LDL3+LDL4+LDL5+LDL6+LDL7}}{\text{LDL1+LDL2+LDL3+LDL4+LDL5+LDL6+LDL7}}\times 100\%.$$

Statistical Analysis

We categorized all cases into 2 groups according to whether there was a change in the LDL particle size. Results are expressed as mean±SD. Comparisons of discrete variables were made using the chi-square method and Student's t-test was used to compare continuous variables. If the distribution was skewed, a non-parametric test was used. Independent predictors of restenosis after stent implantation were determined using multiple logistic regression analysis, in which variables were chosen such that $p<0.1$, based on simple linear regression analysis, was considered to be a significantly association with atherosclerosis or restenosis after stent implantation. All statistical analyses were performed using SPSS 11.5 (SPSS Inc, Chicago, IL, USA). A p-value <0.05 was considered to be statistically significant.

Results

Clinical Characteristics

Baseline characteristics were similar between the 2 groups of patients (Table 1). TC, LDL-cholesterol and TG were significantly higher in group 1 at baseline (183.4±36.6 vs 165.3±29.0 mg/dl, $p<0.001$; 110.1±32.5 vs 95.5±24.7 mg/dl, $p<0.001$; 146.6±70.2 vs 118.0±61.5 mg/dl, $p<0.001$, respectively). HDL-cholesterol and the fraction of sd-LDL at baseline were lower (42.3±10.3 vs 44.9±9.6 mg/dl, p=0.040; 22.9±20.2 vs 6.1±8.0%, $p<0.001$, respectively) and LDL

Table 2 Lipid Profiles at Baseline and Follow-up After Stent Implantation

	Increase in LDL particle size (n=151)	*No change or decrease in LDL particle size (n=121)*	*p value*
TC (mg/dl)			
Initial	*183.4±36.6*	*165.3±29.0*	*<0.001*
Follow-up	*155.1±34.4*	*162.4±33.4*	*0.081*
HDL-C (mg/dl)			
Initial	*42.3±10.3*	*44.9±9.6*	*0.040*
Follow-up	*42.8±9.8*	*44.5±10.9*	*0.170*
LDL-C (mg/dl)			
Initial	*110.0±32.5*	*95.5±24.7*	*<0.001*
Follow-up	*87.9±25.5*	*91.5±27.3*	*0.263*
TG (mg/dl)			
Initial	*146.6±70.2*	*118.0±61.5*	*<0.001*
Follow-up	*116.6±55.9*	*128.0±68.1*	*0.130*
*LDL size (nm)**			
Initial	*26.1±1.2*	*27.0±0.4*	*<0.001*
Follow-up	*26.9±0.4*	*26.7±0.6*	*0.007*
sd-LDL-C (%)			
Initial	*22.9±20.3*	*6.1±8.0*	*<0.001*
Follow-up	*7.9±9.4*	*11.8±13.5*	*0.006*
sd-LDL-C (mg/dl)			
Initial	*26.8±27.3*	*6.2±8.7*	*<0.001*
Follow-up	*6.9±9.0*	*11.8±14.6*	*0.002*

Values are n (%) or mean ± SD.
TC, total cholesterol; HDL, high-density lipoprotein; C, cholesterol; TG, triglycerides; sd-LDL, small dense LDL. Other abbreviation see in Table 1.
LDL size: mean particle size of LDL.

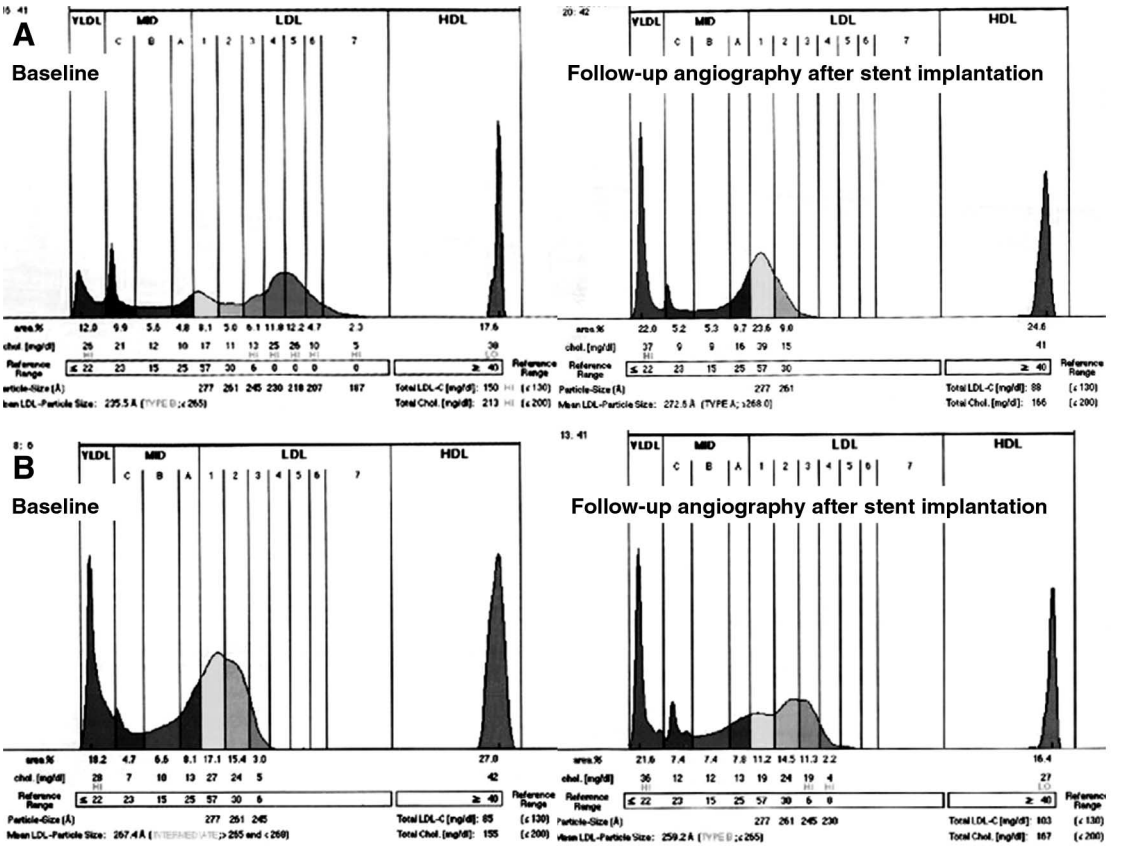

Fig 1. Changes in the low-density lipoprotein (LDL) subfraction pattern between baseline and follow-up angiography. (A) Case of no in-stent restenosis and increased LDL particle size from 23.6 nm at baseline to 27.3 nm at 6 months later. (B) Case of in-stent restenosis and decreased LDL particle size from 26.7 nm at baseline to 25.9 nm at 6 months.

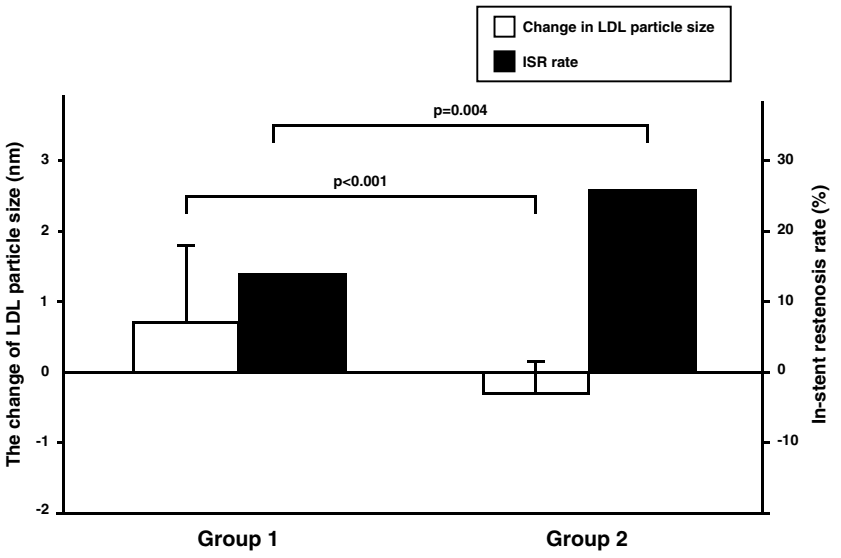

Fig 2. Change in low-density lipoprotein (LDL) particle size and in-stent restenosis (ISR) rate in group 1 (patients with increased LDL particle size between baseline and follow-up angiography) and group 2 (patients with no increase or decrease of LDL particle size in same period).

Table 3 Angiographic Findings at Baseline and Follow-up After Stent Implantation

	Increase in LDL particle size (n=226)	*No change or decrease in LDL particle size (n=186)*	*p value*
Target vessel			*0.495*
LAD	*100 (44.2%)*	*88 (47.3%)*	
LCX	*56 (24.8%)*	*37 (19.9%)*	
RCA	*70 (31.0%)*	*61 (32.8%)*	
B2 or C lesion	*208 (92.0%)*	*162 (87.1%)*	*0.138*
Lesion length (mm)	*19.9±7.5*	*19.4±6.1*	*0.389*
DES	*64 (28.3%)*	*70 (37.6%)*	*0.057*
Stent diameter (mm)	*3.28±0.38*	*3.25±0.40*	*0.375*
RD (mm)	*3.30±0.39*	*3.25±0.39*	*0.164*
Pre-PCI MLD (mm)	*0.81±0.35*	*0.79±0.35*	*0.554*
Post-PCI MLD (mm)	*3.30±0.39*	*3.24±0.40*	*0.118*
Follow-up MLD	*2.59±0.89*	*2.38±1.00*	*0.024*

Values are n (%) or mean±SD.
LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DES, drug-eluting stent; RD, reference diameter; PCI, percutaneous coronary intervention; MLD, minimal luminal diameter. Other abbreviation see in Table 1.

size was smaller in group 1 (26.1±1.2 vs 27.0±0.4 nm, p< 0.001). LDL size was larger and the fraction of sd-LDL was smaller in group 1 on follow-up CAG (26.9±0.4 vs 26.7±0.6 nm, p=0.007; 7.9±9.4 vs 11.8±13.5%, p=0.006, respectively). The decrement of TC, LDL-cholesterol and TG was larger (28.22±35.07 vs 2.90±37.39 mg/dl, p<0.001; 21.90±31.99 vs 3.97±33.40 mg/dl, p<0.001; 30.00±58.44 vs –10.04±63.52 mg/dl, p<0.001, respectively) in group 1 (Table 2). Frequency of statin use was similar between groups, but fibrates were used more in group 1 (33 (21.8%) vs 7 (3.8%), p<0.001, Table 1). The change in mean LDL particle size between baseline and follow-up CAG was 0.75±0.99 nm in group 1 and –0.28±0.41 nm in group 2 (p<0.001) (Figs 1,2).

Angiographic Findings

ISR developed in 80 lesions (19.4%) at the time of follow-up CAG. The incidence of ISR in group 1 was 32 lesions (14.2%) and 48 lesions (25.8%) in group 2. The incidence of ISR in bare-metal stents (BMS) was 57 lesions (20.6%) and 23 lesions (17.1%) for drug-eluting stents (DES). Follow-up MLD (2.59±0.89 vs 2.38±1.00 mm, p= 0.024) was significant larger in group 1. Stent diameter (3.28±0.38 vs 3.25±0.40 mm, p=0.375), reference diameter (3.30±0.39 vs 3.25±0.39 mm, p=0.164), pre-PCI MLD (0.81±0.35 vs 0.79±0.35 mm, p=0.554) and post-PCI MLD (3.30±0.39 vs 3.24±0.40 mm, p=0.118) were similar between the 2 groups (Table 3). Also, there was no difference in the distribution of target vessels and the frequency of DES use (Table 3).

Multivariate Analysis for Independent Predictors of ISR After Coronary Stent Implantation

Logistic multivariate analysis showed that stent length (≥24 mm) (odds ratio (OR)=1.913, p=0.027), post-PCI MLD (>3.0 mm) (OR=0.528, p=0.028), ACS on initial admission (OR=2.294, p=0.005), decrease in HDL-cholesterol (OR= 1.028, p=0.050) and increase in LDL particle size (OR= 0.523, p=0.031) were independent predictors for reducing the occurrence of ISR in all lesions (Fig 3).

However, a decrease in the LDL-cholesterol level between baseline and follow-up (OR=0.992, p=0.056) and DES use (OR=0.559, p=0.067) had a tendency to reduce the occurrence of ISR (Fig 3). Also, when the predictors of ISR was evaluated separately according to the use of different stents, and post-PCI MLD (≥3.0 mm) and increased

LDL particle size (modest significance in BMS, p=0.053) were independent predictors for both DES and BMS, but ACS on initial admission was a significant predictor for BMS only (Table 4).

Discussion

In the present study, a change in the size of the LDL particles after stent implantation was associated with ISR. Therefore, modification of LDL particle size may help to reduce ISR in patients already undergoing previously proven treatment.

Several large prospective studies have suggested that the size and amount of LDL are risk factors, adding to other lipid variables for CAD[8,14–17] We have also shown that sd-LDL was independently associated with the incidence and extent of CAD in a Korean population[18,19]

DES have been recently introduced and have significantly reduced the rate of ISR after implantation. However, ISR remains a serious medical problem because of neointimal hyperplasia, which is related to endothelial dysfunction and vascular inflammation[2,3] Because sd-LDL is also related to vascular inflammation, endothelial dysfunction and the progression of CAD, we evaluated the rate of ISR according to changes in LDL particle size between initial and 6–9-month follow-up CAG. According to our results, angiographic ISR rates at follow-up were higher in group 2 (patients with no increase or a decrease in LDL size), even after controlling for other angiographic parameters and CAD clinical risk factors. Consistent with previous studies, we found that angiographic parameters, such as stent length and post-procedural MLD, were the most significant predictors of ISR.

A previous study reported an increase in LDL particle size with colespitol/lovastatin therapy and this was strongly associated with angiographic regression[20] In the Diabetes Atherosclerosis Intervention Study (DAIS), a decrease in LDL particle size after treatment with fenofibrate was associated with CAD regression; however, TG and HDL-cholesterol were strong confounders and obscured any independent relationship between a change in sd-LDL and CAD regression[14] In contrast, we demonstrated in the present study that a decrease in LDL particle size was associated with ISR after controlling for LDL as well as TG and HDL-cholesterol, but we cannot explain clearly the reason for the decreasing LDL particle size because of the retrospective nature of the study. We considered the use of fibrates to be one factor related to the change in LDL particle size and several other factors, such as exercise, diet, and response to statin, could also have an influence. Our result suggests that the quality, as well as the quantity, of LDL-cholesterol might be important in CAD. Although statin therapy did not significantly reduce the rate of ISR, the treatment regimen may not have been sufficient to affect the quality of LDL and other components of cholesterol. Therefore, other TG-lowering or HDL-cholesterol-raising agents might also be helpful in conjunction with LDL-cholesterol lowering therapy for reducing the rate of ISR.

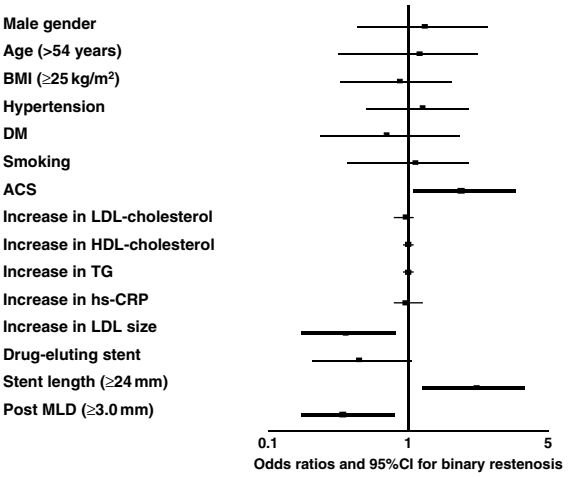

Fig 3. Multiple logistic regression analysis for independent determinants of restenosis after stent implantation. The odds ratios are shown with the 95% confidence intervals (CI). BMI, body mass index; DM, diabetes mellitus; ACS, acute coronary syndrome; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; hs-CRP, high-sensitivity C-reactive protein; MLD, minimal luminal diameter. Increase in LDL size was defined as an increase in LDL particle size between baseline and follow-up angiography and the delta value was defined as the difference between the values obtained at baseline and follow-up angiography.

Study Limitations

First, this study included a relatively small number of patients. Second, the study was not randomized according to statins or other lipid-lowering drugs, so it is difficult to evaluate the effect of dose or type. Despite that, this study showed for the first time that an increase in the LDL particle size can reduce the rate of ISR. Third, we did not measure the LDL size directly but obtained the data indirectly by a commercial tube gel electrophoresis method, which cannot

Table 4 Multiple Logistic Regression Analysis for Independent Determinants of Restenosis According to the Types of Stent

	BMS (n=278)			*DES (n=134)*		
	OR	*95%CI*	*p value*	*OR*	*95%CI*	*p value*
ACS	*2.393*	*1.149–4.981*	*0.020*	*2.404*	*0.799–7.237*	*0.119*
Delta-LDL	*0.990*	*0.980–1.000*	*0.058*	*1.007*	*0.991–1.023*	*0.400*
Delta-HDL	*1.036*	*0.991–1.083*	*0.120*	*1.018*	*0.977–1.061*	*0.386*
Delta-TG	*1.002*	*0.996–1.008*	*0.494*	*1.002*	*0.992–1.013*	*0.668*
Increase in LDL size	*0.510*	*0.258–1.009*	*0.053*	*0.189*	*0.047–0.749*	*0.018*
Stent length >24 mm	*3.906*	*1.889–8.075*	*<0.001*	*0.587*	*0.184–1.871*	*0.368*
Post-PCI MLD >3.0 mm	*0.385*	*0.197–0.754*	*0.005*	*0.175*	*0.043–0.711*	*0.015*
Use of fibrates	*0.676*	*0.231–1.979*	*0.475*	*0.454*	*0.038–5.368*	*0.531*

After controlling for age (>54 years) gender, BMI (>25 kg/m²), hypertension, DM, and smoking status.
BMS, bare metal stent; OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1–3.
Increase in LDL size was defined as an increase in LDL particle size between initial and follow-up angiography and the delta value was defined as the difference in the values at initial and follow-up angiography.

be compared directly with other methods such as gradient gel electrophoresis or nuclear magnetic resonance?[21,22]

In conclusion, our results suggest that a change in the LDL particle size between baseline and follow-up CAG was associated with ISR, even after controlling for lipid levels, lipid-lowering drugs and angiographic parameters. Therefore, modification of LDL particle size may additionally reduce ISR in combination with previously proven treatments. A large randomized trial is needed to validate our study.

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