



Lower Level of Low Density Lipoprotein Cholesterol is Associated with a Higher Increase in the Fractional Flow Reserve in Patients with Fixed-dose Rosuvastatin

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Aim: Fractional flow reserve (FFR) reflects on the diffuse atherosclerosis per coronary artery. It is unknown whether the statin therapy affects long term FFR after stenting. The aim of this study was to evaluate the long term FFR after stent implantation in patients who are intaking fixed-dose rosuvastatin.

Methods: A total of 22 patients with stable angina pectoris were enrolled. The values of FFR were measured before, immediately after, and 18 months after (follow-up day) the implantation of everolimus eluting stent (EES; Promus ElementTM or Promus Element PlusTM). A fixed dose of rosuvastatin at 5 mg/day was administrated to all patients.

Results: Of the 22 patients, 2 were excluded because of adverse effect of rosuvastatin and in-stent total occlusion after EES implantation. Overall, the values of FFR immediately after and 18 months after EES implantation did not show significant change (from 0.90 ± 0.05 to 0.88 ± 0.06 , $p=0.16$). However, there was a significant negative correlation between low density lipoprotein (LDL) cholesterol level at follow-up day and changes in the value of FFR ($p=0.01$, $r=-0.74$). There was an increase in the FFR value after stenting in 8 out of 9 patients with LDL cholesterol level below 75 mg/dl (area under the curve 0.92, $p=0.0005$).

Conclusions: LDL cholesterol level was associated with the change in the FFR value in patients following stent implantation. Lower LDL cholesterol tended to improve in the long-term FFR, underscoring the importance of lowering LDL cholesterol to prevent the progression of coronary atherosclerosis.

Key words: Everolimus eluting stent, Statin, Functional ischemia, Coronary pressure

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Introduction

Diffuse coronary atherosclerosis without focal stenosis on coronary angiography can be associated with coronary flow hemodynamics by increasing the resistance of conductive vessels and contributing to myocardial ischemia¹. Pressure-based fractional flow reserve

(FFR) is an invasive test that can be used to assess the functional significance of coronary stenosis to guide decisions on percutaneous coronary intervention (PCI)^{2,3}. Previous studies have demonstrated that the FFR value has a moderate correlation with the minimum lumen area measured by intravascular ultrasound in patients with stable and unstable angina pectoris⁴⁻⁸. In addition, not only the segmental lumen narrowing but also the extent of diffuseness atherosclerosis of conductive artery showed a strong correlation with the FFR value in the left anterior descending coronary artery⁹. A strategy of FFR guided-PCI, compared with medical therapy alone, resulted in a significant decrease in major adverse cardiac events for 2 years after the

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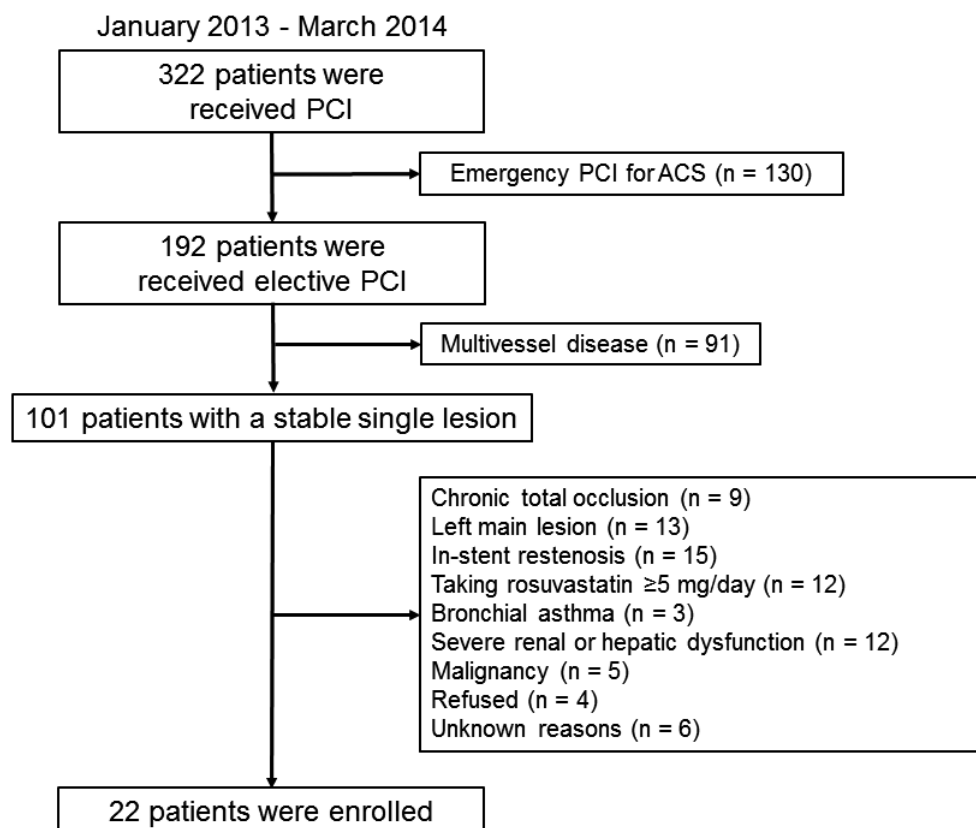


Fig. 1. Flow chart of the study design

index procedure^{10, 11}). Therefore, FFR guided-PCI is often chosen in patients with moderate and diffuse stenosis in the coronary artery in clinical settings.

Low-density lipoprotein (LDL) cholesterol lowering therapy using statin in particular has been well known to result in a significantly lower risk of cardiovascular events in patients with or without cardiovascular disease(s)¹²⁻¹⁴. Moreover, statin therapy slows down the progression of coronary plaque after stent implantation and stabilizes the thin-cap fibroatheroma¹⁵⁻¹⁷. However, it is unknown whether the statin therapy affects the long term FFR after stenting. The aim of this study was to evaluate the long term FFR after stent implantation in patients taking fixed-dose rosuvastatin.

Methods

Study Protocols

This prospective, single-center study was performed to evaluate the change of FFR values between immediately and 18-month after the implantations of everolimus eluting stent (EES; Promus ElementTM or Promus Element PlusTM) in stable coronary artery disease patients with fixed-dose of rosuvastatin-naïve (5

mg/day). From January 2013 to March 2014, 22 patients who had stable angina in the single vessel and consented to the study protocol were enrolled (**Fig. 1**). All participants were evaluated at baseline and at 18 months after EES implantations.

The inclusion criteria for this study were as follows: (1) *de novo* stable single-vessel lesion with $\geq 75\%$ diameter stenosis by visual estimation and (2) objective evidence of myocardial ischemia in a culprit lesion. The exclusion criteria were as follows: (1) lesion with acute coronary syndrome, (2) lesion with chronic total occlusion, (3) left main lesion, (4) in-stent restenosis lesion, (5) patients taking rosuvastatin ≥ 5 mg/day at baseline, (6) patients with bronchial asthma, (7) severe renal [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m²] or hepatic dysfunction (Child-Pugh score ≥ 10), (8) malignancy, and (9) drug or alcohol abuse. The study protocol was approved by the institutional review board of Kitasato University and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients received oral and written information about the study and signed an informed consent form before participating in the study.

Data Collection

The patients were followed monthly or once in 2 months during the study registration period. At the time of entry (baseline), complete medical history, physical examination, and anthropometric and laboratory evaluations were obtained. All coronary angioplasties were performed according to standard techniques using vascular imaging modality (optical coherence tomography or intravascular ultrasonography). Before intervention, all patients with stable angina pectoris started receiving dual antiplatelet therapy (DAPT; aspirin 100 mg/day and clopidogrel 75 mg/day) at least from 5 days before intervention. After the intervention, all patients continued to receive DAPT during the entire study period. Enrolled patients were prescribed rosuvastation 5 mg/day at baseline. Fifteen patients (68%) had been taken statin at baseline, others had not. The levels of lipid parameter [LDL cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride], hemoglobin A1c, icosapentaenoic acid (EPA), arachidonic acid (AA), and the eGFR were measured at Kitasato University Hospital.

Coronary Pressure and Flow Measurements

FFR, coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) were measured in the present study. A coronary guidewire (Pressure wire Certus, St Jude Medical, MN, USA) was introduced through a 6Fr guiding catheter, equalized, and was advanced above 10 mm distal from distal edge of the stent. The sensors were placed at the same point with angiography among the phases as possible: pre-stenting, just after stenting, and at follow-up. After achieving maximum hyperemia with intravenous administration of adenosine (150 µg/kg/min), the distal coronary pressure was recorded from the pressure wire and coronary flow (ml/min) was recorded from the external flow probe, which measures volume flow directly and independently of vessel diameter. The hyperemic mean transit time was recorded after rapid injection of 5 ml of room-temperature saline through the coronary catheter. The hyperemic mean transit time was measured 3 times and then averaged^{18, 19}. FFR was defined as the ratio between the mean distal coronary pressure and the mean aortic pressure. The FFR was measured 60–120 s after intravenous the administration of adenosine (150 µg/kg/min) to induce maximum hyperemia²⁰. The stenosis was considered to be functionally significant when the FFR value was ≤ 0.80 ¹¹. CFR was calculated as the ratio of hyperemic to resting coronary flow recorded from the flow probe. IMR was calculated as the distal coronary pressure at maximal hyperemia divided by the inverse of the hyperemic mean transit time.

Table 1. Patient, lesion, and procedural characteristics at baseline

	N=22
Clinical variables	
Age, years	73.8 ± 5.0
Male, n	17 (77)
Body Mass Index, kg/m ²	24.9 ± 3.6
Hypertension, n	16 (73)
Diabetes mellitus, n	8 (36)
History of ASVD, n	10 (45)
Current Smoking, n	8 (28)
eGFR, mL/min/1.73 m ²	60.8 ± 10.5
Angiographic variables	
LAD/LCx/RCA, n	14/3/5
Type B2 or C lesions, n (%)	17 (77)
Mean reference diameter, mm	2.53 ± 0.48
Lesion length, mm	21.0 ± 7.4
Minimal luminal diameter, mm	1.14 ± 0.39
Diameter stenosis, %	78.5 ± 10.4
Hemodynamic variables	
FFR value	0.60 ± 0.12
CFR value	2.49 ± 1.49
IMR value, U	29.6 ± 22.5
The procedures of EES implantation	
Stent diameter, mm	3.09 ± 0.43
Total stent length, mm	28 (16–44)
Maximum balloon diameter, mm	3.12 ± 0.25
Maximum inflation pressure, atm	19.2 ± 3.5
Acute gain, mm	1.50 ± 0.60

Continuous variables are expressed as mean ± SD and categorical variables as number (percentage). ASVD, atherosclerotic vascular disease; eGFR, estimated glomerular filtration rate; LAD, left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery; FFR, fractional flow reserve; CFR, coronary flow reserve; IMR, index of microcirculatory resistance; EES, everolimus eluting stent

Assessment of Quantitative Coronary Angiography

Quantitative coronary angiography parameters were measured using a computerized edge-detection quantitative coronary angiographic analysis system (CASS system, Pie Medical Instruments, Maastricht, The Netherlands) by a single individual who was blinded to patient information. Values were obtained at 3 points: before PCI (pre-intervention), immediately after PCI (post-intervention), and at 18 months after intervention (follow-up). In-stent minimal lumen diameter, % diameter stenosis, and mean reference diameter were measured. In addition, we calculated acute gain (post- minus pre-intervention minimal lumen diameter) and late lumen loss (post-intervention minus follow-up minimal lumen diameter).

Table 2. Comparison of clinical, hemodynamic, and angiographical variables at baseline (just after stenting) and 18 Months after stenting.

<i>N</i> = 20	Baseline	18 months	<i>P</i>
LDL cholesterol, mg/dL	100 ± 30	79 ± 16	0.008
HDL cholesterol, mg/dL	47 ± 9	54 ± 13	0.02
Triglyceride, mg/dL	175 ± 76	181 ± 85	0.43
Hemoglobin A1c, %	6.3 ± 0.7	6.2 ± 0.5	0.25
Icosapentaenoic acid, µg/mL	74.5 ± 29.1	95.7 ± 40.7	0.01
Arachidonic acid, µg/mL	167 ± 40	174 ± 31	0.21
FFR value	0.90 ± 0.05	0.88 ± 0.06	0.16
CFR value	2.29 ± 1.36	2.96 ± 1.48	0.15
IMR value	22.5 ± 11.7	19.4 ± 7.2	0.21
Minimum lumen diameter, mm	2.64 ± 0.36	2.18 ± 0.47	<0.001

Continuous variables are expressed as mean ± SD. L (H) DL, low (high) density lipoprotein; FFR, fractional flow reserve; CFR, coronary flow reserve; IMR, index of microcirculatory resistance

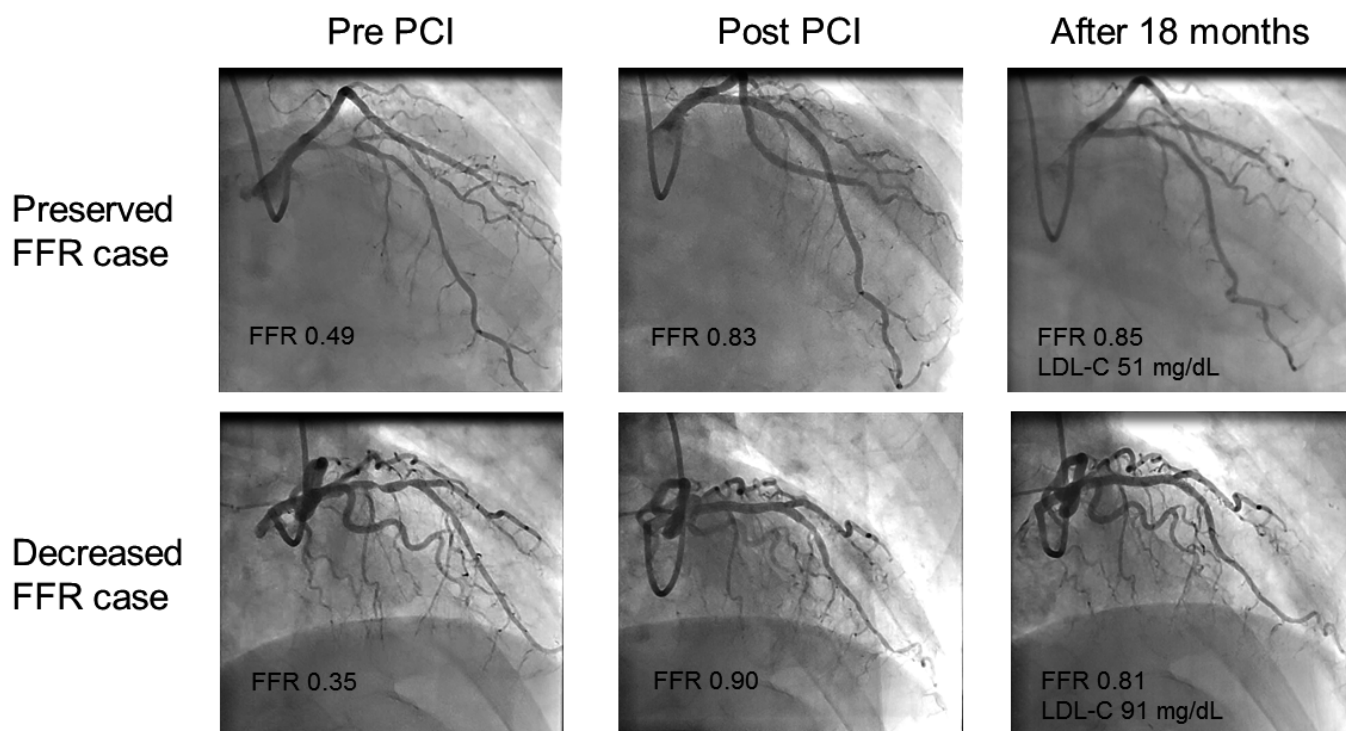


Fig. 2. Representative cases in both groups. Angiographical findings in each case did not significantly change between post- PCI and 18 months after PCI.

Statistical Analysis

Categorical variables were expressed as numbers and frequencies and were compared using the chi-square test. Continuous variables are expressed as mean ± standard deviation (SD) and were compared using the paired *t*-test. Linear regression analysis was performed to determine the association between the changes in FFR value and in other clinical parameters. Receiver

operating characteristics (ROC) curve analysis was performed to determine the LDL cholesterol cut-off value in order to discriminate preserving FFR values in patients with EES implantation. All analyses were performed using JMP 9.0 software for Windows (SAS Institute, Cary, North Carolina). A value of $p < 0.05$ was considered statistically significant.

Table 3. Patient characteristics between Preserved and Decreased FFR groups.

	Preserved FFR (<i>n</i> = 10)	Decreased FFR (<i>n</i> = 10)	<i>p</i>
Age, years	73 ± 6	74 ± 3	0.28
Body mass index	22.9 ± 1.7	26.7 ± 4.0	0.07
eGFR, ml/min/1.73 m ²	65.4 ± 12.7	61.8 ± 6.8	0.83
LDL cholesterol, mg/dL	68.3 ± 17.6	87.9 ± 7.0	0.02
HDL cholesterol, mg/dL	52.3 ± 14.6	87.1 ± 8.9	0.43
Triglyceride, mg/dL	169 ± 73	157 ± 68	0.88
Hemoglobin A1c, %	6.5 ± 0.4	6.1 ± 0.6	0.22
Icosapentaenoic acid, µg/mL	110 ± 21	83 ± 51	0.28
Arachidonic acid, µg/mL	176 ± 37	174 ± 28	0.72
FFR value post procedure	0.87 ± 0.05	0.91 ± 0.04	0.20
FFR value at follow up	0.90 ± 0.06	0.86 ± 0.06	0.43
CFR value post procedure	2.00 ± 0.98	2.63 ± 1.55	0.47
CFR value at follow up	2.65 ± 1.51	2.95 ± 1.41	0.47
IMR value post procedure, U	22.0 ± 9.8	24.2 ± 16.2	0.89
IMR value at follow up, U	20.6 ± 7.7	20.8 ± 8.0	0.94
Mean stent diameter, mm	2.91 ± 0.40	2.75 ± 0.25	0.41
Total Stent length, mm	28.3 ± 11.6	28.0 ± 8.2	0.94

Continuous variables are expressed as mean ± SD. L (H) DL, low (high) density lipoprotein; FFR, fractional flow reserve; CFR, coronary flow reserve; IMR, index of microcirculatory resistance

Results

In this study, among the enrolled 22 patients, 2 patients were excluded after the procedure because of side effects of rosuvastatin and total occlusions in the stent at the follow up. Finally, 20 patients were evaluated at baseline and at 18 months after EES implantations. According to lipid-lowering agents, no medication except rosuvastatin was administered to the enrolled patients during the study registration period. Clinical characteristics at baseline are summarized in **Table 1**. Approximately half of the patients (10/22 patients) had a history of atherosclerotic vascular disease at baseline. Out of 22 patients, 15 (68%) were receiving statin therapy other than ≥ 5 mg rosuvastatin at baseline and were switched to the 5 mg/day of rosuvastatin as per the study protocol. The FFR values in all enrolled lesions were ≤ 0.80; thus, there was no lesion excluded after registration due to no establishment of myocardial ischemia. Additionally, there were no complications related to the procedure.

After switching to or addition of 5 mg/day of rosuvastatin, there was a decrease in the LDL cholesterol levels (from 100 ± 30 mg/dL to 79 ± 16 mg/dL, *p* = 0.008) and a significant increase in the HDL cholesterol and the EPA levels (from 47 ± 9 mg/dL to 54 ± 13 mg/dL, *p* = 0.02, and from 74.5 ± 29.1 µg/dL to 95.7 ± 40.7 µg/dL, *p* = 0.01, respectively) compared to the baseline levels. The minimum lumen diameter

at follow up was lower than that of post procedure (late loss; 0.46 ± 0.42 mm) however, the FFR, CFR, and IMR values did not show significant changes from the immediate post-procedure to the follow-up (**Table 2**) stage. The FFR values did not change between post- and pre-stent segment in all enrolled patients at 18 months after stenting.

The FFR values 18 months following procedure compared to those immediate post-procedure in half of evaluated patients remained same or increased (Preserved FFR group, *n* = 10); the same decreased in others (Decreased FFR group, *n* = 10). The representative cases in each group are shown in **Fig. 2**. The clinical characteristics of the two groups are shown in **Table 3**. The LDL cholesterol level at follow up in Preserved FFR group was significantly lower than in Decreased FFR group. Other clinical and hemodynamic parameters of the two groups did not differ significantly. Additionally, there was a significant negative correlation between changes in the FFR values and LDL cholesterol levels at follow-up (*p* = 0.01, *r* = -0.74; **Fig. 3**); in contrast, there was no significant correlation between changes in the FFR values and other parameters (see the **Supplementary Appendix**). The LDL cholesterol levels cut-off for discriminating preserved and decreased long-term FFR value after stenting was 75 mg/dL (**Fig. 4**). The sensitivity was 73.4%, and the specificity was 100%. There was no significant correlation between the change of the CFR or IMR value and LDL chole-

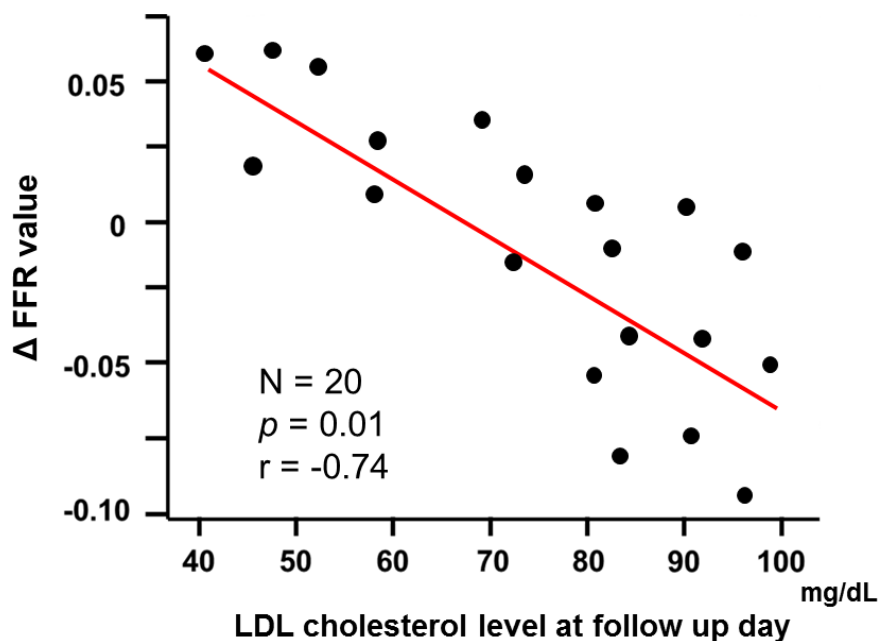


Fig. 3. showed a significant negative correlation between changes in the FFR value and the LDL cholesterol levels on follow-up day. FFR Value of delta (Δ) indicates the FFR value at follow-up day minus FFR value at baseline (post stenting).

terol level in follow up period in the present study (CFR: $p=0.58$, $r=-0.05$; and IMR: $p=0.44$, $r=-0.23$).

Discussion

This is a pioneering prospective study for evaluating the long-term coronary pressure and flow in patients who have undergone drug eluting stent implantation plus a fixed dose of statin therapy. The major findings of this study are as follows: (1) the overall values of coronary pressure and flow did not significantly change between immediate post-procedure and 18 months after EES implantation in patients taking 5 mg/dL of rosuvastatin; (2) the mean LDL cholesterol level of patients with preserved FFR value after the procedure was lower than that of patients with decreased FFR value; and (3) there was a significant negative correlation between changes in the FFR value and in the LDL cholesterol level on follow-up day.

It is well known that platinum chromium EES (Promus Element™, Promus Element Plus™) and other second generation DES provide the good clinical outcomes^{21, 22}. The 12-month rate of target lesion failure occurred in 2.9%–3.4% patients assigned to platinum chromium EES. Out of 22 patients, 1 had a total occlusion at proximal edge of the stent at follow-up in the present study. Though there was morphological decrease of the vessel diameter at stenting area 18

months after EES implantations in some cases, the FFR value did not increase across the segment of stenting in all evaluated patients in the present study. We believe that diffuse atherosclerotic burden in the non-culprit as well as the culprit part of the vessel may have affected the FFR value.

We speculate there are at least two possible mechanisms behind the change of FFR value in our study: plaque burden and endothelial function. First, we speculate that a possible reduction of plaque burden in the lower LDL cholesterol group may have influenced the change of FFR value. FFR value has been used to assess the physiologic severity of a certain stenosis. However, a recent report suggested that the plaque burden of a stented segment affects the FFR value rather than the luminal area²³. In addition, another study has shown that not only luminal narrowing but also plaque burden may affect the FFR derived from CT scanning²⁴. Unfortunately, we have no evidence that there was a difference in atherosclerotic burden between the lower LDL cholesterol group and the higher LDL cholesterol group in the present study. Second, endothelial function may also be responsible for the FFR changes. Reduction of LDL cholesterol levels has been shown to be associated with improved endothelial function, whether with statin therapy or non-statin therapy²⁵. Recent studies have shown that endothelial function may also affect the FFR value, although the

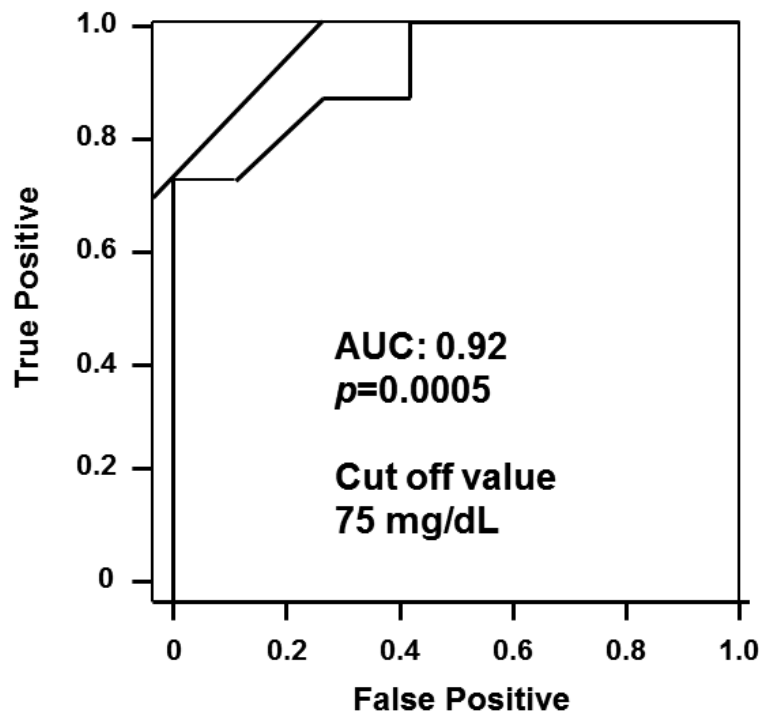


Fig. 4. ROC curve analysis to determine the LDL cholesterol cut-off value of preserving FFR values in enrolled patients. The LDL cholesterol levels cut-off for discriminating preserved and decreased long-term FFR value after stenting was 75 mg/dL with 73.4% sensitivity and 100% specificity.

mechanism is not completely understood²⁶). We did not measure endothelial function in this study; however, we speculate that endothelial function may have influenced the FFR values. Further studies are necessary to clarify the factors that change the FFR value.

It has been reported that the higher value of FFR immediately after and long after the stenting is associated with a decrease in the incidence of major adverse cardiac event²⁷⁻²⁹). Statin usage led to significant regression of coronary atherosclerosis and resulted in a reduction of cardiovascular diseases^{30, 31}). Particularly, the LDL cholesterol lowering effect of statin is widely known to reduce coronary atherosclerotic events. In addition, it is now majorly considered that lower LDL cholesterol levels lead to better cardiac clinical outcomes³¹⁻³⁵). Several reports have shown that lower LDL cholesterol and non-HDL cholesterol levels led to the stability and reduction of coronary plaque using intravascular imaging modalities such as intravascular ultrasound and optical coherence tomography³⁶⁻³⁸). Prospective trials demonstrated the FFR measurement, which reflects on the functional coronary ischemia and diffuse atherosclerosis per coronary artery, was superior in predicting the prospective cardiac adverse events than morphological assessments using angiog-

raphy or intravascular imaging modalities in patients with both *de novo* lesion and lesion after the stenting^{10, 27, 28, 39}). The result of the present study also demonstrated the LDL cholesterol levels <75 mg/dL led to the preserving of the functional coronary flow at follow-up. This study may indicate that lower LDL cholesterol levels prevent or reduce the diffuse atherosclerotic change in the coronary artery long after the stent implantation.

This study has several limitations. First, the present study was a single-center, prospective study with a small number of patients, which may have led to selection bias. Second, we could not evaluate the coronary pressure per each part of coronary artery—right coronary artery, left anterior descending coronary artery, and left circumflex coronary artery. Because each coronary artery has a different size of perfusion area, the evaluation of coronary pressure might be different. Third, we could not evaluate plaque burden with vascular imaging on follow-up day, and we could not obtain the finding that could suggest the mechanism for improving the FFR value, such as the increase of plaque burden with the decline of LDL cholesterol value. Finally, this study did not discuss the long term cardiac clinical outcomes of all patients because the

number of enrolled patients was too small to analyze. In the present study, 21 out of 22 patients did not require revascularization 18 months after the EES implantations. Finally, we only compared the effect of a fixed dose of statin in our study; however, comparison between standard statin therapy and intensive statin therapy would also be of clinical importance, and further studies are therefore necessary.

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Conflict of Interest

This study was partly supported by International Grants-in-Aid for Research from the Kitasato University School of Allied Health Sciences, Daiichi-Sankyo, MSD K.K., Bayer Pharma, Tanabe Mitsubishi, and Boehringer Ingelheim (M. Y-T.). Dr. Junya Ako received speaking honorarium from Astra zeneca. The other authors have nothing to disclose regarding the present study.

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Supplemental data. Regression Analysis for change of FFR value (Univariate)

	β -coefficient (95% CI)	<i>p</i> value
Age, per year	0.11 (-0.01-0.01)	0.76
Sex, male	0.28 (-0.02-0.04)	0.56
Body mass index, per kg/m ²	0.11 (-0.01-0.01)	0.75
LDL cholesterol, per mg/dL	-0.74 (-0.01-0.00)	0.01
HDL cholesterol, per mg/dL	0.20 (-0.00-0.00)	0.56
Triglyceride, per mg/dL	-0.22 (-0.00-0.00)	0.51
Hemoglobin A1c, per %	-0.03 (-0.06-0.06)	0.92
Icosapentaenoic acid, per μ g/mL	0.34 (-0.07-0.19)	0.31
eGFR, per ml/min/1.73 m ²	0.22 (-0.00-0.00)	0.52
Stent size, per mm	0.34 (-0.06-0.16)	0.31
Stent length, per mm	-0.01 (-0.00-0.00)	0.99
FFR value just after stenting	-0.07 (-0.79-0.67)	0.85
Minimum stent area, per mm ²	-0.04 (-0.03-0.02)	0.92

FFR, fractional flow reserve; L (H) DL, low (high) density lipoprotein; eGFR, estimated glomerular filtration rate;

