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Original article

Effect of evolocumab therapy on coronary fibrous cap thickness assessed by optical coherence tomography in patients with acute coronary syndrome

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ABSTRACT

Background: The addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, evolocumab, to statin therapy produced incremental regression of atherosclerotic plaques and a collaborative prevention of cardiovascular events in patients with coronary artery disease. The effect on fibrous-cup thickness, or extension of the atherosclerotic plaque with PCSK9-inhibitor, for several weeks after onset of acute coronary syndrome (ACS) has never been reported.

Methods: This study aimed to examine the effect of evolocumab on fibrous-cap thickness, as well as the extent of the atherosclerotic plaque, by serial optical coherence tomography (OCT) analysis in patients with ACS. All patients received rosuvastatin 5 mg/day from at least 24 h after onset of ACS. Patients received evolocumab (140 mg every 2 weeks) 1 week after the onset of ACS in the statin plus evolocumab group. Patients took only rosuvastatin in the statin monotherapy group. OCT was performed to assess intermediate, non-culprit lesions just 4 and 12 weeks after emergent percutaneous coronary intervention.

Results: OCT analysis revealed that the increase in fibrous-cap thickness and decrease in macrophage grade were greater with a narrower lipid arc and shorter lipid length, which were associated with lower low-density lipoprotein cholesterol (LDL-C) in the statin plus evolocumab group than in the statin alone treatments, even for a short term after ACS onset.

Conclusions: Addition of the PCSK9-inhibitor evolocumab to statin therapy might produce incremental growth in fibrous-cap thickness and regression of the lipid-rich plaque, which were associated with greater reduction of LDL-C even for a short term in the early phase of ACS.

Introduction

The clinical benefit of lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, statins, on ischemic cardiac events or death has been demonstrated by several large-scale, multicenter, randomized primary and secondary prevention trials [1,2].

Studies with grayscale intravascular ultrasound (IVUS) imaging demonstrated that using a statin resulted in significant suppression [3], or even regression, in atheroma volume in the atherosclerotic coronary arteries [4]. Although grayscale IVUS is suitable for assessing plaque volume, it does not have the spatial resolution to assess fibrous-cap thickness precisely. In contrast, optical coherence tomography (OCT) can evaluate small changes in the fibrous-cap thickness [5], which are reported to be increased by statin therapy after acute myocardial infarction [6]. Moreover, it was reported that the percentage decrease in low-density lipoprotein cholesterol (LDL-C) by statin treatment inversely correlated with the percentage increase in fibrous-cap thickness by serial OCT analysis in patients with stable angina [7]. Thus, a beneficial increase in fibrous-cap thickness after statin treatment may be a benchmark for future investigational agents that target plaque instability.

Evolocumab is a fully human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) from binding to LDL receptors on the liver surface. With PCSK9 inhibition, there are more LDL receptors on the surface of liver cells to remove LDL-C from the blood. Evolocumab reduces LDL-C levels by approximately 60% [8]. More recent experimental data indicated that PCSK9 might also accelerate atherosclerosis by

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promoting inflammation, endothelial dysfunction, and hypertension by mechanisms independent of the increasing degradation of LDL receptors [9,10].

The GLobal Assessment of plaque reGression with a PCSK9 antibOdy as measured by intraVascular ultrasound (GLAGOV) trial demonstrated that treatment with statins plus evolocumab achieved extremely low LDL-C and produced significant atheroma regression, and induced regression in a greater percentage of patients compared to statin therapy alone [11]. Moreover, the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) trial showed that inhibiting PCSK9 with evolocumab, on a background of statin therapy, lowered LDL-C levels and reduced the risk of cardiovascular events [12].

Therefore, the present study's aim was to examine the effect of the PCSK9 inhibitor evolocumab, on a background of statin therapy, on fibrous-cap thickness, as well as extension of coronary atherosclerosis by serial OCT analysis, in patients with acute coronary syndrome (ACS). To our knowledge, this is the first such study of these effects.

Methods

Study patients and design

This was a retrospective, non-randomized, observational, single-center study. Sixty-four patients with multi-vessel disease—who had untreated dyslipidemia (defined as serum LDL-C level >100 mg/dL) and who underwent emergent percutaneously coronary intervention (PCI) after ACS—were enrolled. After receiving informed consent, we performed staged PCI to the residual lesion 4 weeks after emergent PCI and conducted follow-up coronary angiography 12 weeks thereafter. The follow-up target lesions of the OCT analysis were selected as follows: de novo, intermediate, and non-culprit coronary lesions of ACS. Six patients were excluded (two patients refused, and four patients failed OCT analysis), and the remaining 58 patients were fully examined in this study (Fig. 1). All patients were treated with rosuvastatin 5 mg once daily for aggressive lipid-lowering therapy, which is a secondary prevention of ACS. Patients who could tolerate long-term self-injection, and were willing to pay expensive drug fees, were administered evolocumab in addition to rosuvastatin. The statin plus evolocumab group of patients received evolocumab 140 mg every 2 weeks, 1 week after onset of ACS, while the statin monotherapy group took only rosuvastatin.

ACS was defined as ST-segment elevation acute myocardial infarction, non–ST-segment elevation myocardial infarction, or unstable angina. The follow-up target lesion of the OCT analysis had a diameter stenosis percentage of 30%–70% by visual estimation on angiogram. If more than two de novo, intermediate, or non-culprit lesions were recognized, the most severely stenotic lesion was selected as the target lesion of the OCT analysis. The target lesion could be in both the PCI-treated and non–PCI-treated coronary artery where the target lesion was >10 mm apart. Exclusion criteria included left main trunk lesions, bifurcation lesions requiring two stents, cardiogenic shock, recommended

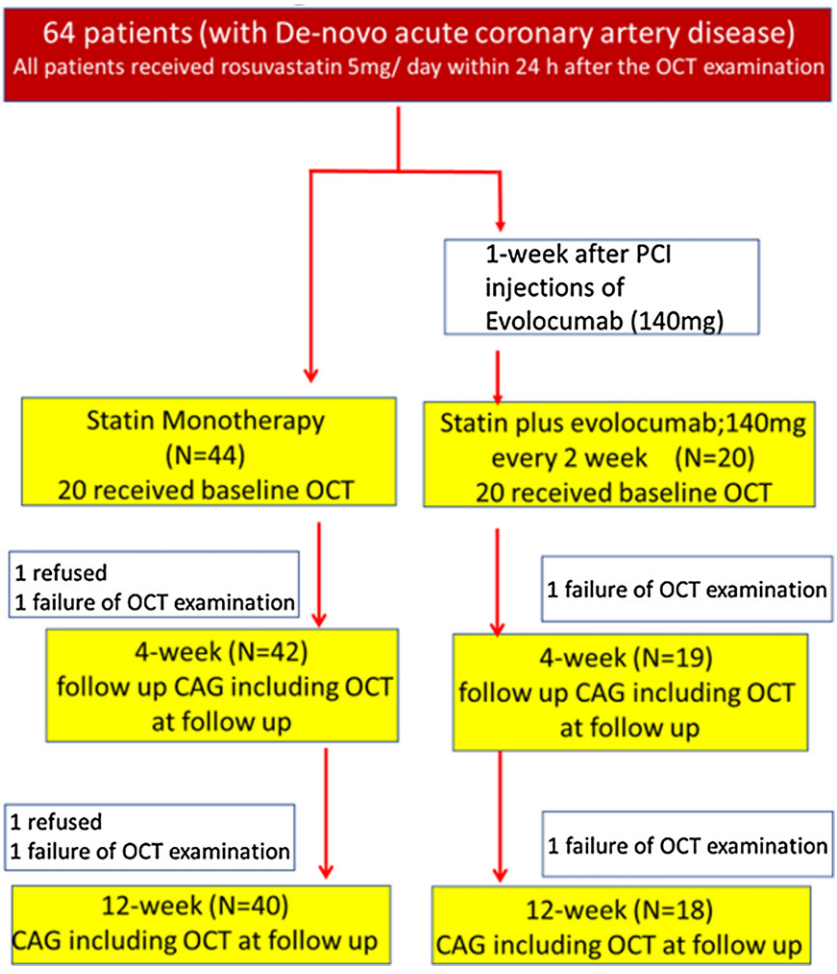

Fig. 1. Study chart flow.

coronary artery bypass grafting, severe chronic kidney disease, unsuccessful PCI, and current use of any lipid-lowering therapy.

OCT image protocol and analysis

OCT was performed using the frequency-domain OCT system (C7-XR™ Intravascular Imaging System and Dragonfly™ OCT catheter; St. Jude Medical, St. Paul, MN, USA) with a motorized pull-back system at 20 mm/s and rotation speed of 100 frames/s, using a non-occlusive technique. OCT images at baseline, 4-week follow-up, and 12-week follow-up were reviewed side by side. The target lesions were matched based on their distances from landmarks, such as branches and calcifications.

Independent, experienced OCT investigators, blinded to the patient groups, measured fibrous-cap thickness using a dedicated offline review system (St. Jude Medical) at the laboratory. The calibration was adjusted before OCT analysis. The minimum lumen area in each target lesion was determined by an automated measurement algorithm and additional manual corrections. The plaque tissue was characterized using previously validated criteria [13]. The fibrous cap was identified as a lesion with high backscattering and relatively homogeneous OCT signal. The lipid or necrotic core was identified as a signal-poor region with poorly delineated borders, little or no signal backscattering, and an overlying signal-rich layer, the fibrous cap. Minimum fibrous cap thickness was calculated using the previously reported method [14]. In brief, fibrous cap thickness of each lipid-rich plaque was measured, first at 1-mm intervals over the lipid plaque then three times at its thinnest part at each cross-section, and the average value was calculated. Minimum fibrous cap thickness was determined as the smallest fibrous cap thickness in the candidate frames (Fig. 2). Maximum lipid arc was determined as the largest lipid arc from the center of the lumen in the three candidate frames selected by visual screening (Fig. 2). Although the fluctuation by the OCT catheter position could be influenced by the largest lipid arc, a frame was selected to be as similar as possible to the side branch and the lesion morphology, and the center of the lumen was determined to measure the largest lipid arc. The lipid length was calculated from the number of frames with lipid cores.

We also performed macrophage semi-quantification on the same OCT cross-sections used for qualitative plaque assessment, according to the OCT macrophage grading system, to semi-quantify the bright spots based on axial and circumferential distribution, as follows: grade 0, no macrophage; grade 1, localized macrophage accumulation; grade 2, clustered accumulation <1 quadrant; grade 3, clustered accumulation ≥ 1 quadrant and <3 quadrants; and grade 4, clustered accumulation ≥ 3 [15] as shown in Figure S1.

The study complied with the ethical principles of the Helsinki Declaration.

Statistical analysis

All calculated data are expressed as the mean $\pm$ SD. One-way repeated analysis of variance, which was subsequently subjected to a post-hoc analysis (Scheffe's test) for multiple comparisons, was used to determine the statistical significance of differences. The chi-squared test was used for analyzing categorical variables with percentages. Statistical analysis was conducted with a commercially available statistical software program (JMP 13, SAS Institute, Cary, NC, USA). Statistical significance was accepted at $p < 0.05$.

Results

Baseline characteristics

Finally, there were 18 patients in the statin plus evolocumab group and 40 patients in the statin monotherapy group, as shown in Fig. 1. Baseline patient and angiographic characteristics, medication, procedural, and lesion characteristics were also comparable between both groups (Table 1). Although the serum total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglyceride, and hemoglobin A1c did not differ between both groups at baseline (Table 2), LDL-C was significantly reduced in both groups at the 12-week follow-up compared to baseline. It was lower in the statin plus evolocumab group compared to the statin monotherapy group (reduction rate: −74.5% vs. −35.0%, respectively, $p < 0.001$) as shown in Fig. 3a.

Serial change of OCT findings

OCT measurements are summarized in Table 3. Minimum fibrous cap thickness, maximum lipid arc, lipid length, and macrophage grade did not differ in both groups at baseline. Minimum fibrous cap thickness in both groups significantly increased from baseline to the 4-week follow-up (statin plus evolocumab group: +32 μm, statin monotherapy group: +22 μm, $p = 0.007$), and to 12-week follow-up (statin plus evolocumab group: +54 μm, statin monotherapy group: +38 μm, $p < 0.001$).

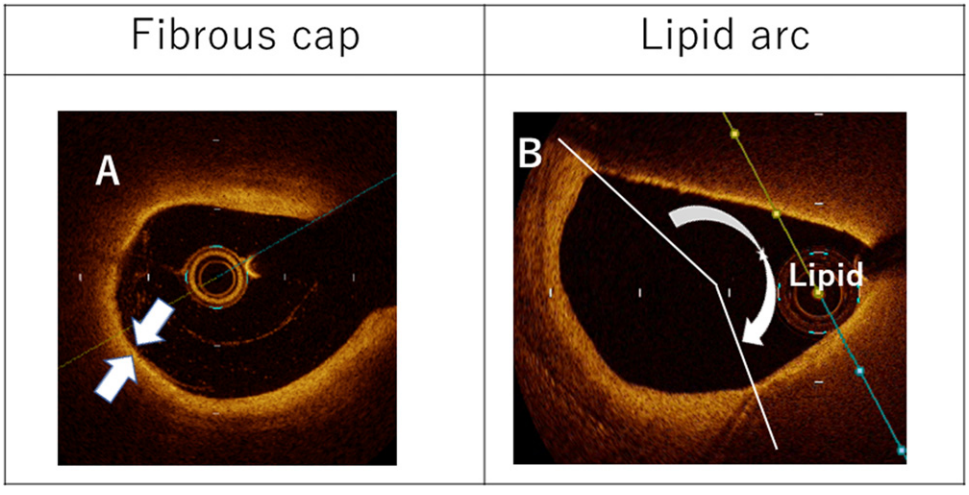

Fig. 2. Representative optical coherence tomography images of (A) fibrous cap and (B) lipid arc.

Table 1
Baseline patient and lesion characteristics in the statin monotherapy and evolocumab groups.

	Statin monotherapy group N = 40	Statin plus evolocumab group N = 18	*p*-value
Age, years	65.2 ± 6.2	64.6 ± 5.3	0.206
Male	31 (77.5%)	14 (77.8%)	0.541
Body Mass Index, (kg/m^2)	24.1 ± 5.5	24.4 ± 4.3	0.558
Hypertension, (%)	28 (70.0%)	13 (72.2%)	0.509
Diabetes mellitus, (%)	15 (37.5%)	8 (44.4%)	0.118
Estimated Glomerular Filtration Rate <60, (%)	12 (30.0%)	7 (38.9%)	0.110
Current smoker, (%)	16 (40.0%)	7 (38.9%)	0.717
Ejection fraction, (%)	50.6 ± 10.1	49.7 ± 7.4	0.302
STEMI / NSTEMI / uAP (n)	24/ 8/ 8	12/ 2/ 4	0.430
The medications just before PCI			
ACEI/ARB (n)	24 (60.0%)	11 (61.1%)	0.716
Calcium channel blockers (n)	13 (32.5%)	6 (33.3%)	0.804
Beta blockers (n)	5 (12.5%)	3 (16.7%)	0.434
Nicolandil (n)	3 (7.5%)	1 (5.6%)	0.693
DAPT (n)	40 (100%)	18 (100%)	1.000
Target lesion			
LMT	0	0	
LAD	14 (35.0%)	7 (38.9%)	0.412
LCX	8 (20.0%)	3 (16.7%)	0.303
RCA	18 (45.0%)	8 (44.4%)	0.747
Location of target plaque			
Culprit vessel	5 (12.5%)	2 (11.1%)	0.547
Non-culprit vessel	35 (87.5%)	16 (88.9%)	0.819
Mean reference diameter (mm)	2.73 ± 0.24	2.75 ± 0.32	0.773
Lesion length (mm)	13.34 ± 3.30	12.49 ± 4.20	0.376
Minimum lumen diameter (mm)	1.59 ± 0.24	1.66 ± 0.35	0.167
Percent stenosis diameter (%)	44.65 ± 11.45	46.78 ± 13.27	0.289

Data are expressed as numbers (%) or mean ± SD.
STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; uAP, unstable angina pectoris; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; *RCA,* right coronary artery, *LAD,* left anterior descending artery; *LCx,* left circumflex artery; LMT, left main trunk; PCI, percutaneous coronary intervention; *ACC/AHA,* American College of Cardiology/ American Heart Association.

Table 2
Blood sample data.

	Baseline			12-week follow-up		
	Statin monotherapy group N = 40	Statin plus evolocumab group N = 18	*p*-value	Statin monotherapy group N = 40	Statin plus evolocumab group N = 18	*p*-value
TC, mg/dL	192.0 ± 32.4	196.4 ± 37.7	0.754	144.0 ± 28.4*	115.7 ± 23.7*	<0.001
LDL-C, mg/dL	118.6 ± 21.5	120.1 ± 20.2	0.606	73.2 ± 13.4*	31.1 ± 11.0*	<0.001
HDL-C, mg/dL	45.2 ± 13.5	46.3 ± 14.2	0.485	46.8 ± 15.0	49.6 ± 14.5*	0.115
TG, mg/dL	106.1 ± 40.9	108.8 ± 44.3	0.339	104.0 ± 46.9	103.4 ± 42.7	0.687
HbA1c, %	5.9 ± 0.4	6.0 ± 0.5	0.665	5.7 ± 0.7	5.8 ± 0.8	0.705

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c.
* $p < 0.05$ vs. baseline.

The maximum lipid arc and macrophage grade in both groups significantly reduced from baseline to 4-week or 12-week follow-up (lipid arc; statin plus evolocumab group: -40°, statin monotherapy group: −24°, $p < 0.001$, macrophage grade: statin plus evolocumab group: −5, statin monotherapy group, −4, $p = 0.002$). The percentage change in fibrous cap thickness was greater, while the maximum lipid arc and macrophage grade were higher at baseline than at the 12-week follow-up, as shown in Fig. 3b ($p < 0.01$, $p = 0.015$, $p = 0.003$, respectively).

Relationship between the increased rate of fibrous cap thickness and the LDL-C reduction rate

Although the LDL-C reduction rate significantly correlated with the increased rate of fibrous cap thickness in the statin monotherapy or statin plus evolocumab groups, the slope was steeper in the statin monotherapy group than in the statin plus evolocumab group (Fig. 4). In this study, statin monotherapy reduced from 25% to 50% in LDL-C, with fibrous cap thickness increasing from 20% to 40%. In contrast, the statin plus evolocumab therapy reduced from 50% to 90% in LDL-C, while fibrous cap thickness increased from 35% to 50% as shown in Fig. 5. Thus, it was necessary to add evolocumab to statin therapy in order to achieve more than 50% reduction in LDL-C, as well as more than 45% increase of fibrous cap thickness for three months.

Major adverse cardiac events

No major adverse cardiac events, such as target vessel revascularization, cardiac death, nonfatal myocardial infarction, and ST elevation myocardial infarction/non-ST elevation myocardial infarction, were observed for 12 weeks after primary PCI or during OCT examination in this study.

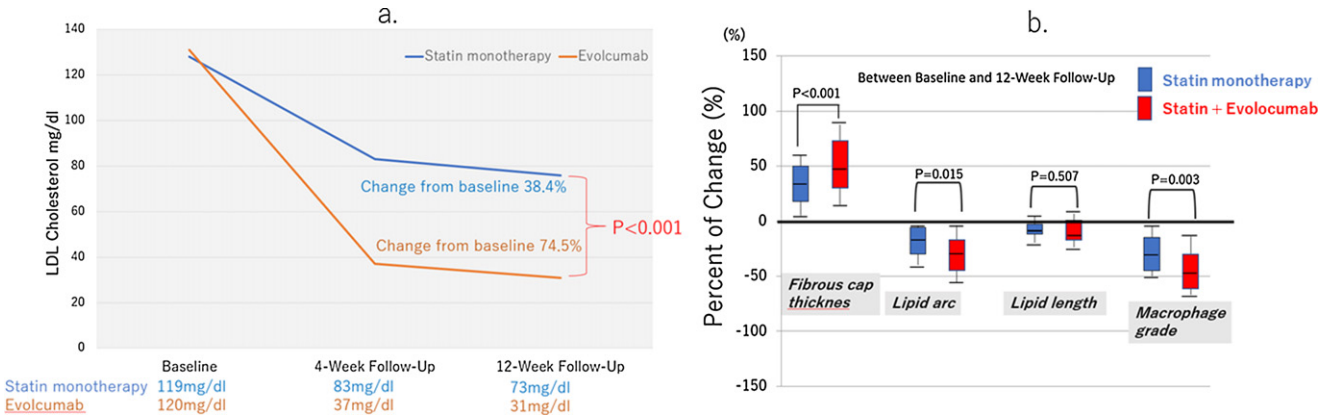

Fig. 3. (a) Low-density lipoprotein (LDL) cholesterol levels. The absolute and percentage reductions in LDL cholesterol level in the evolocumab plus statin group are compared to those in the statin monotherapy group.
Statin monotherapy group
Evolocumab plus statin group
(b) Percentage of change in optical coherence tomography measurements between baseline and 12-week follow-up. Between baseline and 12-week follow-up, percentages of change in fibrous cap thickness, lipid arc, and macrophage grade were significantly greater in the evolocumab plus statin group than in the statin monotherapy group. The percentage of change in lipid length was similar in both groups.

Statin monotherapy group

Evolocumab plus statin group

Table 3
Optical coherence tomography measurements.

	Baseline			4-week follow-up			12-week follow-up		
	Statin monotherapy group N = 40	Statin plus evolocumab group N = 18	*p*-value	Statin monotherapy group N = 40	Statin plus evolocumab group N = 18	*p*-value	Statin monotherapy group N = 40	Statin plus evolocumab group N = 18	*p*-value
Minimum fibrous cap thickness, μm	126.0 ± 31.8	123.4 ± 39.7	0.264	147.9 ± 28.4*	155.4 ± 30.8*	0.007	164.0 ± 30.4**	177.7 ± 33.2**	<0.001
Lipid arc, degree	134.4 ± 36.0	136.0 ± 41.5	0.503	125.0 ± 36.9*	116.6 ± 41.2*	0.009	110.8 ± 39.7**	96.2 ± 37.0**	<0.001
Lipid length, mm	8.7 ± 2.5	8.8 ± 2.8	0.565	8.5 ± 2.3	8.4 ± 2.5	0.238	8.4 ± 2.2	8.0 ± .3**	0.078
Macrophage grade	12.0 ± 2.5	12.2 ± 2.2	0.588	10.1 ± 3.0*	9.3 ± 2.1*	0.008	8.0 ± 2.2**	7.0 ± 1.8**	0.002

* $p <$ 0.05 vs. baseline.
** $p <$ 0.05 vs. 4-week follow-up.

Discussion

This study showed that the PCSK9-inhibitor evolocumab had an additional effect on increasing fibrous cap thickness, even in the short treatment period of 4 weeks or 12 weeks, along with statin therapy in patients with ACS. Thus, early therapy with PCSK9-inhibitor might have a salutary effect for reducing plaque vulnerability since the non-culprit lesions in patients with ACS have more vulnerable plaque characteristics compared to those with non-ACS [16]. To the best of our knowledge, this was the first study to investigate changes in fibrous cap thickness with PCSK9-inhibitor therapy by using OCT in patients with ACS.

Fibrous cap thickness is a major determinant of coronary plaque vulnerability [17–19]. The fibrous cap thins because of degrading collagen tissue from excessive release of matrix metalloproteinases from the accumulated macrophages [20,21]. The balance between degradation and synthesis of fibrous cap might be important [16,22]. Interestingly, increased fibrous cap thickness and decreased macrophage accumulation grade were greater with the PCSK9-inhibitor, evolocumab, plus statin treatment than with the statin treatment alone in this study. Therefore, the reduction of matrix metalloproteinases release, combined with decreased accumulation of macrophages, might induce fibrous cap thickening with the evolocumab plus statin treatment. Although several

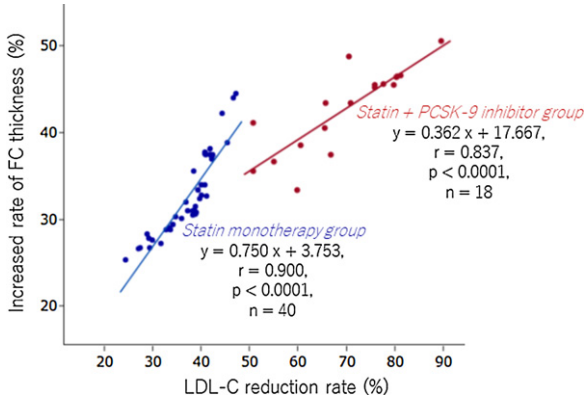

Fig. 4. Correlation between the increase rate of fibrous cap thickness and low-density lipoprotein cholesterol reduction rate.
FC, fibrous cap.

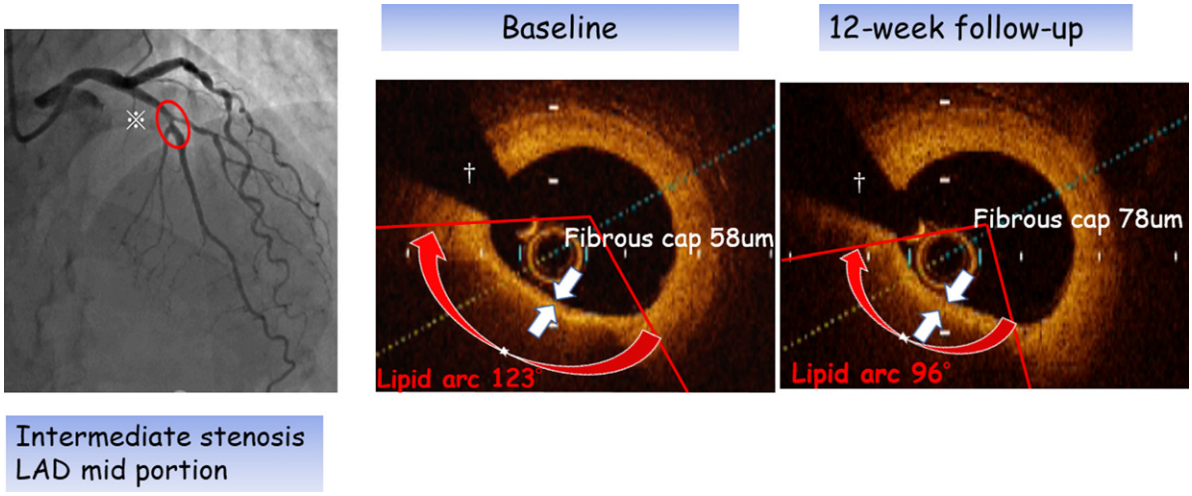

Fig. 5. Representative OCT imaging in the evolocumab plus statin group. Fibrous-cap thickness (white arrows) increased between baseline (58 μm) and 12-week follow-up (78 μm). Lipid arc (red arrows) decreased during the follow-up period.
※Intermediate stenosis (mid portion of the left anterior descending artery) †Side branch.
OCT, optical coherence tomography.

studies using OCT demonstrated that statin therapy alone could increase fibrous cap thickness in patients with coronary artery disease [6,7,14], adding PCSK9 inhibitor evolocumab to statin therapy showed a more potent effect on increasing fibrous cap thickness in patients with ACS in this study. Statins have been shown to have a limit to lower LDL-C by promoting the synthesis of PCSK-9. Therefore, it is reasonable to expect an additive LDL-C lowering effect by using a statin together with a PCSK9 inhibitor. Interestingly, the increased ratio of fibrous cap thickness, associated with the LDL-C lowering ratio, was somewhat weakened in the evolocumab plus statin group compared to the statin monotherapy group. Although this mechanism is unknown, a pleiotropic effect, such as an anti-inflammatory effect independent of lowering LDL-C by statin may be involved.

In addition, non-obstructive coronary lesions could reduce the atheroma volume by almost 1.0% after long-term administration of high-dose statins by the assessment of IVUS [23–25]. Recently, treatment with statins plus evolocumab achieved lower LDL-C and greater atheroma regression compared to statin therapy alone at 76 weeks [11]. In particular, lipid-rich fibroatheromas are at increased risk for plaque rupture [26]. An experimental study suggested that, in mice, a lack of PCSK9 is protective against atherosclerosis and overexpression of it increased accumulation of cholesteryl-esters in the aorta, leading to accelerated atherosclerosis. The study also implied that PCSK9 modulates atherosclerosis, mainly via the LDL receptor [27]. Indeed, our study showed that the lipid arc was narrower and the lipid length was shorter in the statin plus PCSK9-inhibitor evolocumab group than in the statin alone group at the 12-week follow-up. Patients presenting with lipid-rich plaques of longer lipid lengths, wider lipid arcs, and higher degrees of luminal narrowing by OCT were at particularly high risk for future cardiac events [28]. Thus, the PCSK9-inhibitor evolocumab prevented the lipid-rich plaque progression by causing a narrower lipid arc and a shorter lipid length by OCT assessment, indicating a reduced extension of atherosclerotic plaque with improved plaque morphology.

Recently, sub-analysis of the FOURIER trial suggested that patients with a history of myocardial infarction, who are closer to their most recent event, are at high risk for major vascular events and experienced substantial relative and absolute risk reductions with LDL-C lowering with evolocumab [29]. Therefore, patients with ACS in this study might be suitable for evolocumab treatment.

Study limitations

There are potential limitations to our data. First, patients were non-randomly and retrospectively selected in the single center, so selection bias may have influenced our results. Second, rosuvastatin 5 mg/day is classified as mild intensity therapy in the USA and Europe. Rosuvastatin 5 mg/day is, however, the approved starting dose for aggressive lipid-lowering therapy in Japanese patients [30] who have lower body weights than Caucasians. Third, it was reported that OCT was not optimal to detect thin-cap fibroatheroma (TCFA) since OCT diagnosis was a false positive when TCFA included an accumulation of foam cell, hemosiderin, microcalcifications, and thrombus on the luminal surface. Thus, the combined use of OCT and IVUS might improve TCFA detection accuracy [31,32].

Conclusion

Adding the PCSK9-inhibitor evolocumab to statin therapy might produce incremental growth in fibrous cap thickness and regression of the lipid-rich plaque, even for a short term, in the early phase after ACS. However, a much larger sample size would be useful to confirm this association in a future study.

Conflicts of interest

The authors indicate no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jjcc.2019.08.002.

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