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Review

Lipid Lowering Therapy to Modify Plaque Microstructures:

Insights from Optical Coherence Tomography Imaging

Yu Kataoka[1], Jordan Andrews[2], Rishi Puri[3], Peter Psaltis[2] and Stephen J. Nicholls[2]

[1]Department of Cardiovascular Medicine, National Cerebral & Cardiovascular Centre, Suita, Japan
[2]Heart Health, South Australian Health & Medical Research Institute, University of Adelaide, Adelaide, Australia
[3]Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada

Due to the pandemics of obesity and diabetes mellitus, especially in the Western countries, atherosclerotic cardiovascular disease (ASCVD) has become a major health burden and is expected to increase in the future. Modifying lipid targets, especially low-density lipoprotein cholesterol (LDL-C) level, has become the first-line therapy for primary and secondary prevention of ASCVD. Intravascular imaging modalities have contributed to elucidating clinical efficacy of lipid lowering therapy on atherosclerotic plaques. Optical coherence tomography (OCT) is a high-resolution imaging tool enables visualization of plaque microstructures associated with its instability. This modality has demonstrated favorable changes in plaque microstructures under lowering LDL-C level. In addition, clinical studies using OCT have suggested potential association of other lipid targets, including triglyceride and high-density lipoprotein cholesterol with plaque microstructures. Given continuing cardiovascular risks despite statin therapy, OCT will be an important imaging modality to evaluate novel therapeutic approaches that potentially modulates plaque instability.

Key words: Optical coherence tomography, Low-density lipoprotein cholesterol, Plaque microstructures, Triglyceride, High-density lipoprotein cholesterol

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, CAD = coronary artery disease, CETP = Cholesteryl ester transfer protein, HDL-C = high-density lipoprotein cholesterol, IVUS = intravascular ultrasound, DL-C = low-density lipoprotein cholesterol, LPL = lipoprotein lipase, OCT = optical coherence tomography, VLDL = very-low-density lipoprotein cholesterol

Introduction

Atherosclerotic cardiovascular disease (ASCVD) has become a major health burden due to the pandemic of obesity and diabetes mellitus, especially in Western countries. This suggests the importance of establishing effective therapeutic approaches for the prevention of ASCVD. Accumulating evidence supports atherogenic lipids as important therapeutic targets associated with the occurrence of ASCVD. In particular, low-density lipoprotein cholesterol (LDL-C) level has been shown as a strong contributor of ASCVD in previous epidemiological and genetic studies[1]. Furthermore, large-scale randomized clinical trials have consistently demonstrated that lowering LDL-C with a statin was associated with a significant reduction of ASCVD[2-7]. This therapeutic regimen also slows progression of coronary atherosclerosis and induces its regression when very low LDL-C level is achieved[8-11]. Based on these observations, the current therapeutic guideline has recommended lowering LDL-C as a first-line therapy for the prevention of ASCVD[12, 13].

Intravascular imaging has elucidated the clinical

Address for correspondence: Yu Kataoka, Department of Cardiovascular Medicine, National Cerebral & Cardiovascular Centre, 5-7-1, Fujishirodai, Suita city, Osaka, Japan
E-mail: yu.kataoka@ncvc.go.jp
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efficacy of lipid lowering therapy on atherosclerotic plaques and provides mechanistic insights into the progression and vulnerability of coronary atherosclerosis. Optical coherence tomography (OCT), a novel intravascular imaging modality, has enabled the visualization of plaque microstructures due to its high imaging resolution[14, 15]. Given that plaque microstructures are considered to be associated with its instability[16, 17], this modality has the great potential to further evaluate the efficacy of lipid lowering therapy on plaque vulnerability. In this review, we summarize accumulating evidences about anti-atherosclerotic efficacy of lipid lowering therapies evaluated by OCT imaging.

Plaque Microstructures

Plaque microstructure is a compositional feature of atherosclerotic lesions related to its instability. The formation of plaque microstructures occurs through atherosclerotic changes derived by the degree of influx of atherogenic lipids and inflammatory materials[18-22]. The uptake of atherogenic cholesterol-rich lipoproteins from macrophages and the influx of inflammatory materials promote the development of the large lipid core. In addition, it is covered by a fibrous cap, which is developed through accumulation of smooth muscle cells. The fibrous cap is modulated by activated inflammatory reactions, making it thinner. This process leads to the development of thin-cap fibroatheroma. Inflammatory cytokines also promote instability of lesions through neovascularization and macrophage infiltration[18, 21]. The pathophysiology of plaque formation indicates that plaque microstructure is an important contributor to vulnerability of atherosclerotic lesions.

Pathohistological analysis has demonstrated distinct characteristics of plaque microstructures at culprit lesions in patients with sudden cardiac death[16, 17]. In the published world-wide survey, plaque rupture is the main cause of coronary thrombosis (60–70%). Ruptured plaque harbors a large and soft lipid-rich necrotic core covered by a thin fibrous cap. Expansive remodeling, neovascularization, plaque hemorrhage, macrophage infiltration, and spotty calcification have also been more frequently observed. These observations suggest that plaque microstructures are important signatures of vulnerable lesions that cause acute coronary syndrome.

OCT Imaging

OCT has the capability to visualize plaque microstructures *in vivo*. OCT is an intravascular imaging modality that uses near-infrared light (1300 nm) to create images of atherosclerotic plaques in the coronary artery[14, 15]. The greatest advantage of OCT is its high resolution of up to 10 μm in an axial resolution and 20 μm in a lateral resolution, which is approximately 10 times higher than that of intravascular ultrasound (IVUS). This produces high quality imaging for plaque microstructures, including fibrous cap, microchannel, and accumulation of lipids and macrophages[14, 15, 23]. A recent study demonstrated that OCT identified thin fibrous cap, plaque rupture site, thrombus, and thin-cap fibroatheroma at culprit lesions in 30 patients with acute myocardial infarction *in vivo*[24]. In another study analyzing 63 patients with coronary artery disease (CAD), culprit plaques harboring vaso vasorum were more likely to associate with thinner fibrous cap, a higher frequency of thin-cap fibroatheroma, and an elevated level of c-reactive protein[25]. Given that other intravascular imaging modalities could not detect plaque microstructures, OCT imaging is an important tool to conduct meticulous evaluation of atherosclerotic lesions and potentially evaluate the efficacy of anti-atherosclerotic therapies.

The disadvantage of OCT imaging is poor tissue penetration. OCT has a penetration depth of 2 to 3 mm, which prohibits imaging beyond the internal elastic lamina. Due to this limited penetration, it is difficult to image atherosclerotic plaques in large arteries. Vessel volume and remodeling pattern cannot be evaluated through this imaging modality. Other limitations of OCT are related predominantly to the features of a light-based energy source, which include poor tissue penetration and interference from blood. It requires continuous infusion of contrast medium during its pullback. As such, OCT is not suitable for quantitative measurement of plaque volume and patients with chronic kidney disease. Despite these limitations, OCT will serve as an important tool for analyzing plaque vulnerability under anti-atherosclerotic medical therapy.

OCT imaging is capable of visualizing other plaque phenotypes associated with acute coronary events. Plaque erosion is characterized by the lesion exhibiting intact fibrous cap and the presence of thrombus, which is observed in 20–30% of subjects with sudden cardiac death[16, 17]. The underlying plaque morphology shows the presence of pathological intimal thickening or a fibroatheroma. Calcified nodules are a rare type of plaque feature related to disruptive nodular calcifications protruding into the lumen[16, 17]. Recent studies have reported frequency of ruptured plaque, erosion, and calcified nodules at culprit lesions in patients with acute myocardial infarction, which is similar to observations in pathohistological analysis[26-28]. The effect of lipid lowering therapy on these atherosclerotic lesions has yet to be determined. Future studies will elucidate natural history of plaque

Table 1. Plaque Microstructures under Lowering LDL-C Levels

Authors	Subjects	Therapy	Outcomes	Findings
Statin				
Kataoka, *et al.*[31]	280 patients with CAD who received a statin	any type of statin therapy	Fibrous cap thickness	Patients with LDL-C <50 mg/dL were more likely to have fibrous plaque and less likely to have lipid plaques. In addition, LDL-C level was significantly associated with lipid arc and fibrous cap thickness.
Hattori *et al.*[33]	42 patients with stable CAD	4 mg pitavastatin vs. standard therapy without any statin	Fibrous cap thickness, percentage lipid volume index	Significant increase in fibrous cap thickness was observed in the pitavastatin group, these changes were not observed in the diet-only group. Differences in the changes in the percentage lipid volume index and fibrous cap thickness over time between the pitavastatin and diet groups were highly significant.
Takarada *et al.*[34]	40 patients with AMI who received PCI	Statin therapy vs. Standard therapy without a statin	Fibrous cap thickness	Percent change in fibrous cap thickness was greater in statin group (188 ± 64 vs. $117 \pm 39\%$, $p<0.01$). when the patients in the statin treatment group were divided into two subgroups (fibrous-cap thickness $<$ median and $>$ or = median), the thin fibrous-cap group ($<$ median) increased their thickness much more than the thick fibrous-cap group ($>$ or = median).
Statin intensity				
Kataoka, *et al.*[29]	275 patients with stable CAD	Standard therapy without a statin vs. low-dose statin vs. high-dose statin	Fibrous cap thickness	Plaques in the high-dose statin group demonstrated a smaller lipid arc and a greater fibrous cap thickness.
Komukai *et al.* (EASY-FIT)[30]	70 patients with unstable angina pectoris	5 mg vs. 10 mg atorvastatin	Change in fibrous cap thickness	The increase in fibrous cap thickness was significantly greater with 20 mg/day compared with 5 mg/day of atorvastatin. The increase in fibrous cap thickness correlated with the decrease in serum levels of low-density lipoprotein cholesterol, malondialdehyde-modified low-density lipoprotein, high-sensitivity C-reactive protein, and matrix metalloproteinase-9, and the decrease in grade of OCT-derived macrophages.
Hou *et al.*[35]	46 patients with CAD	Atorvastatin 60 mg vs. atorvastatin 20 mg	Change in fibrous cap thickenss	Atorvastatin 60 mg induced greater increase in fibrous cap thickness at 6 months. The prevalence of thin-cap fibroatheroma and the presence of macrophage were significantly lower in atorvastatin 60 mg group at 6 months.
Ezetimibe				
Habara *et al.*[37]	63 patients with CAD	Combination of fluvastatin + ezetimibe versus fluvastatin alone for 9 months	Change in fibrous cap thickenss	Fibrous cap thickness was significantly increased and the angle of the lipid plaque was significantly decreased in both groups. The change in the fibrous cap thickness was significantly greater in the ezetimibe + fluvastatin group.

AMI = acute myocardial infarction, CAD = coronary artery disease, EASY-FIT = Effect of Atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque assessed by optical coherence tomography, LDL-C = low-density lipoprotein cholesterol, PCI = percutaneous coronary intervention

erosion and calcified nodules under lipid modifying therapy by using OCT imaging.

Lowering LDL-C Levels and Plaque Microstructures

The effect of lowering LDL-C levels on atherosclerotic plaques has been analyzed by a variety of intravascular imaging studies. Recently, OCT imaging has been used to investigate plaque microstructures under LDL-C lowering therapy with statin or ezetimibe on coronary atheroma *in vivo* (**Table 1**). It has provided mechanistic insights into plaque stabilization effects under LDL-C lowering therapy.

1) Statin: Plaque microstructures at non-culprit lesions under low- and high-dose statin were investi-

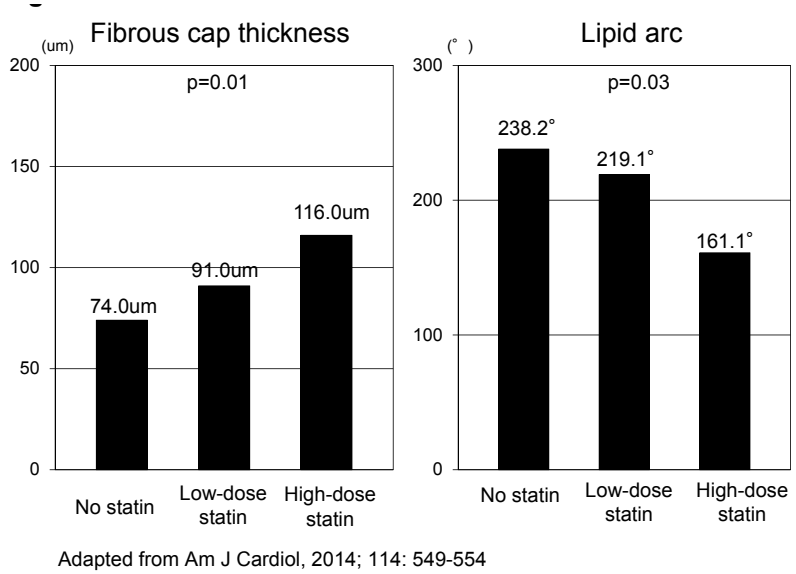


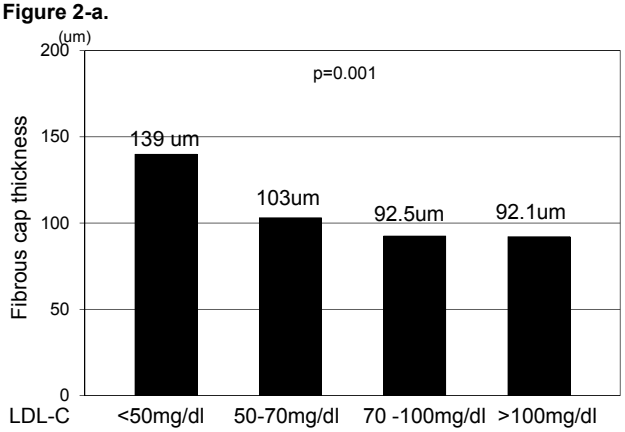
Fig. 1. Fibrous Cap Thickness, Lipid Arc, and Intensity of Statin

gated in 275 patients with stable CAD who required percutaneous coronary intervention[29] (**Fig. 1**). Achieved LDL-C levels were 103.1±37.9, 96.3±40.7, and 80.5±31.2 mg/dl in no statin, low-dose, and high-dose statin groups, respectively. Compared to subjects who did not take a statin, thicker fibrous cap ($p=0.01$) and smaller lipid arc ($p=0.03$) were observed in association with dose of statins. In addition, patients receiving a statin were more likely to exhibit a lower frequency of thin-cap fibroatheroma ($p<0.001$) and vaso vasorum ($p=0.01$). These favorable features were more frequently observed in subjects under high-dose statin who achieved the lowest LDL-C level. The EASY-FIT (Effect of Atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque assessed by optical coherence tomography) trial compared the efficacy of 20 mg and 5 mg atorvastatin on OCT-derived plaque microstructures in 70 patients with unstable angina pectoris[30] (**Table 1**). On-treatment LDL-C level was significantly lower in 20 mg atorvastatin group [69 mg/dl (interquartile range: 61–80) vs. 78 mg/dl (interquartile range: 66–108), $p=0.03$]. On serial evaluation, 20 mg atorvastatin use was associated with greater increase in fibrous cap thickness [69% (interquartile range: 25–104) vs. 17% (interquartile range: −1–34), $p<0.001$]. Furthermore, more favorable changes in lipid arc [−27% (interquartile range: from −37 to −20) vs. −8% (interquartile range: −13 to −4), $p<0.001$] and macrophage grade [−38% (interquartile range: −44 to −31) vs. −24% (interquartile range: −33–0), $p<0.001$] were also observed in patients receiving 20 mg atorvastatin. Biomarkers associated with fibrous cap thickness included percent change in LDL-C ($R=-0.450$, $p<0.001$), malondialdehyde-modified low-density lipoprotein ($R=-0.283$, $p=0.029$), high-sensitivity c-reactive protein ($R=-0.276$, $p<0.001$), and matrix metalloproteinase-9 ($R=-0.502$, $p<0.001$) levels[30].

The association of achieved LDL-C level with plaque microstructures at non-culprit lesions was investigated in another retrospective analysis[31]. This study included 280 patients with CAD who received a statin. LDL-C levels <50 mg/dl and 70 mg/dl were achieved by 13.9% and 29.2% of study subjects, respectively. Fibrous cap thickness was thicker and lipid arc was smaller in association with achieved LDL-C level (**Fig. 2-a** and **-b**). Patients with LDL-C <50 mg/dl exhibited the thickest fibrous cap, smallest lipid arc, and the lowest frequency of thin-cap fibroatheroma (**Fig. 2a**, **b**, and **c**). Even after adjusting for differences in clinical demographics, LDL-C level (β coefficient=−0.254, $p=0.009$) and high-dose statin use (β coefficient=1.814, $p=0.003$) were independent determinants for fibrous cap thickness. Subgroup analysis elucidated consistent efficacy of achieving very low LDL-C levels in various subsets except diabetic patients (**Table 2**). Favorable effects of achieving very low LDL-C level on fibrous cap thickness were observed in non-diabetic subjects (94.6±52.9 vs. 203.5±93.7 μm, $p<0.001$), whereas there was no significant difference in fibrous cap thickness of diabetic patients with LDL-C < vs. >50 mg/dl (106.4±86.9 vs. 93.2±79.6 μm, $p=0.27$).

Plaque microstructures in obese patients were analyzed in another OCT imaging study[32]. This study

Figure 2-a.



Adapted from Atherosclerosis, 2015; 242: 490-495

Figure 2-b.

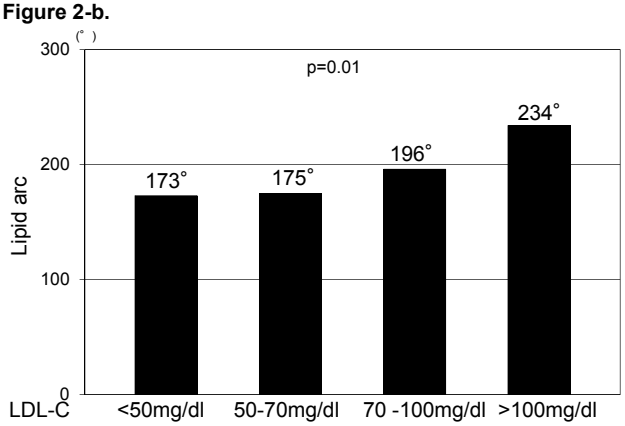


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Figure 2-c.

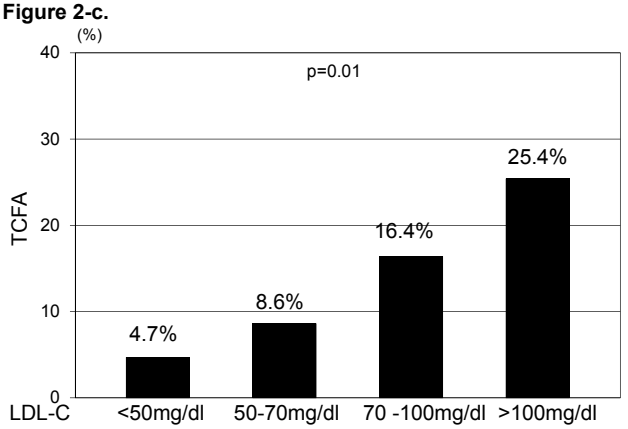

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Fig. 2. Achieving Very Low LDL-C Level and Plaque Microstructures

a. fibrous cap thickness

b. lipid arc

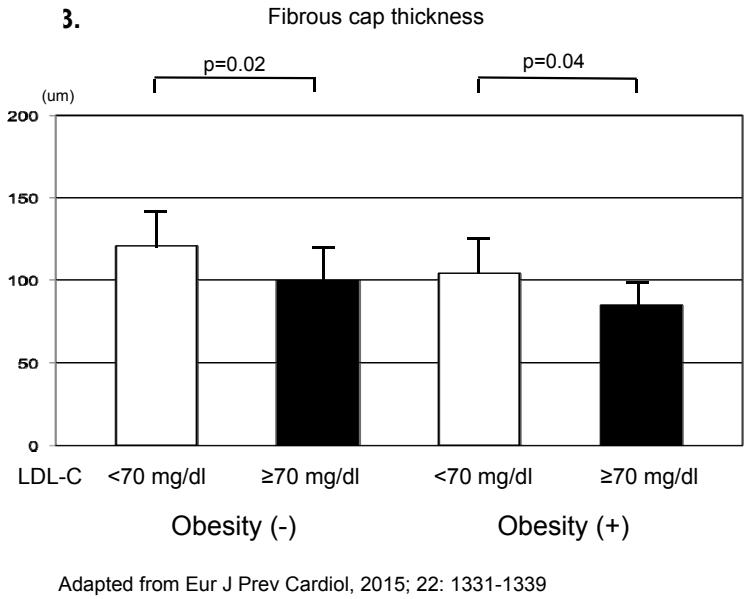
c. TCFA

LDL-C = low-density lipoprotein cholesterol, TCFA = thin-cap fibroatheroma

Table 2. Fibrous Cap Thickness under Very Low LDL-C Level in Various Subgroups

	Fibrous cap thickness (um)		*p*-value	*p*-value for interaction
	LDL-C < 50 mg/dl	LDL-C ≥ 50 mg/dl		
Age < median (62 years)	203.5 ± 93.7	94.6 ± 52.9	< 0.001	0.12
Age ≥ median (62 years)	112.2 ± 79.3	87.9 ± 40.0	0.03	
Male	163.7 ± 94.0	95.9 ± 57.1	< 0.001	0.13
Female	128.6 ± 38.1	91.1 ± 35.2	0.03	
BMI < median (29.2 kg/m^2)	122.3 ± 83.3	95.1 ± 49.1	0.03	0.004
BMI ≥ median (29.2 kg/m^2)	269.3 ± 66.3	93.7 ± 52.9	< 0.001	
Hypertension (−)	120.1 ± 86.3	94.7 ± 56.3	0.03	0.002
Hypertension (+)	202.6 ± 96.5	93.8 ± 48.3	< 0.001	
Diabetes (−)	203.5 ± 93.7	94.6 ± 52.9	< 0.001	0.003
Diabetes (+)	106.4 ± 86.9	93.2 ± 79.6	0.27	
Non-smoker	183.0 ± 48.3	95.7 ± 57.8	0.003	0.13
Smoker	131.7 ± 98.9	92.7 ± 45.2	0.003	
Atorvastatin use	155.2 ± 110.3	99.1 ± 67.2	0.02	0.51
Rosuvastatin use	233.2 ± 68.2	90.3 ± 51.4	< 0.001	

BMI = body mass index, LDL-C = low-density lipoprotein cholesterol



Adapted from Eur J Prev Cardiol, 2015; 22: 1331-1339

Fig. 3. Fibrous Cap Thickness under Lowering LDL-C Levels in Obese and Non-obese Patients

LDL-C = low-density lipoprotein cholesterol

investigated 129 obese and 179 non-obese patients with CAD on whom OCT imaging was conducted. In obese patients, thinner fibrous cap (85.3 ± 31.1 vs. 110.1 ± 32.4 μm, $p = 0.01$) and a higher prevalence of thin-cap fibroatheroma (28.8% vs. 14.3%, $p = 0.01$) were observed. These features persisted in multivariate analysis adjusting for clinical demographics. Achieving LDL-C levels <70 mg/dl were associated with thicker fibrous cap in both obese and non-obese patients. However, the fibrous cap thickness in obese patients with LDL-C levels <70 mg/dl were almost similar to that in non-obese subjects with less optimal control of LDL-C (**Fig. 3**). These findings from OCT imaging highlight the benefit of intensive lowering LDL-C with high-intensity statin, whereas diabetic and obese patients are still high-risk categories who require stricter LDL-C control and/or additional therapy targeting other atheorgenic targets. Optimizing therapeutic approaches in these subjects will be warranted in future studies.

2) Ezetimibe: Ezetimibe is another agent that lowers LDL-C levels by 20% to 30%. It reduces cholesterol absorption through inhibition of the Niemann-Pick C1-like1 protein[33, 36]. The effect of ezetimibe on plaque microstructures was investigated by one recent clinical study that included 63 patients with CAD[37] (**Table 1**). Study subjects were divided into two groups: 1) ezetimibe (10 mg/day) + fluvastatin (30 mg/day) and 2) fluvastatin (30 mg/day) alone. Combination therapy of ezetimibe and fluvastatin was associated with a greater reduction of LDL-C levels at nine months after therapy (−34.0 ± 32.0 mg/dl vs. −8.3 ± 17.4 mg/dl, $p < 0.001$). Serial OCT imaging revealed that change in fibrous cap thickness was significantly greater in the ezetimibe + fluvastatin group (0.08 ± 0.08 mm vs. 0.04 ± 0.06 mm, $p < 0.001$). Change in LDL-C ($r = -0.60$, $p < 0.001$), total cholesterol ($r = -0.57$, $p < 0.001$) and high-sensitivity c-reactive protein ($r = 0.42$, $p = 0.001$) levels were significantly correlated to changes in fibrous cap thickness. This result suggests a plaque stabilization effect of ezetimibe, which may account for the lower occurrence of cardiovascular disease in subjects receiving both ezetimibe and statins in a recent clinical trial[38].

Residual Lipid Targets and Plaque Microstructures

Substantial amounts of cardiovascular events still occur, even under intensive control of LDL-C level[39, 40]. This residual cardiovascular risk supports the concept that atherosclerosis is a multifactorial process that potentially responds to therapeutic approaches modulating global risks. Considerable attention has been focused on other lipid targets to achieve further reduction of ASCVD. Epidemiological studies have demonstrated the association of high-density lipoprotein cholesterol (HDL-C)[41-49] and triglyceride[50-55] with ASCVD. This evidence indicates that controlling these lipid targets can modulate atherosclerotic plaques and reduce ASCVD under optimal control of LDL-C levels.

1) High-density Lipoprotein

HDL particles are an attractive therapeutic target that exhibits a variety of anti-atherosclerotic properties. One major atheroprotective ability of HDL is to promote cholesterol efflux from cells such as macrophages and the related complex physiological process of reverse cholesterol transport[56-58]. HDL also harbors several anti-atherosclerotic properties such as anti-oxidative, anti-inflammatory and anti-thrombotic effects, and vasodilatory abilities[57, 58]. A recent cross-sectional study has elucidated that HDL cholesterol efflux capacity is inversely associated with carotid intima-media thickness (β coefficient per 1-SD increase in efflux capacity; −0.03, 95% CI; from −0.06 to −0.01, $p=0.003$) and the likelihood of angiographic CAD (odds ratio per 1-SD increase, 0.75; 95% CI, 0.63–0.90; $p=0.002$) in 2,924 adults without any cardiovascular disease[59]. This observation suggests great potential of HDL modulating therapy to halt atherosclerosis and prevent atherosclerotic cardiovascular events.

The relationship of HDL-C levels with plaque instability at culprit lesions was investigated in 261 subjects with acute coronary syndrome who received percutaneous coronary intervention by using OCT imaging[60]. In this analysis, 47.5% of study subjects exhibited thin-capped fibroatheroma at their culprit sites. They were more likely to have a lower level of HDL-C level (39.6 ± 10.1 mg/dl vs. 46.7 ± 11.7 mg/dl, $p<0.001$) and a higher level of LDL-C (120.7 ± 31.1 mg/dl vs. 110.0 ± 28.2 mg/dl, $p=0.004$) compared to those without thin-cap fibroatheroma. In addition, HDL-C level was significantly associated with fibrous cap thickness ($r=0.27$, $p<0.001$) and lipid arc ($r=-0.18$, $p=0.02$). Multivariate analysis indicated that HDL-C (odds ratio = 0.93, 95% CI: 0.90–0.95, $p<0.001$) and LDL-C (odds ratio = 1.01, 95% CI: 1.005–1.025, $p=0.002$) levels were independent predictors for the presence of thin-capped fibroatheroma at culprit lesions[60]. Predictors for thinner fibrous cap thickness included HDL-C (β coefficient = 0.302, $p<0.001$), LDL-C (β coefficient = −0.172, $p=0.008$), high-sensitivity c-reactive protein (β coefficient = −0.145, $p=0.017$), and current smoking (β coefficient = −0.124, $p=0.028$) after adjusting the presence of coronary risk factors and the use of statin, angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker. These observations highlight more high-risk plaque phenotypes in CAD patients with a lower level of HDL-C.

Recent studies have elucidated the association of HDL-C with another novel vulnerable plaque feature, cholesterol crystal, on OCT imaging. Cholesterol crystallization within coronary atheroma has been shown to promote a local inflammatory response via a Nod-like receptor, NLRP3 inflammasome protein[61, 62], and induce apoptosis of foam cells, leading to further attraction of macrophages and development of a lipid-rich necrotic core[63, 64]. These inflammatory and apoptotic effects indicate a potential contribution of cholesterol crystal to plaque destabilization. We have already reported more vulnerable features of culprit and non-culprit plaques harboring cholesterol crystals in 250 patients with CAD who undertook percutaneous coronary intervention[65]. At least one cholesterol crystal was found within a target vessel of 36.3% of study population.. On OCT imaging analysis, non-culprit lipid plaques containing cholesterol crystals exhibited a smaller fibrous cap thickness (84.1 ± 27.9 μm vs. 106.9 ± 40.1 μm, $p=0.003$), larger lipid index (2,357.4 ± 1,742.7 mm° vs. 914.2 ± 1,151.7 mm°, $p<0.0001$), greater prevalence of thin-cap fibroatheroma (26.9% vs. 5.5%, $p=0.005$), and microchannel (46.1% vs. 19.4%, $p<0.0001$). Larger lipid index (1,975.1 ± 765.7 mm° vs. 793.8 ± 1,237.8 mm°, $p=0.001$) and a higher prevalence of thin-cap fibroatheroma (30.3% vs. 2.1%, $p=0.01$) were also observed at culprit lesions with cholesterol crystals. Another study analyzing 173 patients with CAD also identified more frequent observation of plaque rupture (31.8% vs. 19.3%, $p=0.001$), thin-cap fibroatheroma (25.8% vs. 7.5%, $p=0.002$), and macrophage accumulation (75.8% vs. 58.0%, $p=0.015$) at lesions with cholesterol crystals[66]. Multivariate logistic regression analysis elucidated that HDL-C level < 35 mg/dl was an independent predictor for the presence of cholesterol crystals (odds ratio = 2.72, 95% CI: 1.27–6.08, $p=0.01$). These findings suggest HDL as a critical player in plaque stability *in vivo*.

Despite atheroprotective efficacy of HDL, therapeutic agents raising HDL-C levels fail to prove their clinical benefit in the reduction of ASCVD. Cholesteryl ester transfer protein (CETP) inhibitor is an oral agent that elevates HDL-C levels and lowers LDL-C levels via modulation of CETP. The ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) study was the first study to evaluate the clinical efficacy of torcetrapib, the first CETP inhibitor on cardiovascular outcomes in 15,067 patients at high cardiovascular risk[67]. While torcetrapib increased HDL-C by 72.1% as well as lowered LDL-C level by 24.9%, significant increases in mortality (hazard ratio = 1.58, 95% CI: 1.14–2.19, $p=0.006$), and cardiovascular events (hazard ratio = 1.25, 95% CI: 1.09–1.44, $p=0.001$) were observed in patients receiving the agent. Additionally, off-target effects, such as elevated blood pressure levels, were observed in the torcetrapib group. The

ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation) study compared progression of coronary atherosclerosis on IVUS imaging between torcetrapib and placebo groups[68]. While torcetrapib increased HDL-C level, there was no significant difference in the atheroma progression rate between the two groups (change in percent atheroma volume, +0.19% vs. +0.12%, $p=0.72$)[68]. Evacetrapib is a potent CETP inhibitor without off-target effects associated with elevated blood pressure levels[69]. The ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High-Risk for Vascular Outcomes) study investigated clinical efficacy of evacetrapib in 12,000 patients with atherosclerotic vascular disease who already received a statin. Evacetrapib was associated with a substantial increase in HDL-C levels (104 vs. 46 mg/dl, $p<0.01$) and a lower level of LDL-C (55 vs. 84 mg/dl, $p<0.01$) without major side effects. However, any additive effect on cardiovascular event rates was not observed (12.8% vs. 12.7%, hazard ratio =1.01, 95% CI: 0.91–1.12, $p=0.85$).

Based on these findings, it could be argued that therapeutic approaches targeting HDL quality rather than its quantity would be beneficial in modifying atherosclerosis. RVX-208 is another novel oral therapeutic agent that generates new HDL particles via enhancing hepatic synthesis of apolipoprotein A-I. This agent has been shown to enhance cholesterol efflux capacities in animal models (ABCA-1 mediated cholesterol efflux capacity: 15.4%±1.7% vs. 7.6%±1.2%, $p<0.001$)[70]. The clinical efficacy of RVX-208 on atheroma progression was investigated by the ASSURE (ApoA-I Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation) study in 310 patients with acute coronary syndrome[71]. Serial IVUS imaging demonstrated that the use of RVX-208 for 6 months did not modulate changes in percent atheroma volume compared to placebo (–0.40% vs. –0.30%, $p=0.81$). However, post-hoc analysis using virtual histology IVUS imaging has elucidated that RVX-208 was associated with a significant increase in fibrous tissue within plaques (+1.6% vs. –1.3%, $p=0.04$). This observation suggests the ability of RVX-208 to stabilize atherosclerotic plaques in ACS cases. It remains to be determined whether agents modulating HDL would modify plaque microstructures. Future studies using OCT will further elucidate the anti-atherosclerotic effects of novel therapies modifying HDL quality on plaque microstructures.

2) Triglyceride

Triglyceride-rich lipoprotein is an atherogenic particle which exhibits the potential ability to promote atherosclerosis. Following the absorption of dietary lipids, one of triglyceride-rich lipoproteins, chylomicron, is formulated and then hydrolyzed by lipoprotein lipase (LPL)[72, 73]. This process leads to the development of chylomicron remnant. Another triglyceride-rich lipoprotein, very-low-density lipoprotein cholesterol (VLDL) is assembled in the endoplasmic reticulum of hepatocytes. VLDL is hydrolyzed by LPL, generating VLDL remnants, intermediate-density lipoprotein and low-density lipoprotein. Chylomicron and VLDL remnants have been reported to accumulate in vessel wall, leading to foam cell formation. Additionally, these remnants have been shown to increase the expression of pro-inflammatory genes and induce apoptosis[72, 73]. These atherogenic aspects of triglycerides support their contribution to atherosclerosis.

Hypertriglyceridemia, as well as low HDL-C levels, are characteristics of diabetic dyslipidemia. The association of this lipid feature with plaque instability was evaluated by using OCT imaging in diabetic subjects with CAD[74]. This analysis included 128 patients with CAD who already received a statin. On OCT imaging, higher triglyceride/HDL-C ratio contributed to more vulnerable features such as larger lipid arc and cholesterol crystals (**Table 3**). Even after adjusting for differences in clinical demographics, triglyceride/HDL-C ratio was still related to lipidic materials within plaques. This finding highlights the potential benefit in modulating triglycerides and HDL-C in diabetic atherosclerosis.

Suggestive evidence from epidemiological studies has stimulated considerable interests to investigate efficacy of lowering triglyceride levels on cardiovascular outcomes. Fibrates, which are peroxisome proliferator-activated receptor-alpha agonist, lower triglyceride levels by 20%–50% and raise HDL-C levels by 10%. The ACCORD-LIPID (Action to Control Cardiovascular Risk in Diabetes) study was a large-scale randomized trial which analyzed 5,518 type 2 diabetic subjects with cardiovascular risks[75]. Study subjects were randomized to two groups who received either simvastatin alone or a combination of simvastatin and fenofibrate. Predictably, addition of fenofibrate induced a significant lowering of triglyceride levels (122 mg/dl vs. 144 mg/dl, $p<0.001$) with an increased level of HDL-C (41.2 mg/dl vs. 40.5 mg/dl, $p=0.01$). During 4.7-year observational period, however, there were no significant differences in the occurrence of major cardiovascular events between two groups (2.2% vs. 2.4%, hazard ratio =0.92, 95% CI:

Table 3. Association of TG/HDL-C Ratio with Plaque Microstructures

	TG/HDL-C ratio ≤ 1.39	TG/HDL-C ratio 1.39-4.67	TG/HDL-C ratio >4.67	*P*-value
Lipid Content				
Lipid arc (°)	196.3 ± 59.2	158.2 ± 78.2	233.9 ± 95.0	0.01
Longitudinal length of lipid plaque (mm)	4.2 ± 3.7	5.7 ± 5.2	6.0 ± 7.4	0.17
Plaque Microstructures				
Microchannel (%)	20	21	19	0.98
Cholesterol crystal (%)	26.6	21	57.1	0.03
Fibrous cap thickenss (um)	115.3 ± 36.0	137.0 ± 97.1	108.6 ± 54.1	0.42
TCFA (%)	13	15	29	0.23
Calcification (%)	80	63.1	66.6	0.56

HDL-C = high-density lipoprotein cholesterol, TCFA = thin-cap fibroatheroma, TG = triglyceride

0.79 to 1.08, $p = 0.32$)[75]. Subgroup analyses identified a favorable trend toward a lower occurrence of major cardiovascular events in diabetic patients with both high triglyceride (≥ 204 mg/dl) and low HDL-C (≤ 34 mg/dl) levels (12.3% vs. 17.3%, $p = 0.06$). Aforementioned OCT findings and this subgroup analysis may support favorable benefits of fibrates in diabetic subjects with high triglyceride and low HDL-C levels.

Conclusion

Lipid modifying therapy is considered as one of the major therapeutic approaches for primary and secondary prevention of ASCVD. Favorable changes in OCT-derived plaque microstructures under lowering LDL-C support its importance as a therapeutic target to halt atherosclerosis. Several OCT imaging studies suggest plaque stabilization effects through modulation of other lipid targets. Recent innovation in pharmacological regimens has enabled the achievement of very low LDL-C levels beyond statins. A variety of novel agents targeting HDL quality and/or metabolism of triglycerides are under development or investigation in on-going clinical trials. OCT imaging will be expected to play a critical role in the assessment of these novel therapies in the future.

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Conflicts of Interest

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