High-Density Lipoprotein Cholesterol Level Is Associated With Fibrous Cap Thickness in Acute Coronary Syndrome

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Background: Although low high-density lipoprotein cholesterol (HDL-C) level has been reported as an independent risk factor for coronary artery disease, few studies addressed the direct relationship between the presence of thin-cap fibroatheroma (TCFA) that is considered as vulnerable plaque in pathology and HDL-C level. The aim of this study was to investigate whether lesion vulnerability is related to HDL-C level in patients with acute coronary syndrome (ACS).

Methods and Results: A total of 261 patients with ACS who underwent optical coherence tomography prior to percutaneous coronary intervention, were enrolled. Patients were divided into a TCFA group (n=124) and a non-TCFA group (n=137). TCFA was defined as a lipid plaque (lipid content in ≥ 1 quadrant) covered with $<70\mu\text{m}$ -thickness fibrous caps. There were no differences in patient characteristics and clinical results between the 2 groups except for HDL-C level, low-density lipoprotein cholesterol (LDL-C) level, and high-sensitive C-reactive protein (hs-CRP) level. On multivariate regression analysis, low HDL-C level (β coefficient: 0.302, $P<0.001$), high LDL-C level (β coefficient: -0.172 , $P=0.008$), hs-CRP level (β coefficient: -0.145 , $P=0.017$), and current smoking (β coefficient: -0.124 , $P=0.028$) were identified as independent contributors to fibrous cap thickness.

Conclusions: HDL-C is correlated with fibrous cap thickness of the culprit lesion in patients with ACS. HDL-C may be considered as a therapeutic target for plaque stabilization. (*Circ J* 2013; **77**: 2982–2989)

Key Words: Acute coronary syndrome; Fibrous cap thickness; High-density lipoprotein cholesterol; Optical coherence tomography

It has been established that recurrence of cardiovascular events, and coronary artery disease (CAD) death rates are reduced by lipid-lowering therapies with statin. Although aggressive statin therapy, aimed at low-density lipoprotein cholesterol (LDL-C), has significantly reduced major cardiovascular events and mortality,^{1–7} cardiac events remain even though LDL-C levels are adequately controlled.⁸ One reason for this may be the presence of a baseline low high-density lipoprotein cholesterol (HDL-C) level even during intensive treatment with statins.⁹ HDL-C has been reported as an independent inverse predictor of cardiovascular disease,^{10–14} and regression of coronary atherosclerosis was correlated with the moderate increase in serum HDL-C level.¹⁵

Although gray-scale intravascular ultrasound (IVUS) has been used to investigate the relationship between blood lipid

profile and coronary tissue characteristics,^{16–18} the current consensus is that IVUS is unable to visualize the details of tissue characterization,¹⁹ including thin-cap fibroatheroma (TCFA), which is a morphological feature of vulnerable plaque. Therefore, it remains unclear whether serum HDL-C level is associated with culprit lesion vulnerability. The aim of this study was to investigate whether lesion vulnerability assessed on optical coherence tomography (OCT) is related to HDL-C level in patients with acute coronary syndrome (ACS).

Methods

Subjects

The subjects consisted of 261 consecutive ACS patients (with or without ST-segment elevation) who were admitted to

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Figure 1. Representative cases of (A) thin-cap fibroatheroma, (B) plaque rupture, (C) thrombus, and (D) calcification. (A) The thickness of the fibrous cap is 50 µm (arrows). (B) Fibrous cap was broken at the midportion (arrows). (C) Fibrous plaque was observed, and intracoronary thrombus (arrows) protruding into the vessel lumen from the surface of the vessel wall. (D) Calcium deposit showing a sharply delineated region with a signal-poor interior (arrows). HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Asterisk, guidewire artifact.

Wakayama Medical University Hospital (Wakayama, Japan) and underwent OCT prior to percutaneous coronary intervention (PCI). We excluded patients with cardiogenic shock, unstable hemodynamic status, unsuccessful reperfusion of Thrombolysis In Myocardial Infarction (TIMI) grade 3 coronary flow on initial aspiration thrombectomy before OCT imaging, and unwillingness to participate. Patients were divided into a TCFA or a non-TCFA group according to pre-intervention OCT findings of the culprit lesion.

This study complied with the Declaration of Helsinki with regard to investigation in humans, and the protocol for this study was approved by the Ethics Committee of Wakayama Medical University. We also obtained written informed consent from all participants before coronary angiography (CAG).

Study Protocol

All patients received oral aspirin (162 mg), an i.v. bolus injection of 5,000 IU of heparin, and i.c. isosorbide dinitrate (2 mg) before CAG. After completion of diagnostic CAG, culprit lesion was identified on the basis of CAG findings as well as those of electrocardiography and echocardiography.

Following CAG, OCT imaging was performed using a 6-F

guiding catheter to observe the culprit lesion before any interventions. If the patient had TIMI grade 0, 1, or 2 coronary flow, aspiration thrombectomy was performed using an aspiration catheter (Export®; Medtronic Japan, Tokyo, Japan) before OCT image acquisition. Frequency-domain OCT (FD-OCT) or time-domain OCT (TD-OCT) was used for OCT image acquisitions. The FD-OCT system (C7-XR™ FD-OCT imaging system; LightLab Imaging, Westford, MA, USA) consists of an intravascular OCT catheter (RX ImageWire II; LightLab Imaging), an imaging engine, probe interface unit, and a computer console, which also contains the data acquisition board. For FD-OCT, the 2.7-F imaging catheter can be delivered as a monorail rapid-exchange catheter over a 0.014-in PCI guidewire through a 6-F guiding catheter and was positioned so that its imaging lens was distal to the culprit lesion. All OCT images from the FD-OCT system were obtained using an automatic pullback device traveling at a rate of 20 mm/s. For tight lesions, alternatively TD-OCT was used for OCT image acquisition with an automatic pullback device traveling at a rate of 1.0 mm/s. To flush the vessel, we infused a mixture of commercially available dextran 40 and lactated Ringer's solution (Low Molecular Dextran L Injection®; Otsuka Pharmaceuti-

Table 1. Patient Characteristics and Clinical Results

	TCFA group (n=124)	Non-TCFA group (n=137)	P-value
Age (years)	66±12	67±10	0.44
Male gender	96 (77)	103 (75)	0.67
Coronary risk factors			
Hypertension	78 (63)	94 (69)	0.33
Diabetes mellitus	47 (38)	57 (42)	0.54
Dyslipidemia	68 (55)	76 (56)	0.92
Current smoking	64 (52)	61 (45)	0.25
Family history	21 (17)	24 (18)	0.90
Obesity	33 (27)	32 (23)	0.54
Total cholesterol (ml/dl)	187.8±36.4	182.1±33.9	0.19
Triglyceride (mg/dl)	118.9±71.5	104.5±47.9	0.06
LDL-C (mg/dl)	120.7±31.1	110.0±28.1	0.004
HDL-C (mg/dl)	39.6±10.1	46.7±11.7	<0.001
LDL-C/HDL-C ratio	3.2±1.0	2.5±0.8	<0.001
HbA1c (%)	6.1±1.4	6.0±1.4	0.76
Peak CK (IU/L)	495 (119–2,071)	400 (99–2,016)	0.29
Peak CK-MB (IU/L)	45 (11–226)	28 (8–180)	0.14
hs-CRP (mg/dl)	0.14 (0.10–0.27)	0.19 (0.10–0.39)	0.003
STEMI	66 (53)	64 (47)	0.29
Pre-treatment TIMI flow grade			0.49
0	45 (36)	46 (34)	
1	13 (11)	14 (10)	
2	39 (31)	36 (26)	
3	27 (22)	41 (30)	
Post-treatment TIMI flow grade			0.38
0	0	0	
1	0	0	
2	16 (13)	13 (9)	
3	108 (87)	124 (91)	
Medication on admission			
ACEI or ARB	49 (40)	53 (39)	0.89
β -blocker	20 (16)	27 (20)	0.45
Statin	42 (34)	43 (31)	0.67
Insulin	9 (7)	17 (12)	0.17

Data given as mean±SD, median (IQR), or n (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CK, creatine kinase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MB, myocardial band; STEMI, ST-elevation myocardial infarction; TCFA, thin-cap fibroatheroma; TIMI, thrombolysis in myocardial infarction.

cal, Tokushima, Japan) via a guiding catheter at a rate of 2.5–4.5 ml/s using an auto injector pump (Mark V; Medrad, Warrendale, PA, USA) for both methods.^{20,21}

A total of 3,000 units unfractionated heparin were given every hour during the procedure to maintain an activated clotting time >300 s. In addition to initial loading of aspirin (100 mg) and clopidogrel (300 mg) prior to PCI, the following dual antiplatelet therapy was also used: aspirin (81 mg/day) and clopidogrel (75 mg/day) after stent implantation. No glycoprotein IIb/IIIa inhibitors were used in this study because these inhibitors have not been approved in Japan.

Analysis of OCT Images

The OCT findings were interpreted by 2 experienced OCT observers who were blinded to the angiographic and clinical data. When there was any discordance between the observers, a consensus reading was obtained. The culprit lesion was de-

termined on CAG, in conjunction with electrocardiography, echocardiography, and angiography. Then, OCT images were co-registered with angiograms using anatomical landmarks such as side branches, morphological features such as calcifications, and fluoroscopy. After identifying the culprit lesion, cap thickness was measured frame by frame to determine the thinnest site. When ruptured cap showed tapered shape, we measured starting point of the taper for cap thickness. If the starting point of the taper was the thinnest in the plaque, we adopted it as the thinnest fibrous cap thickness. For other cases, we simply adopted the thinnest part as the thinnest cap thickness regardless of the cap interval. The highest number of lipid quadrants was analyzed using the OCT frame containing the thinnest cap. OCT images were analyzed according to Consensus Standards for Acquisition, Measurement, and Reporting of Intravascular Optical Coherence Tomography Studies.²² Fibrous cap was identified as a tissue layer that is a signal-

Table 2. OCT Findings of Culprit Lesion

	TCFA group(n=124)	Non-TCFA group(n=137)	P-value
Plaque rupture	84 (68)	57 (42)	<0.001
Thrombus	100 (81)	79 (58)	<0.001
Calcification	70 (57)	70 (51)	0.386
Intimal vasculature	68 (55)	56 (41)	0.024
Fibrous cap thickness (μm)	55.8 $\pm$ 7.0	93.5 $\pm$ 20.0	<0.001
Lipid arc ($^{\circ}$)	145 $\pm$ 65	104 $\pm$ 53	<0.001
Lipid plaque			<0.001
0 $^{\circ}$	0	94 (69)	
1–90 $^{\circ}$	38 (31)	25 (18)	
91–180 $^{\circ}$	57 (46)	14 (10)	
181–360 $^{\circ}$	29 (23)	4 (3)	
Lipid length (mm)	15.7 $\pm$ 2.5	16.1 $\pm$ 1.4	0.242

Data given as mean $\pm$ SD or n (%).

OCT, optical coherence tomography. Other abbreviation as in Table 1.

rich homogenous region overlying a lipid core characterized by a diffusely bordered, signal-poor region on the OCT image.²² Lipid was semi-quantified according to the number of involved quadrants on the cross-sectional OCT image. Cap thickness was measured frame by frame and 3 times for each image to determine the thinnest site, and the average was calculated. In this study, TCFA was defined as plaque with lipid content in ≥ 1 quadrant and the thinnest part of the fibrous cap measuring $<70\mu\text{m}$ because the physical spatial resolution of any current commercially available OCT systems is $>10\mu\text{m}$ (Figure 1A).²³ Plaque rupture was defined as the presence of fibrous cap discontinuity and a cavity formation in the plaque.²⁴ Intracoronary thrombus was identified as a mass attached to the luminal surface or floating within the lumen. Calcification was identified as a signal-poor or heterogeneous region with a sharply delineated border (Figures 1B–D). Intimal vasculature appeared as a signal-poor void that was sharply delineated.

To assess the reproducibility of measurements, all OCT images were analyzed by 2 independent observers, and the plaque characterization and fibrous cap thickness were compared to examine inter-observer variability. To determine intra-observer variability, the images were analyzed again by the same 2 observers at least 2 weeks after the initial measurement, and these 2 measurements were compared.

Clinical and Biochemical Parameters

The following classical coronary risk factors were assessed: age, sex, hypertension (blood pressure $\geq 140/90$ mmHg, and/or a history of taking antihypertensive medication), diabetes mellitus (fasting plasma glucose ≥ 126 mg/dl, casual plasma glucose ≥ 200 mg/dl, or a diabetic pattern on 75-g oral glucose tolerance test), dyslipidemia (serum total cholesterol level ≥ 220 mg/dl), obesity (body mass index ≥ 25 kg/m²), current smoking, and family history.

Blood was collected in the emergency department. The blood samples were centrifuged, and the serum was removed and stored at -80°C until the assays could be performed. High-sensitivity C-reactive protein (hs-CRP) was analyzed using a commercially available testing kit (N-Latex CRP II; Dade Behring Marburg, Marburg, Germany).

Statistical Analysis

All statistical analyses were performed using SPSS version 11.0

(SPSS, Chicago, IL, USA). Data are expressed as mean $\pm$ SD deviation for normally distributed variables and median (interquartile range [IQR]) for skewed variables. Categorical data are presented as n (%). Differences between 2 groups were tested using unpaired t-test for normally distributed variables; Mann-Whitney test for skewed variables; and chi-squared test or Fisher's exact test as appropriate for categorical variables. Simple linear regression was used for assessing the correlation between 2 parameters. To test the intra- and inter-observer agreement, κ was calculated for TCFA and the correlation coefficient was calculated for fibrous cap thickness. In addition, the bias between observers was tested. Multivariate linear regression was used to identify the contributors for fibrous cap thickness and multivariate logistic regression was used to determine the contributors for presence of TCFA. Those variables that had $P<0.05$ on univariate analysis for the presence of TCFA (HDL-C, LDL-C, and hs-CRP) and clinically meaningful factors for plaque vulnerability (classical coronary risk factors and medication of statin and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker) were included in multivariate regression analysis. $P<0.05$ was considered statistically significant.

Results

Patient Characteristics and Clinical Results

TCFA at culprit site was observed in 124 (48%) of the 261 patients. Patient characteristics and clinical results at baseline for both groups are summarized in Table 1. There were no statistically significant differences between the 2 groups except for HDL-C level (TCFA, 39.6 $\pm$ 10.1 mg/dl vs. non-TCFA, 46.7 $\pm$ 11.7 mg/dl; $P<0.001$), LDL-C level (TCFA, 120.7 $\pm$ 31.1 mg/dl vs. non-TCFA, 110.0 $\pm$ 28.1 mg/dl; $P=0.004$), LDL-C/HDL-C ratio (TCFA, 3.2 $\pm$ 1.0 vs. non-TCFA, 2.5 $\pm$ 0.8; $P<0.001$), and hs-CRP level (TCFA, 0.14 mg/dl, IQR 0.10–0.27 mg/dl vs. non-TCFA, 0.19 mg/dl, IQR 0.10–0.39 mg/dl; $P=0.003$). There was no significant difference in terms of the time from onset to blood sampling between the 2 groups (TCFA, 2.6 h, IQR 1.7–4.3 h vs. non-TCFA, 2.8 h, IQR 2.0–4.0 h; $P=0.606$), although significant difference was observed in ST-elevation myocardial infarction (STEMI) vs. non-STEMI patients (2.5 h, IQR 1.9–3.5 h vs. 3.2 h, IQR 1.8–4.8 h; $P=0.012$).

OCT Findings

Culprit lesions were successfully observed on OCT without any serious complications. The median time from symptom onset to OCT was 4.2 h (IQR, 3.3–5.8 h). TD-OCT was used in 36 patients (14%) and FD-OCT in 225 patients. Pre-intervention OCT findings for both groups are summarized in **Table 2**. Plaque rupture (TCFA, 68% vs. non-TCFA, 42%; $P<0.001$), thrombus (TCFA, 81% vs. non-TCFA, 58%; $P<0.001$), and intimal vasculature (TCFA, 55% vs. non-TCFA, 41%; $P=0.024$) at the culprit lesion were significantly more prevalent in patients with TCFA. Lipid plaque was observed in 167 (64%) patients. Distribution of thinnest cap thickness is given in **Figure 2**.

The intra- and inter-observer agreements for TCFA were good (intra-observer, $\kappa=0.939$; inter-observer, $\kappa=0.923$, respectively) and the correlation coefficients were high for repeated measurements of fibrous cap thickness by the same observer (bias, $-0.9\mu\text{m}$; limits of agreement, -17.7 to $+16.1\mu\text{m}$, $r=0.923$) and by 2 different observers (bias, $-1.2\mu\text{m}$; limits of agreement, -18.7 to $+16.3\mu\text{m}$, $r=0.916$).

Lipoproteins and OCT Findings

HDL-C level was significantly correlated with fibrous cap thickness ($r=0.275$, $P<0.001$), but LDL-C, total cholesterol, and triglyceride levels were not (LDL-C, $r=-0.054$, $P=0.489$; total cholesterol, $r=0.044$, $P=0.572$; triglyceride, $r=-0.092$, $P=0.238$, respectively; **Figure 3**). Moreover, lipid arc was also significantly correlated with HDL-C level ($r=-0.180$, $P=0.020$), but not with LDL-C level ($r=0.065$, $P=0.402$). Lipid length was not associated with both HDL-C level ($r=-0.030$, $P=0.696$) and LDL-C level ($r=0.056$, $P=0.473$).

Contributing Factors to TCFA and Fibrous-Cap Thickness

On multivariate logistic regression model analysis, HDL-C level (odds ratio [OR], 0.930; 95% confidence interval [CI]: 0.904–0.958; $P<0.001$) and LDL-C level (OR, 1.015; 95% CI: 1.005–1.025; $P=0.002$) were independent contributors to TCFA at the culprit lesion (**Table 3**). In patients with lipid plaque, multivariate regression model analysis indicated that HDL-C level (β coefficient, 0.302; $P<0.001$), LDL-C level (β coefficient, -0.172 ; $P=0.008$), hs-CRP level (β coefficient, -0.145 ; $P=0.017$), and current smoking (β coefficient, -0.124 ; $P=0.028$) were independent contributors to fibrous cap thickness of the culprit lesion.

When we excluded patients with statin pre-treatment, HDL-C level (OR, 0.933; 95% CI: 0.901–0.965; $P<0.001$) and LDL-C level (OR, 1.020; 95% CI: 1.008–1.033; $P=0.001$) were also independent contributors to TCFA at the culprit lesion. In patients assessed using FD-OCT, both HDL-C level and LDL-C level were independent contributors to TCFA at the culprit lesion. Furthermore, HDL-C level, LDL-C level, and hs-CRP level were also independent contributors to fibrous cap thickness of the culprit lesion.

Discussion

This study has shown that HDL-C is associated with the presence of TCFA and fibrous cap thickness at the culprit lesion. Furthermore, LDL-C, hs-CRP, and smoking were related to plaque vulnerability in patients with ACS.

Lipid Profile and Vulnerable Plaque

Many clinical trials using statin to lower LDL-C have consistently demonstrated substantial reductions in major cardiovascular events.^{1–7} In spite of the statin therapy, there remains a

Table 3. Contributors to TCFA

	OR	95% CI	P-value
hs-CRP (mg/dl)	2.124	0.930–4.848	0.074
LDL-C (mg/dl)	1.015	1.005–1.025	0.002
HDL-C (mg/dl)	0.930	0.904–0.958	<0.001

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

residual risk in patients with well-controlled LDL-C level. In the Framingham Heart Study, HDL-C level was a more potent risk factor for CAD than LDL-C.¹³ It was also reported that HDL-C level was a predictive factor of major cardiovascular events in patients treated with statin, even when LDL-C level was $<70\text{ mg/dl}$.²⁵ The “pleiotropic effects” of statins may contribute to plaque stabilization. In the present study, however, when we excluded patients with statin pre-treatment, HDL-C and LDL-C levels were also independent contributors to TCFA at the culprit lesion. It could be possible that statin treatment prevented ACS in some patients via plaque stabilization and thus they were not entered into this study. A different design would be required to evaluate this hypothesis. The present result that HDL-C had an effect on fibrous cap thickening after adjustment for LDL-C could be the missing link between HDL-C level and CAD risk.

Several studies have reported that low HDL-C level is an important risk factor for CAD,²⁶ and HDL-C has various potentially anti-atherogenic properties, including the mediation of reverse transport of cholesterol from cells of the arterial wall to the liver and steroidogenic organs.^{27–29} Reverse cholesterol transport describes the metabolism and an important anti-atherogenic function of HDL-C, namely, HDL-C-mediated efflux of cholesterol from non-hepatic cells and its subsequent delivery to the liver and steroidogenic organs, in which it is used for the synthesis of lipoprotein, bile acids, vitamin D, and steroid hormones.^{27–29} Khera et al reported that the ability of HDL-C to promote cholesterol efflux from macrophage foam cells was strongly and inversely associated with both sub-clinical atherosclerosis and obstructive CAD.³⁰ According to the present results, a treatment strategy solely targeting LDL-C with statin may not be sufficient for CAD management. Therapeutic lipid treatment strategies that involve additional targets beyond LDL-C reduction are needed to improve clinical outcome and it is necessary to pay more attention to modulation of HDL-C similarly to that of LDL-C. Furthermore, it has been reported that low HDL-C is also caused by smoking:³¹ current smokers were less common in the higher HDL-C levels,²⁵ and HDL-C and current smoking were independent determinants of plaque rupture.³² These data are in accordance with the present results.

Inflammation and Plaque Stability

Inflammation plays an important role in the development and destabilization of atherosclerotic plaque.³³ We have previously reported that broken fibrous cap thickness in ruptured plaque had an inverse correlation with hs-CRP level.²⁴ Another study demonstrated that hs-CRP was associated with positive remodeling, fibrous cap thickness, and the presence of TCFA.^{34,35} The current finding that the TCFA group had higher hs-CRP suggests that hs-CRP may also serve as a surrogate marker for plaque stability during HDL-C-targeting lipid therapy. Alwaili et al reported that the ability of HDL-C to promote cholesterol efflux was preserved in ACS, but that the

HDL-C proteome increased in ACS patients.³⁶ Inflammatory proteins in HDL-C from ACS patients might alter the protective effects of HDL-C on the atherosclerosis plaque. Therefore, simple use of HDL-C as a biomarker should be done with caution. Further study is needed in the near future.

Study Limitations

The present study had a number of limitations. First, the limited penetration depth of OCT does not allow for evaluation of plaque volume.³⁷ Therefore, it is difficult to estimate and quantify the amount of lipids on OCT, without spectroscopy.³⁸ Second, in the present study, 179 patients (69%) had thrombus. Furthermore, among them, 32 (12%) had remaining thrombi that might disturb observation of fibrous cap even after thrombectomy. This intracoronary thrombus at a culprit site may also affect OCT, especially the measurement of fibrous cap thickness, given that thrombus limits the penetration of light or the presence of thrombus itself hinders observation of the microstructure of plaque. Therefore, it is possible that some TCFA might be misdiagnosed as non-TCFA. Third, we did not perform a 3-vessel assessment, therefore it is possible that some patients might have a vulnerable plaque in another coronary artery as previously reported.³⁹ Fourth, the frame level definition of TCFA is deficient because plaque morphology is inherently a 3-D phenomenon. Fifth, the present subjects consisted of patients with 2 different conditions: STEMI and non-STEMI. The physiopathology of non-STEMI is much less uniform, ranging from a situation similar to STEMI to a mismatch between a severe chronic coronary pathology with severe old lesions and a sudden increase in oxygen demand from the myocardium. In such case, there would be a possibility that OCT might mis-identify the culprit site. Sixth, the number of patients with lipid plaque in the non-TCFA group might have been too small to draw a conclusion. Seventh, discussion would be needed for measurement of broken fibrous cap thickness. Finally, the exclusion of patients without adequate blood flow even after aspiration thrombectomy means that the present results may not be completely representative of all patients with ACS.

Conclusions

HDL-C is independently correlated with fibrous cap thickness of the culprit lesion in patients with ACS, as well as LDL-C, hs-CRP and current smoking. In addition, the clinical background would be different between patients with and without TCFA. This suggests that various mechanisms are involved in provoking ACS. HDL-C may be considered as a therapeutic target for plaque stabilization.

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