Vulnerable Plaque Detection:
Between Biological & Morphological (OCT) Approach

Takashi Akasaka, MD, PhD, FESC
Department of Cardiovascular Medicine
Wakayama Medical University, Japan

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Wakayama Medical University

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- **Grant/Research Support** : **Abbott Vascular Japan**
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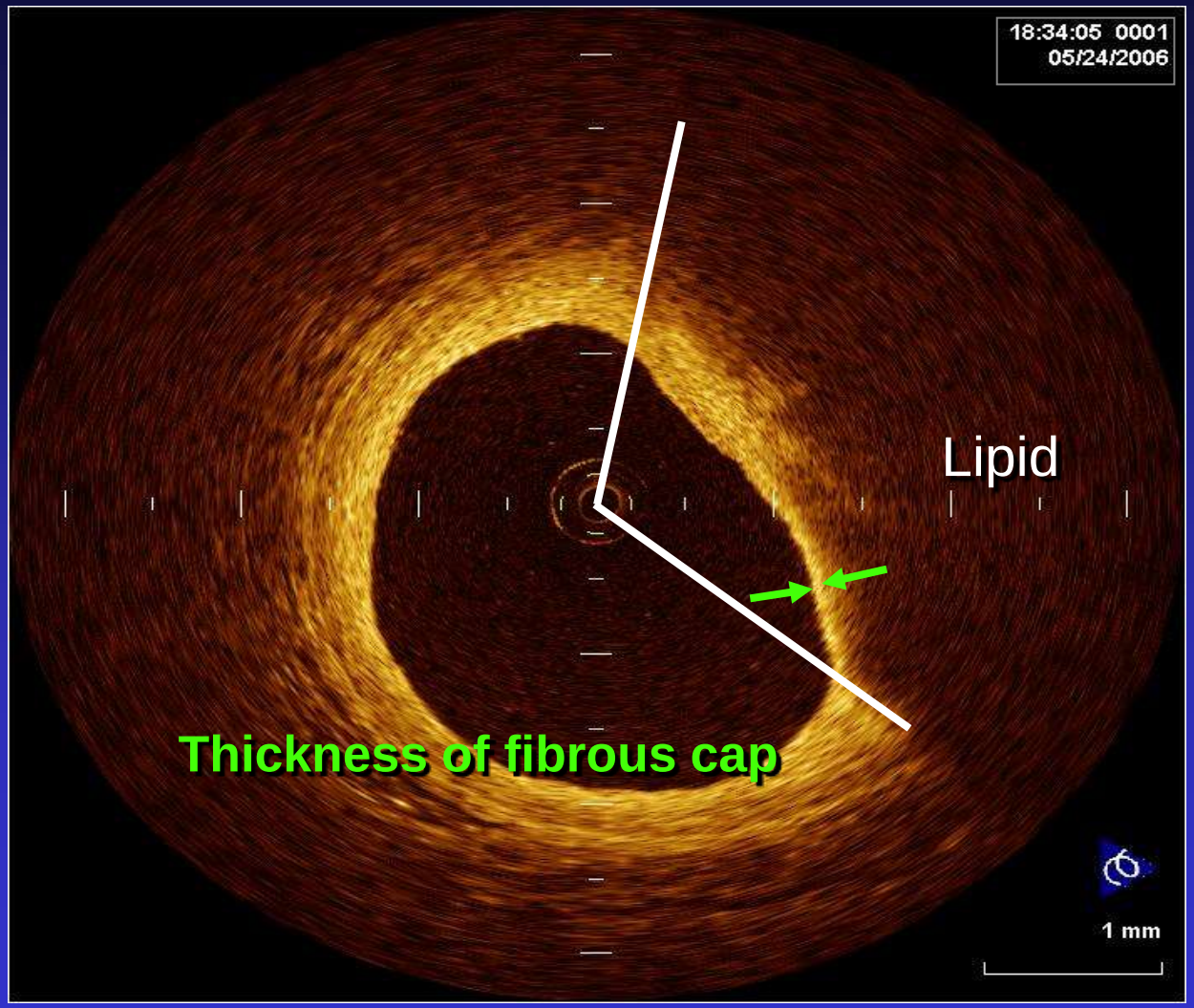
  St. Jude Medical Japan
  Terumo Inc.

Thin-capped Fibroatheroma (TCFA)



TCFA was defined as a plaque with lipid content in more than 2 quadrants and the thinnest part of a fibrous cap measuring less than 65 μm by histology.

The cap thickness is measured from the surface of the lumen to the portion just starting the attenuation.

TCFA is thought to be a plaque prone to rupture and vulnerable

Identification of vulnerable plaque

- Plaque prone to disruption

960 TCFA
f/u:38 (1-72) months

Rupture (-)

Rupture (+) 13

8 Event (-)

Silent plaque rupture

Event (+) 5

UAP 2

AMI 3

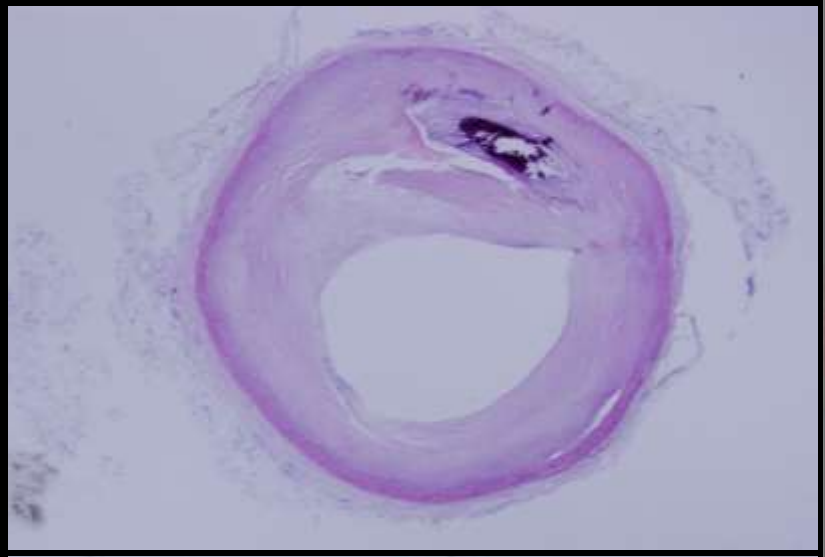
Sudden cardiac death 0

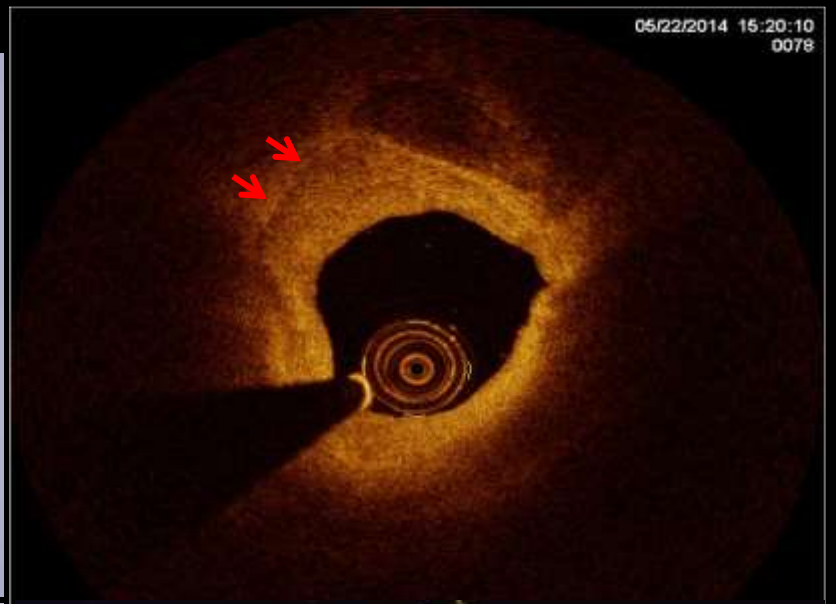
13 lesions assessed by OCT before plaque rupture

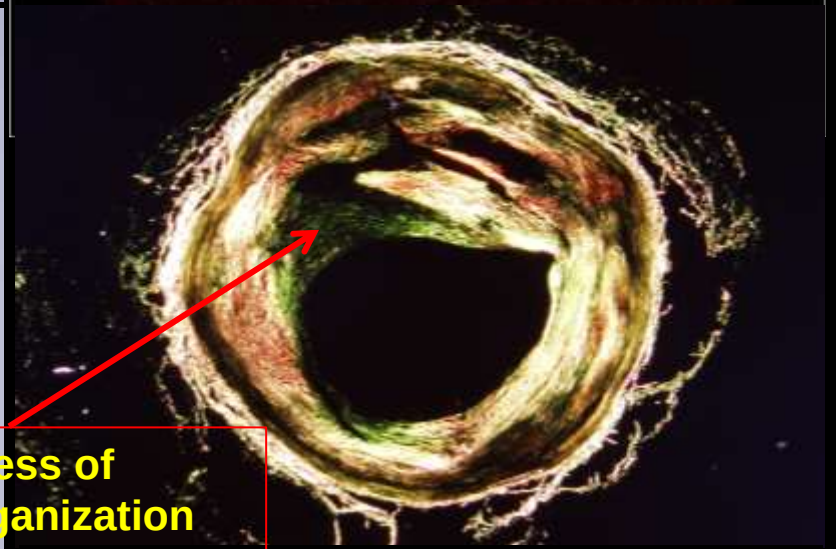
	1st OCT (Baseline)					2nd OCT (Follow-up)	
Case	Vessels	TCFA	Fibrous-cap thickness (μm)	Lipid-arc (degree)	Macro phages	Duration (M)	Clinical presentation
1	RCA	+	60	360	-	7	subclinical
2	LCX	+	60	360	+	11	subclinical
3	RCA	-	140	210	+	8	subclinical
4	LCX	+	50	330	+	7	UAP
5	LCX	-	110	270	-	3	AMI
6	LAD	+	40	270	+	8	UAP
7	RCA	+	50	170	+	9	subclinical
8	RCA	+	40	210	+	10	subclinical
9	RCA	-	80	150	-	9	subclinical
10	RCA	+	40	340	+	1	subclinical
11	RCA	-	100	360	-	27	AMI
12	RCA	+	60	270	+	5	NSTEMI
13	LAD	+	80	360	+	27	NSTEMI

An Example of layered structure

HE







S/O process of
thrombus organization

Sirius red stain
(Collagen : red)

Sirius red stain with polarized
Type Ⅲ (immature) collagen : green
Type Ⅰ (mature) collagen: orange

Vulnerable Plaque Detection: How to improve ?

OCT Findings of Culprit Lesions

	STEMI (n=40)	NSTEACS (n=49)	p value
Plaque rupture, n(%)	28(70)	23(47)	0.033
Lipid-rich plaque (>=2 quadrants), n(%)	36(90)	35(71)	0.036
Fibrous cap thickness, μm	55±20	109±55	<0.0001
TCFA, n(%)	31(78)	24(49)	0.008
Thrombus, n(%)			<0.0001
Red thrombus	31(78)	13(27)	
White thrombus	9(22)	20(41)	
None	0(0)	16(32)	

（Ino Y, et al. JACC Cardiovasc Interv. 2011;4:76-82）

OCT Findings of Ruptured Plaque

	STEMI (n=28)	NSTEACS (n=23)	P value
Maximum ruptured cavity CSA, mm^2	2.52±1.36	1.67±1.37	0.034
Lumen CSA at maximum ruptured cavity site, mm^2	2.44±1.34	2.96±1.91	0.250
Minimum lumen CSA, mm^2	1.95±0.80	1.88±0.86	0.756
Longitudinal morphological features of plaque rupture, n(%)			0.036
Proximal-type	13(46)	4(17)	
Mid-type	12(43)	11(48)	
Distal-type	3(11)	8(35)	

（Ino Y, et al. JACC Cardiovasc Interv. 2011;4:76-82）

Difference of ruptured plaque morphology between asymptomatic coronary artery disease and non-ST elevation acute coronary syndrome patients: An optical coherence tomography study

Kunihiro Shimamura, Yasushi Ino*, Takashi Kubo, Tsuyoshi Nishiguchi, Takashi Tanimoto, Yuichi Ozaki, Keisuke Satogami, Makoto Orii, Yasutsugu Shiono, Kenichi Komukai, Takashi Yamano, Yoshiki Matsuo, Hironori Kitabata, Tomoyuki Yamaguchi, Kumiko Hirata, Atsushi Tanaka, Toshio Imanishi, Takashi Akasaka

Department of Cardiovascular Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-8509, Japan

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ABSTRACT

Background: Autopsy studies have reported that rupture of a thin-cap fibroatheroma and subsequent thrombus formation is the major mechanism leading to acute coronary syndrome (ACS). However, it is not clear why only some plaque ruptures lead to ACS. Optical coherence tomography (OCT) is a high-resolution imaging modality which is capable of investigating detailed coronary plaque morphology in vivo. The objective of this study was to determine whether ruptured plaque morphology assessed by OCT differs between asymptomatic coronary artery disease (CAD) and non-ST elevation acute coronary syndrome (NSTEACS).

Methods: We examined ruptured plaque morphology using OCT in 80 patients, 33 with asymptomatic CAD and 47 with NSTEACS.

Results: The frequency of lipid-rich plaque and intracoronary thrombus was significantly lower in asymptomatic CAD than in NSTEACS (61% vs. 85%, $p = 0.013$ and 9% vs. 83%, $p < 0.001$, respectively). Although maximal ruptured cavity cross-sectional area (CSA) was similar in both groups, lumen area at the rupture site and minimal lumen area were significantly larger in asymptomatic CAD than in NSTEACS (3.78 ± 1.50 mm^2 vs. 2.70 ± 1.55 mm^2, $p = 0.003$ and 2.75 ± 0.99 mm^2 vs. 1.72 ± 0.90 mm^2, $p < 0.001$, respectively).

Conclusions: OCT revealed that the morphology of ruptured plaques differs between asymptomatic CAD and NSTEACS in terms of lumen area and the frequency of lipid-rich plaques and thrombi. These morphological features may be associated with the clinical presentation of CAD.

Table 3

OCT findings of target lesions.

	Asymptomatic CAD ($n = 33$)	NSTEACS ($n = 47$)	p-Value
Lipid-rich plaque, n (%)	22 (67)	40 (85)	0.013
Lipid arc, degree	133 ± 71	169 ± 71	0.031
Thrombus, n (%)	3 (9)	39 (83)	<0.001
Red thrombus, n (%)	0 (0)	15 (32)	<0.001
White thrombus, n (%)	3 (9)	24 (51)	<0.001
Ruptured cap thickness, μm	69 ± 24	62 ± 22	0.165
Maximal ruptured cavity area, mm^2	1.63 ± 0.86	1.66 ± 1.35	0.884
Lumen area at rupture site, mm^2	3.78 ± 1.50	2.70 ± 1.55	0.003
MLA, mm^2	2.75 ± 0.99	1.72 ± 0.90	<0.001
Location of maximum ruptured cavity			0.380
Proximal to the MLA site, n (%)	9 (27)	10 (21)	
MLA site, n (%)	11 (33)	23 (49)	
Distal to the MLA site, n (%)	13 (40)	14 (30)	

Values are given as n (%) or mean ± standard deviation. CAD = coronary artery disease; MLA = minimal lumen area; NSTEACS = non-ST elevation acute coronary syndrome.

Table 4

OCT findings of target lesions after excluding patients with thrombus aspiration.

	Asymptomatic CAD ($n = 33$)	NSTEACS ($n = 32$)	p-Value
Lipid-rich plaque, n (%)	22 (67)	28 (88)	0.046
Lipid arc, degree	133 ± 71	171 ± 71	0.037
Thrombus, n (%)	3 (9)	25 (78)	<0.001
Red thrombus, n (%)	0 (0)	9 (28)	<0.001
White thrombus, n (%)	3 (9)	16 (50)	<0.001
Ruptured cap thickness, μm	69 ± 24	60 ± 23	0.142
Maximal ruptured cavity area, mm^2	1.63 ± 0.86	1.79 ± 1.43	0.573
Lumen area at rupture site, mm^2	3.78 ± 1.50	2.76 ± 1.58	0.009
MLA, mm^2	2.75 ± 0.99	1.79 ± 0.92	<0.001
Location of maximum ruptured cavity			0.538
Proximal to the MLA site, n (%)	9 (27)	7 (22)	
MLA site, n (%)	11 (33)	15 (47)	
Distal to the MLA site, n (%)	13 (40)	10 (31)	

Values are given as n (%) or mean ± standard deviation. CAD = coronary artery disease; MLA = minimal lumen area; NSTEACS = non-ST elevation acute coronary syndrome.

Vulnerable Plaque Detection: How to improve ?

- Not only the presence of TCFA but also the amount of plaque burden, MLD, MLA, the presence of thrombus, and so on would improve to detect vulnerable plaque .

Vulnerable Plaque Detection: How to improve ?

- Not only the presence of TCFA but also the amount of plaque burden, MLD, MLA, the presence of thrombus, and so on would improve to detect vulnerable plaque .
- Biological inflammatory markers, such as hs-CRP, various type of cytokines, etc. may allow us to support in identifing VP more correctly in addition to plaque characteristics.

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Inflammatory markers and plaque morphology: An optical coherence tomography study

Konstantina P. Bouki [a,*],
Konstantinos P. Toutouz
Georgios K. Liakos [b], Thc

[a] Second Department of Cardiology, Gene
[b] Department of Biochemistry, General H
[c] Medical School of Athens University, Hi

ABSTRACT

Background: OCT with its unique image resolution is the ideal method to detect culprit lesion characteristics in different clinical presentations. The identification of inflammatory markers related to plaque characteristics may be of clinical importance.

Methods: Thirty-two patients with acute coronary syndromes (ACS) and fourteen patients with stable angina pectoris (SAP) were enrolled in this study. Culprit lesion morphology was assessed by optical coherence tomography (OCT) in patients with ACS and SAP. The possible relations between serum levels of high sensitivity-C reactive protein (hs-CRP) and interleukin-18 (IL-18) with plaque characteristics were investigated in those patients.

Results: Plaque rupture and thin-cap fibroatheroma (TCFA) were detected more frequently in ACS patients compared with SAP patients, (78.6% vs. 14.3%, $p<0.001$, 92.9% vs. 14.3%, $p<0.001$, respectively). Higher levels of serum hs-CRP and IL-18 were found in patients with plaque rupture vs. those with no plaque rupture (median value: 19.2 mg/L vs. 1.6 mg/L, $p<0.001$ and 219.5 pg/ml vs. 127.5 pg/ml, $p=0.001$ respectively), and TCFA vs. those without TCFA (median value: 15.2 mg/L vs. 1.6 mg/L, $p=0.004$ and 209.0 pg/ml vs.153.2 pg/ml, $p=0.03$ respectively). Serum hs-CRP was the only independent predictor of plaque rupture ($p=0.02$, odds ratio 1.1, 95% confidence interval 1.0 to 1.2). A cut-off value of hs-CRP>4.5 mg/L could detect ruptured plaque with a sensitivity of 91.7% and a specificity of 77.8%.

Conclusions: OCT detected plaque rupture and TCFA more frequent in ACS patients compared with SAP. Elevated hs-CRP and IL-18 were positively related to plaque instability and rupture.

Baseline patients' characteristics.

	ACS group n = 32	SAP group n = 14	p value
Age (years)	61 ± 11	65 ± 10	0.9
Male gender	30 (94.0)	12 (86.0)	0.3
Hypertension	20 (62.5)	8 (57.1)	0.7
Diabetes mellitus	8 (25.0)	6 (42.9)	0.3
Cigarette smoking	20 (62.5)	6 (42.9)	0.3
Total cholesterol	161.3 ± 33.9	183.8 ± 52.4	0.1
HDL cholesterol	32.0 ± 7.6	35.8 ± 5.8	0.05
LDL cholesterol	103.0 ± 29.0	116.6 ± 38.4	0.4
Triglycerides	163.7 ± 34.5	148.9 ± 49.7	0.2
hs-CRP (mg/L), median (min–max)	15.2 (0.5–70.4)	1.6 (0.7–7.9)	0.001
IL-18 (pg/ml), median (min–max)	197.5 (123.0–370.0)	113.5 (99.4–259.0)	0.03
Culprit vessel			0.089
LAD	12 (37.5)	4 (28.6)	
CX	12 (37.5)	2 (14.3)	
RCA	8 (25.0)	8 (57.1)	

Values are mean ± SD or n (%).

Bouki KP, et al. Int J Cardiol, 2012;154; 287- 292

OCT plaque characteristics and serum levels of inflammatory markers.

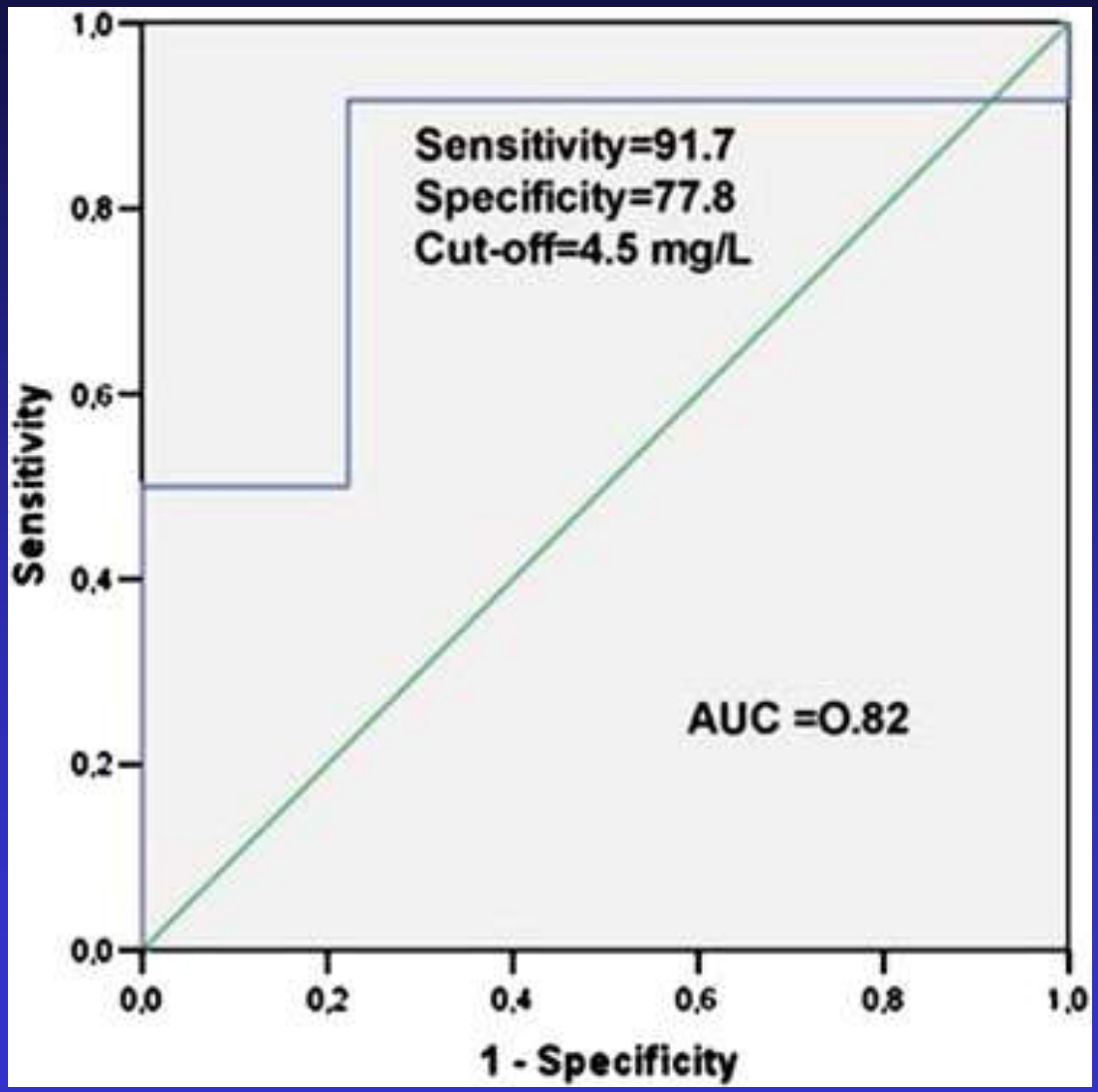
		Number n = 42	hs-CRP (mg/L)	p value	IL-18 (pg/ml)	p value
TCFA	Yes	28	15.2 (0.5–70.4)	0.004	209.0 (123.0–370.0)	0.03
	No	14	1.6 (0.7–63.6)		153.2 (99.4–259.0)	
RUPTURE	Yes	24	19.2 (0.5–70.4)	<0.001	219.5 (143.0–370.0)	0.001
	No	18	1.6 (0.7–17.8)		127.5 (99.4–259.0)	
THROMBUS	Yes	17	10.1 (0.5–54.8)	0.3	216.0 (143.0–306.0)	0.1
	No	25	2.9 (0.7–70.4)		193.0 (99.4–370.0)	
CALCIUM	Yes	22	6.0 (0.7–33.7)	0.2	132.0 (99.4–370.0)	0.002
	No	20	12.5 (0.5–70.4)		216.0 (164.0–306.0)	

Values are n, or median (min–max).

Bouki KP, et al. Int J Cardiol, 2012;154; 287- 292

ROC curve of hs-CRP for the prediction of plaque rupture in patients with ACS and SAP

Bouki KP, et al. Int J Cardiol, 2012;154; 287- 292



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Circulating malondialdehyde-modified low-density lipoprotein levels are associated with the presence of thin-cap fibroatheromas determined by optical coherence tomography in coronary artery disease

Yoshiki Matsuo[1]*, Takashi Kubo[1], Yasushi Okumoto[1], Kohei Ishibashi[2], Kenichi Kor
Kumiko Hir

[1]Division of Cardiology, S
University, Tanabe, Waka

Received 30 October 2011

Aims The importance of oxidized low-density lipoprotein (oxLDL) has been implicated in the process of plaque rupture. However, few previous studies demonstrated the relationship between plaque morphology and oxLDL. We evaluated the relationship between coronary plaque vulnerability assessed by optical coherence tomography (OCT) and circulating malondialdehyde-modified low-density lipoprotein (MDA-LDL).

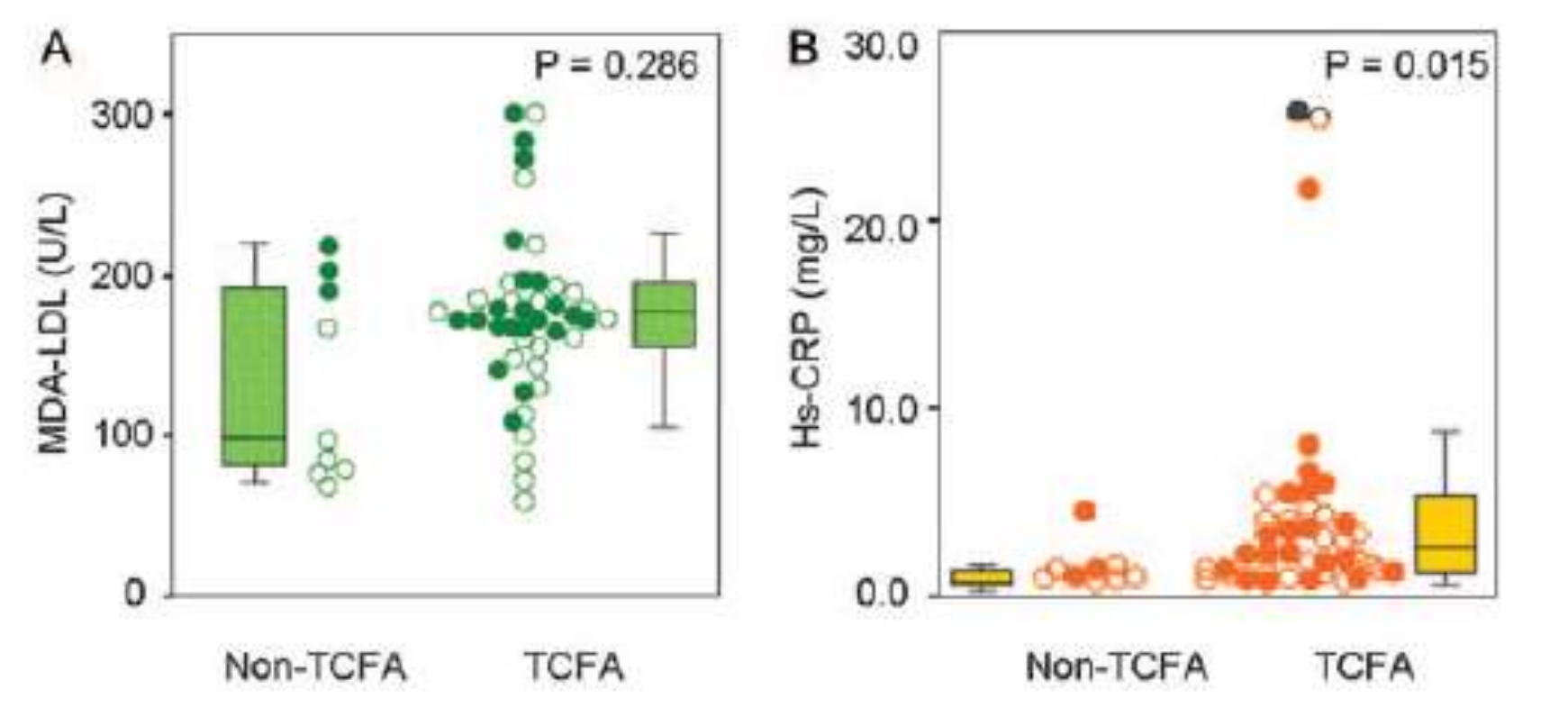
Methods and results OCT was used to determine plaque vulnerability in 102 patients with acute coronary syndrome (ACS; $n = 53$) and stable angina pectoris (SAP; $n = 49$). Circulating levels of MDA-LDL were measured by using enzyme-linked immunosorbent assay. Thin-cap fibroatheromas (TCFAs; defined as lipid-rich with plaque cap thickness < 65 μm) were detected more frequently in ACS than in SAP (83% vs. 16%, $P < 0.001$). The circulating levels of MDA-LDL were significantly higher in patients with ACS compared with SAP ($P = 0.008$). The levels of MDA-LDL were significantly higher in SAP patients with TCFA than those with non-TCFA ($P < 0.001$). Although the levels of MDA-LDL were not significant between ACS patients with TCFA and those with non-TCFA, patients with ruptured TCFA had higher levels of MDA-LDL compared with those with morphologically intact TCFA ($P = 0.023$). MDA-LDL levels were associated with the presence of TCFA (odds ratio, 1.45 per 10-unit increment of MDA-LDL; 95% CI, 1.24–1.68; $P < 0.001$) in multivariable logistic regression analysis.

Conclusion Circulating MDA-LDL levels might be associated with the presence of TCFA in the culprit lesion.

（Matsuo Y, et al. Eur Heart J Cardiovasc Img. 2013;14:43-50）

Circulation MDA-LDL & hs-CRP in cases with and without TCFA in ACS

（Matsuo Y, et al. Eur Heart J Cardiovasc Img. 2013;14:43-50）

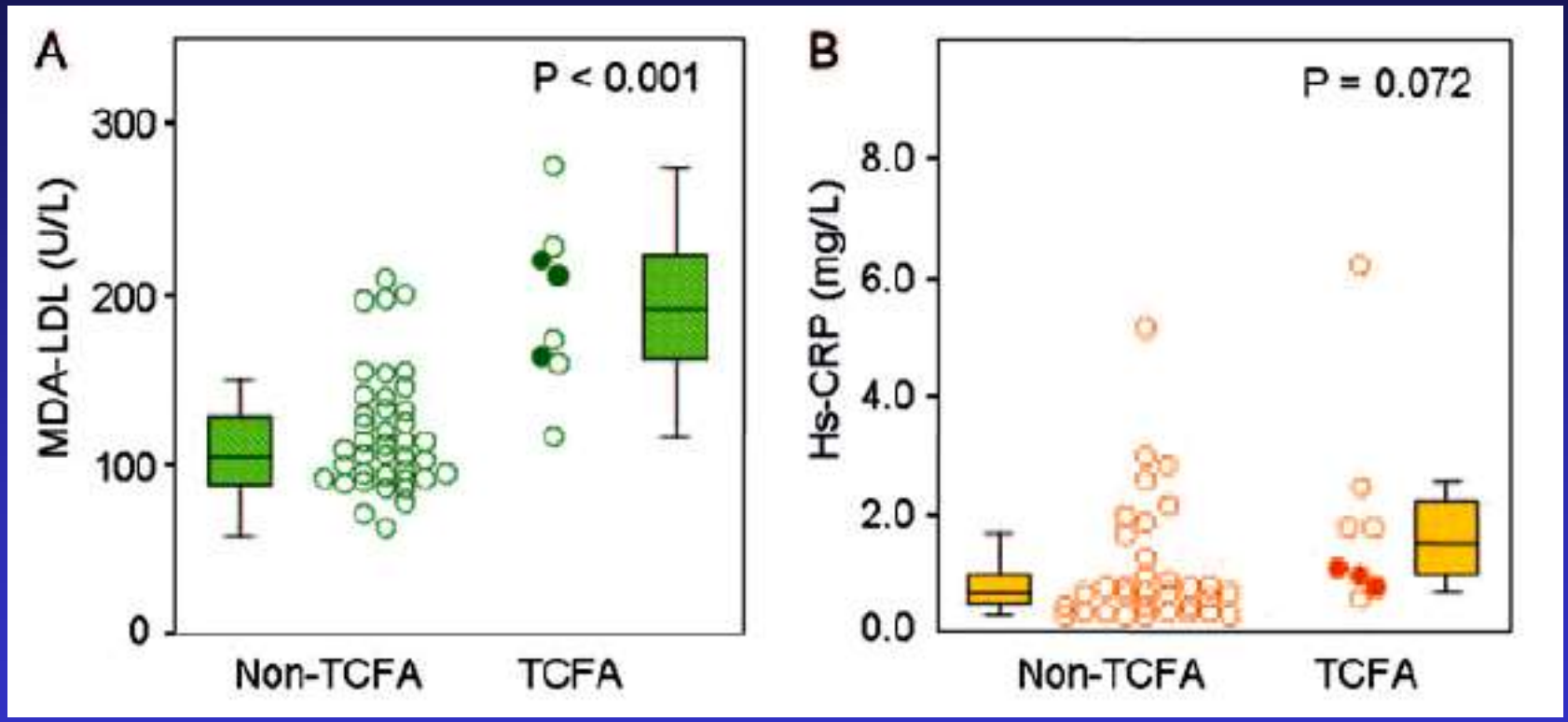


● Rupture

○ Non-rupture

Circulation MDA-LDL & hs-CRP in cases with and without TCFA within stable angina

（Matsuo Y, et al. Eur Heart J Cardiovasc Img. 2013;14:43-50）



● Rupture

○ Non-rupture

Table 4 Multivariate logistic regression model for the presence of TCFA

Variables	Odds ratio	95% CI	*P*
Age	0.97	0.90–1.05	0.51
Male gender	1.16	0.32–4.23	0.82
Hypertension	0.98	0.29–3.34	0.97
Diabetes	2.93	0.76–11.3	0.12
Smoking	1.49	0.34–6.57	0.60
Dyslipidaemia	1.34	0.42–4.22	0.62
MDA-LDL (per 10-unit increment)	1.45	1.24–1.68	<0.001
log CRP	3.98	1.47–10.7	0.006

MDA-LDL, malondialdehyde-modified low-density lipoprotein cholesterol; log CRP, natural logarithm of high-sensitivity C-reactive protein; TCFA, thin-cap fibroatheroma.

（Matsuo Y, et al. Eur Heart J Cardiovasc Img. 2013;14:43-50）

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Soluble lectin-like oxidized LDL receptor-1 (sLOX-1) as a valuable diagnostic marker for rupture of thin-cap fibroatheroma: Verification by optical coherence tomography☆,☆☆

Nobuaki Kobayashi [a,*], Masam
Shinya Yokoyama [a], Takuro Sh
Yoshihiko Seino [b], Kyoichi Miz

[a] Division of Intensive Care Unit, Chiba-Hokusoh Ho
[b] Cardiovascular Center, Chiba-Hokusoh Hospital, N
[c] Division of Clinical Pharmacy, Faculty of Pharmace
[d] Department of Hygiene and Public Health, Nippon
[e] Division of Cardiology, Nippon Medical School, Tok

ABSTRACT

Background: Relationships between plaque morphology on optical coherence tomography (OCT) and biomarker levels in the patients with acute coronary syndrome (ACS) have not been fully investigated.

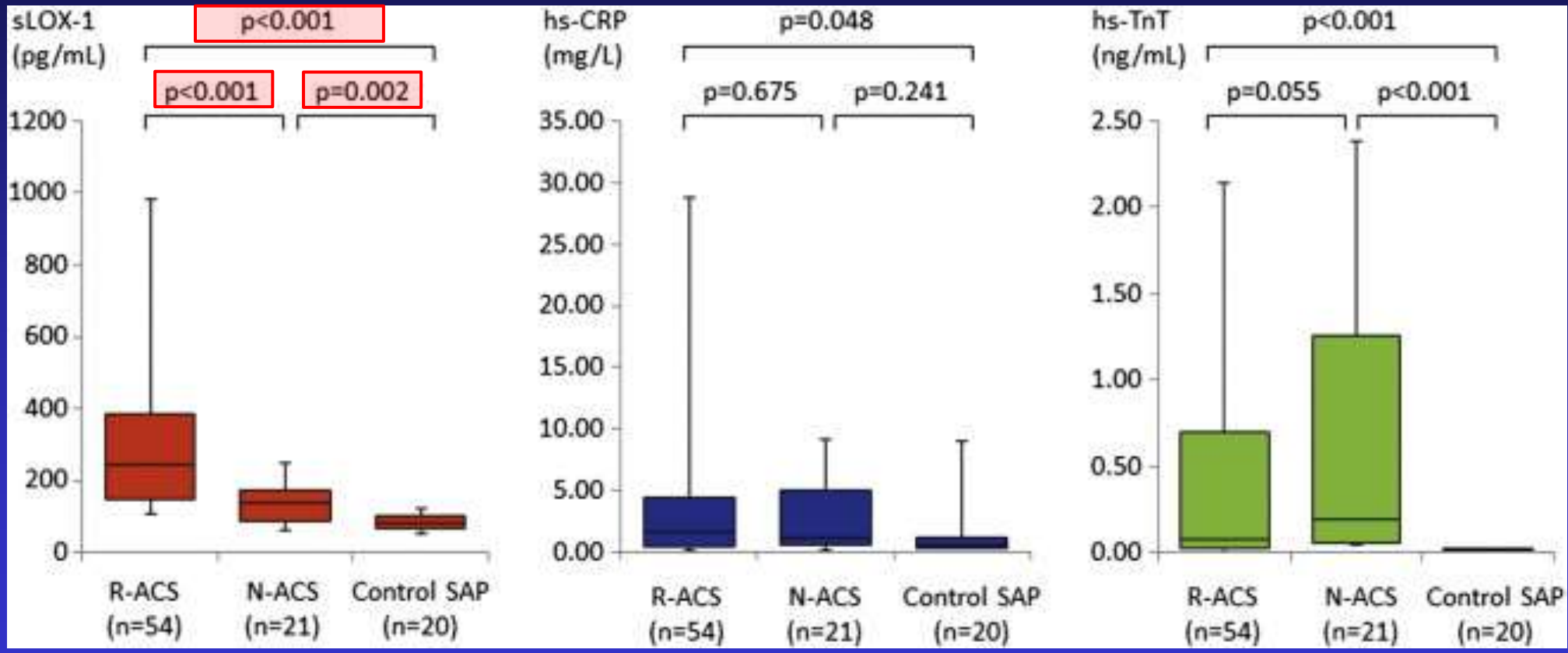
Methods: ACS patients (n = 128) were prospectively enrolled and their plasma levels of soluble lectin-like oxidized LDL receptor-1 (sLOX-1), high-sensitivity C-reactive protein (hs-CRP), and high-sensitivity troponin T (hs-TnT) were measured. Another set of 20 patients with stable angina pectoris (SAP) without plaque rupture or erosion served as controls. Among 128 ACS patients, 75 patients underwent OCT procedure to evaluate culprit plaque morphology, and were categorized into two groups; ACS with plaque rupture (ruptured ACS; R-ACS, n = 54) and ACS without plaque rupture (non-ruptured ACS; N-ACS, n = 21).

Results: Levels of sLOX-1 ($p < 0.001$), hs-CRP ($p = 0.048$) and hs-TnT ($p < 0.001$) were significantly higher in R-ACS than SAP. Levels of sLOX-1 were also significantly higher in R-ACS than in N-ACS ($p < 0.001$); whereas levels of hs-CRP ($p = 0.675$), as well as those of hs-TnT ($p = 0.055$), were comparable between R-ACS and N-ACS. Comparison of receiver operating characteristic (ROC) curves among sLOX-1, hs-CRP and hs-TnT to differentiate R-ACS from N-ACS revealed that the area under the curve (AUC) values of sLOX-1, hs-CRP and hs-TnT were 0.782, 0.531 and 0.643, respectively. ROC curves, generated for these biomarkers, to differentiate ACS with thin-cap fibroatheroma (TCFA) from those without demonstrated that the AUC values of sLOX-1, hs-CRP and hs-TnT were 0.718, 0.506 and 0.524, respectively.

Conclusion: sLOX-1, but not hs-CRP or hs-TnT, can differentiate ACS with plaque rupture from those without, and ACS with TCFA from those without.

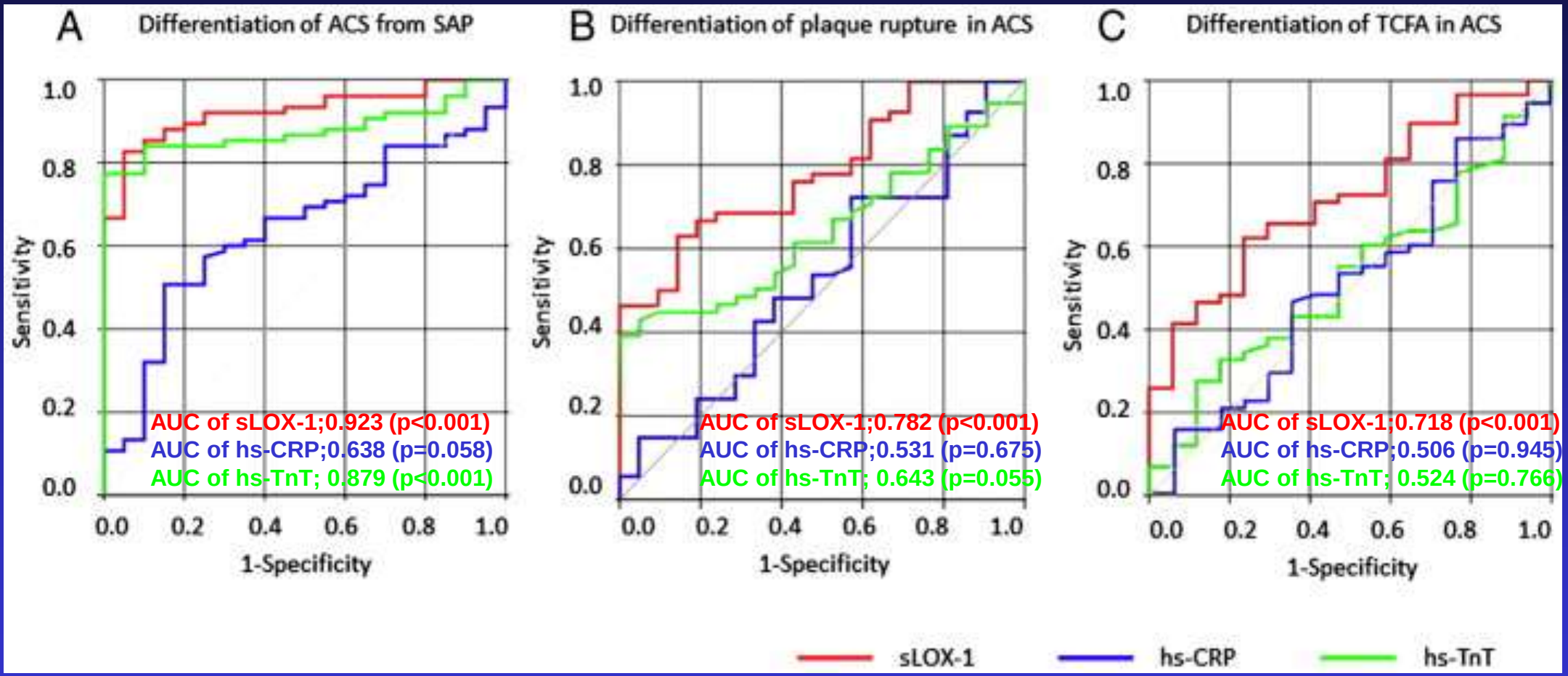
Comparison of sLOX-1, hs-CRP and hs-TnT levels among plaque rupture, non-rupture and control.

Kobayashi N, et a. Int J Cardiol 2013;168:3217-3223



R-ACS; Ruptured-ACS, N-ACS; Non-ruptured ACS, SAP; stable effort angina

ROC curve analyses of sLOX-1, hs-CRP & hs-TnT for differentiation of plaque rupture and TCFA in ACS

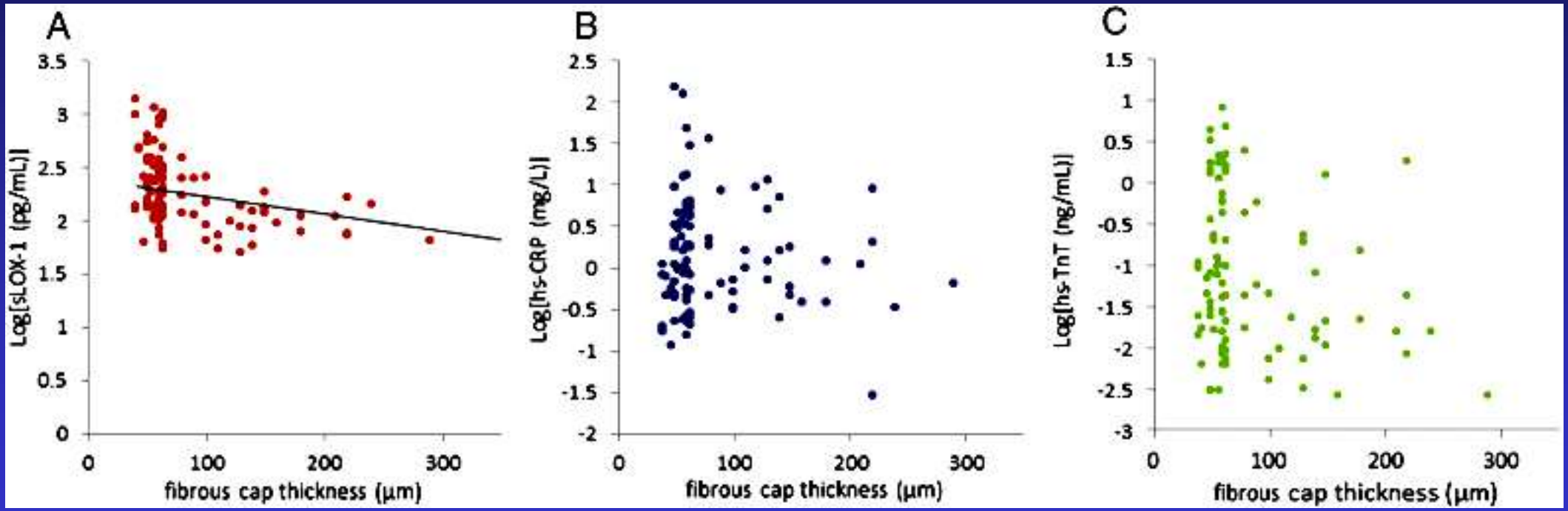


Kobayashi N, et a. Int J Cardiol 2013;168:3217-3223

Correlation between fibrous cap thickness & biomarkers levels

Kobayashi N, et a. Int J Cardiol 2013;168:3217-3223

sLOX-1 hs-CRP hs-TnT



Methods

Consecutive 160 NSTEACS patients who underwent emergency PCI

Exclusion:
3 left main, 6 CHF, 8 CKD (Cr>1.5 mg/dl)
12 lipid-lowering therapy

110 patients could be evaluated by IVUS & OCT

9-month follow-up period

28 patients withdraw

82 patients were enrolled in this study

58 patients (71%) received statin during follow up

OCT and IVUS study :

Measured plaque :

Non-culprit site atheroma (>10mm proximal or distal to the PCI site)

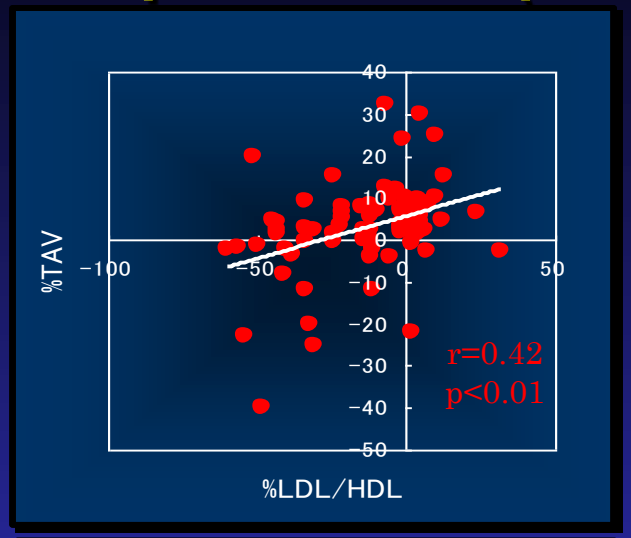
Analysis

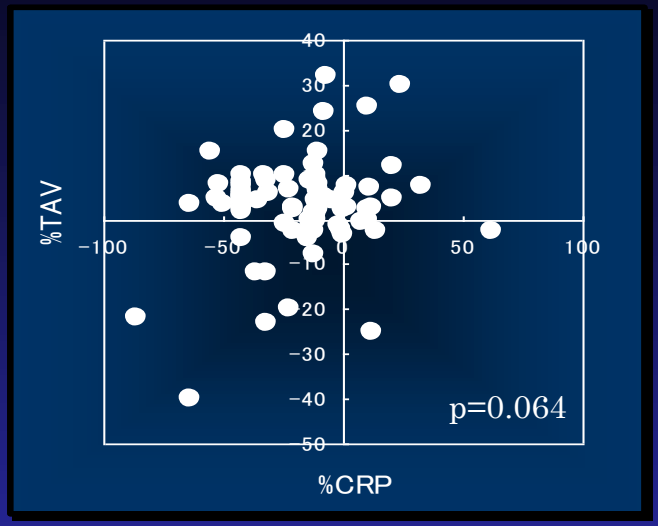
Fibrous-cap thickness (OCT)
Total atheroma volume (IVUS)

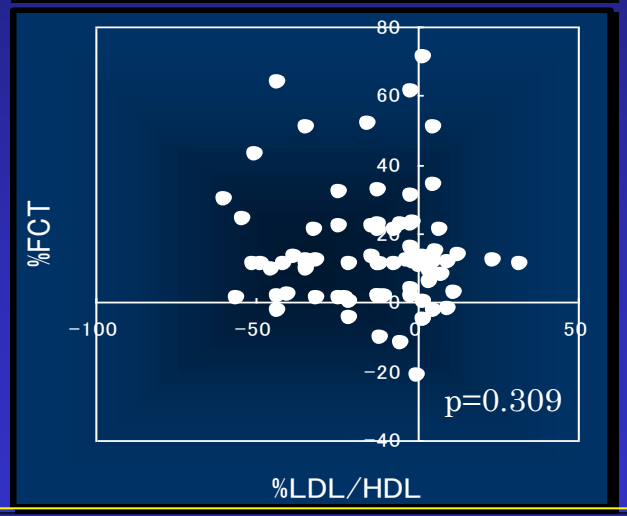
Laboratory examination :

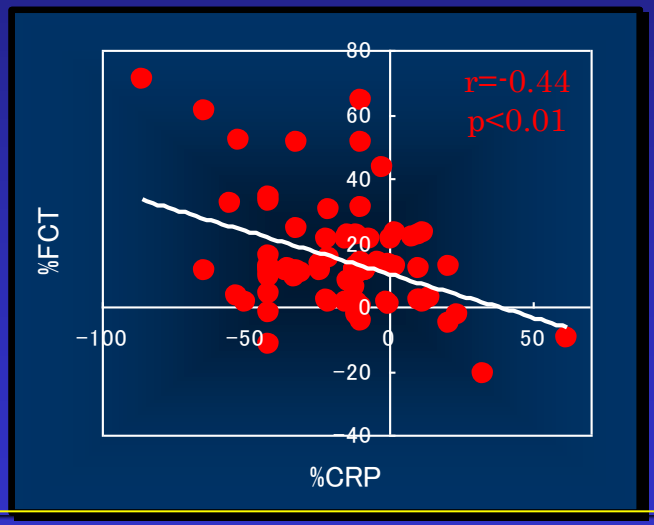
LDL-C,HDL-C,hs-CRP
(The days of discharge, & the time of follow-up)

The correlation between the lipid profile and the % change of fibrous-cap thickness (FCT) and total atheroma volume (TAV).







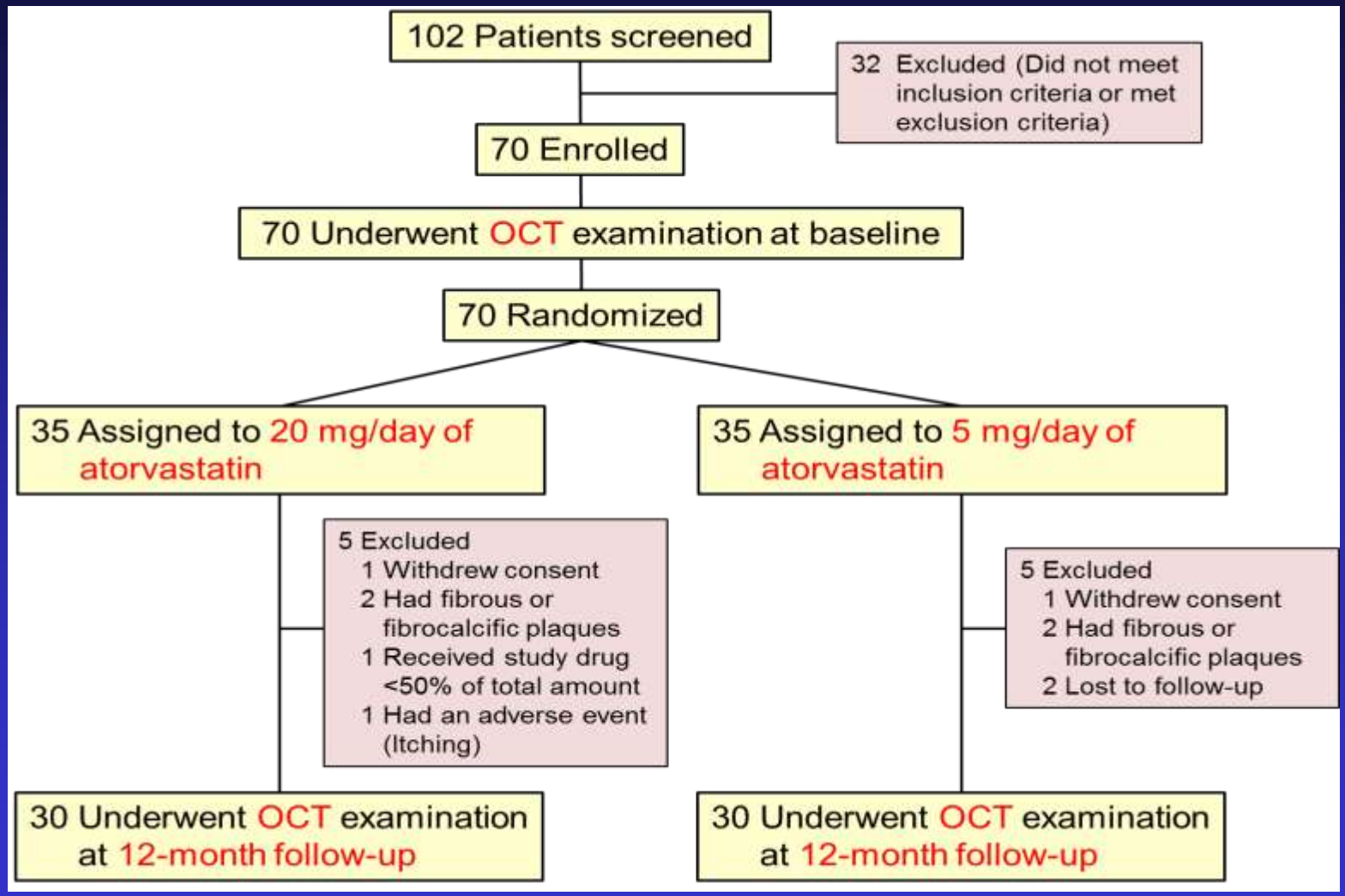


%TAV and %LDL/HDL were positively correlated (p<0.01, r = 0.42).
%FCT and %CRP were inversely correlated (p<0.01, r = -0.44).

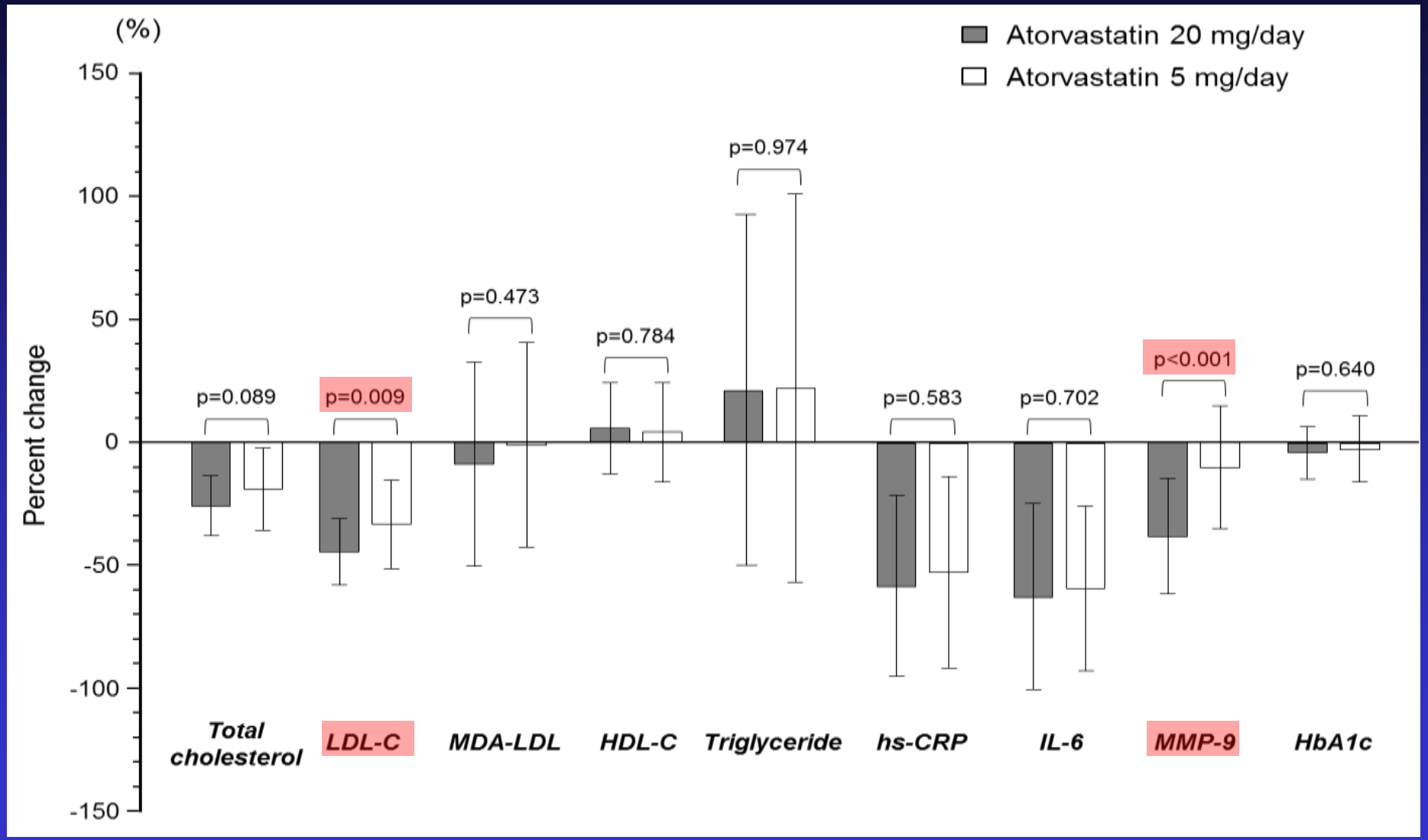
（Takarada S, et al. JACC Interv. 2010;3: 766-772）

Effect of Atorvastatin Therapy on the Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by OCT (EASY-FIT)

National Clinical Trial Identifier Number: 00700037



Percent change in laboratory results between baseline and 12-month follow-up

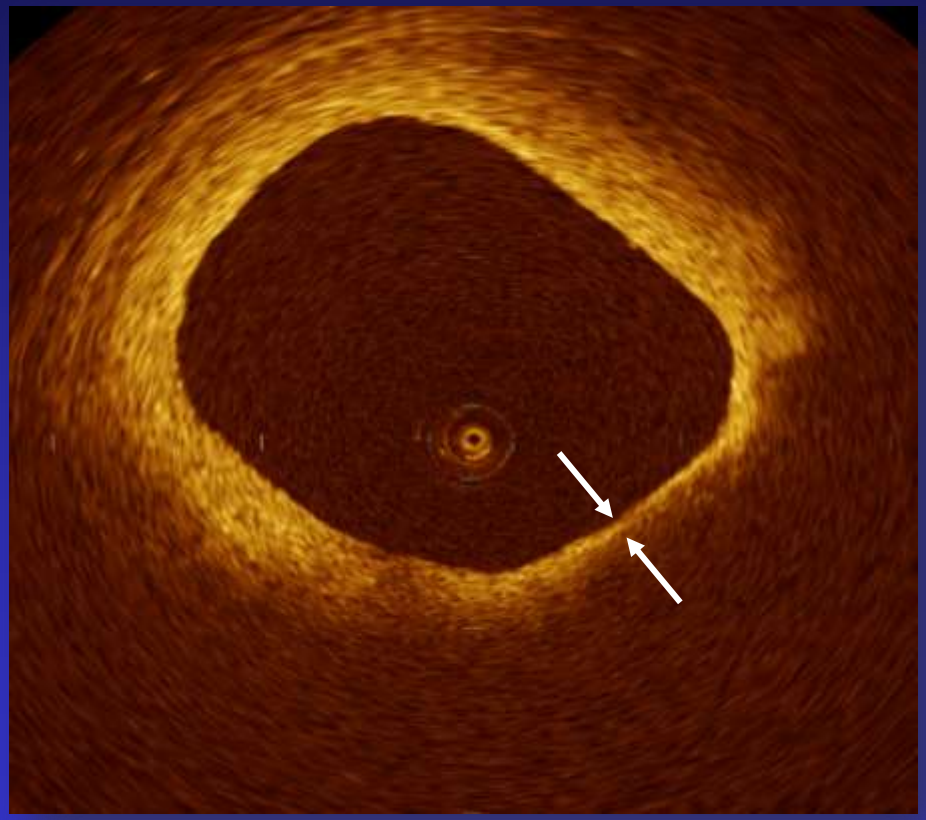


Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

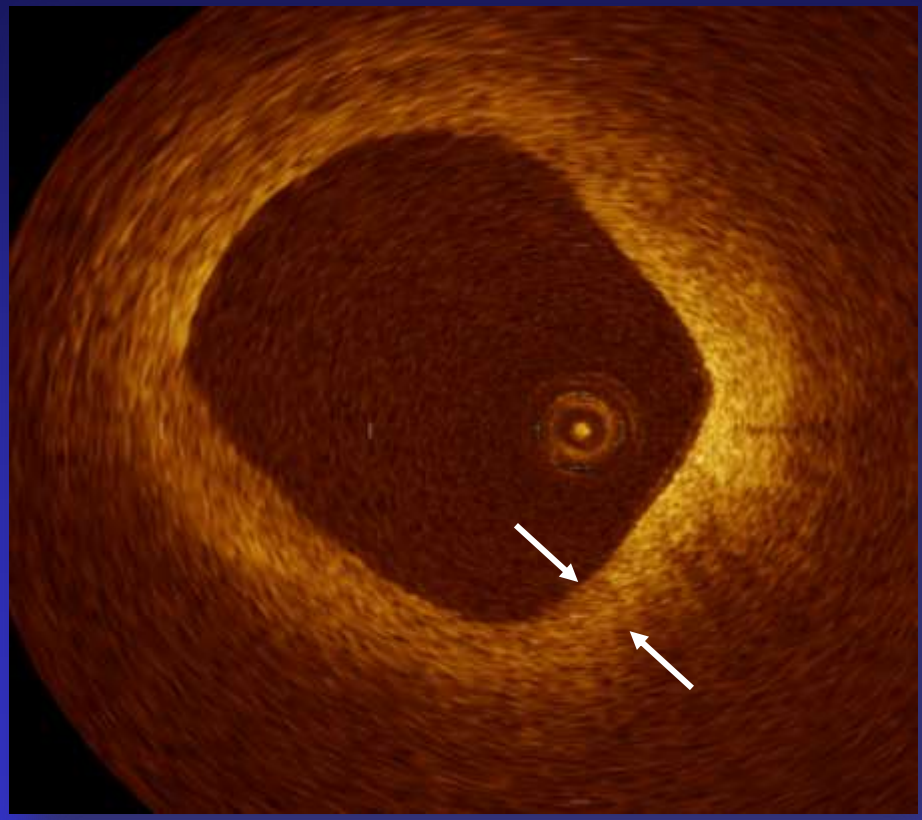
Wakayama Medical University

Increase of fibrous cap thickness during 20mg/day of Atorvastatin

Baseline

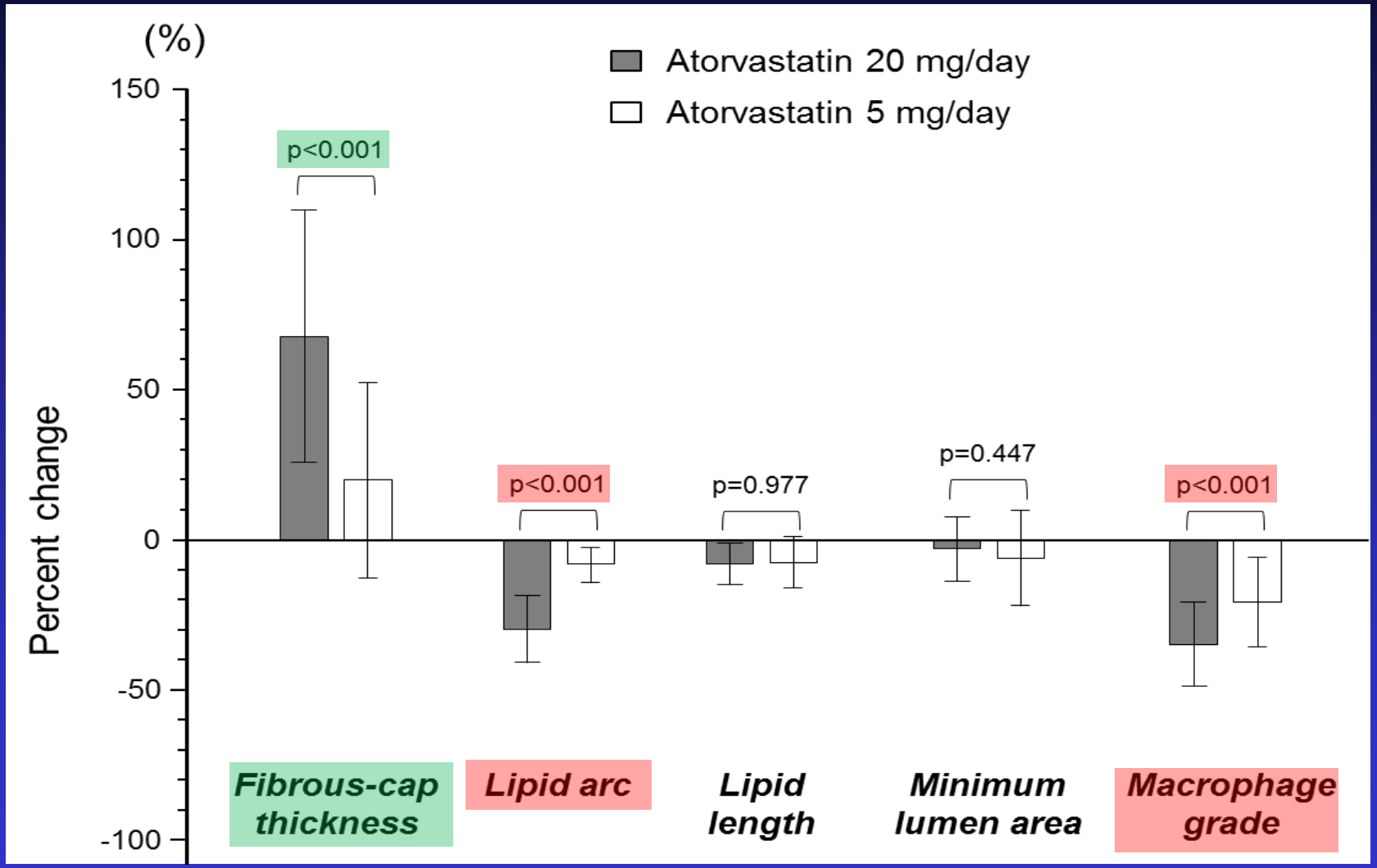


12-month follow-up



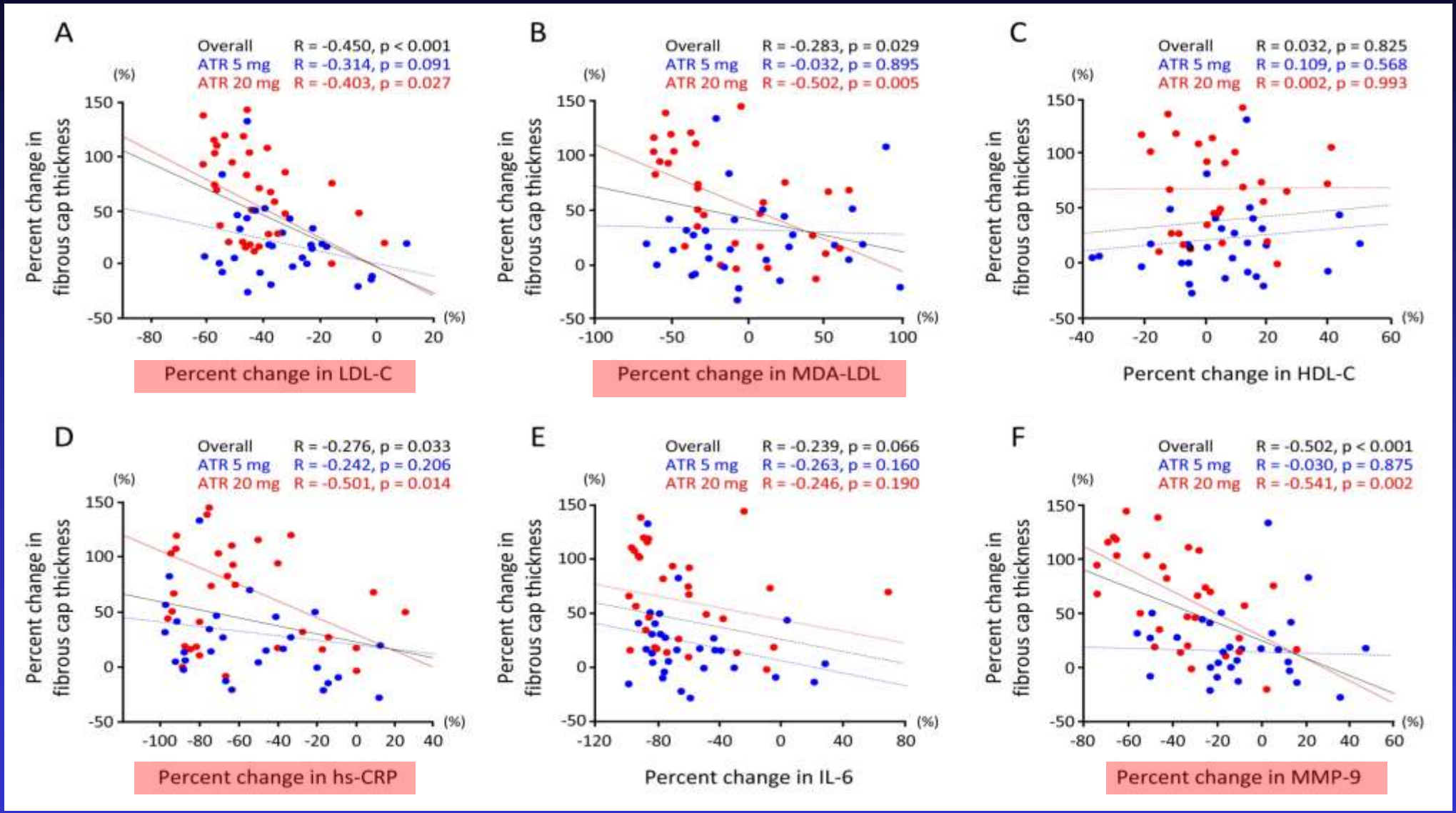
Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

Percent change in OCT measurements between baseline and 12-month follow-up



Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

Relationships between percent changes in biomarkers and fibrous cap thickness

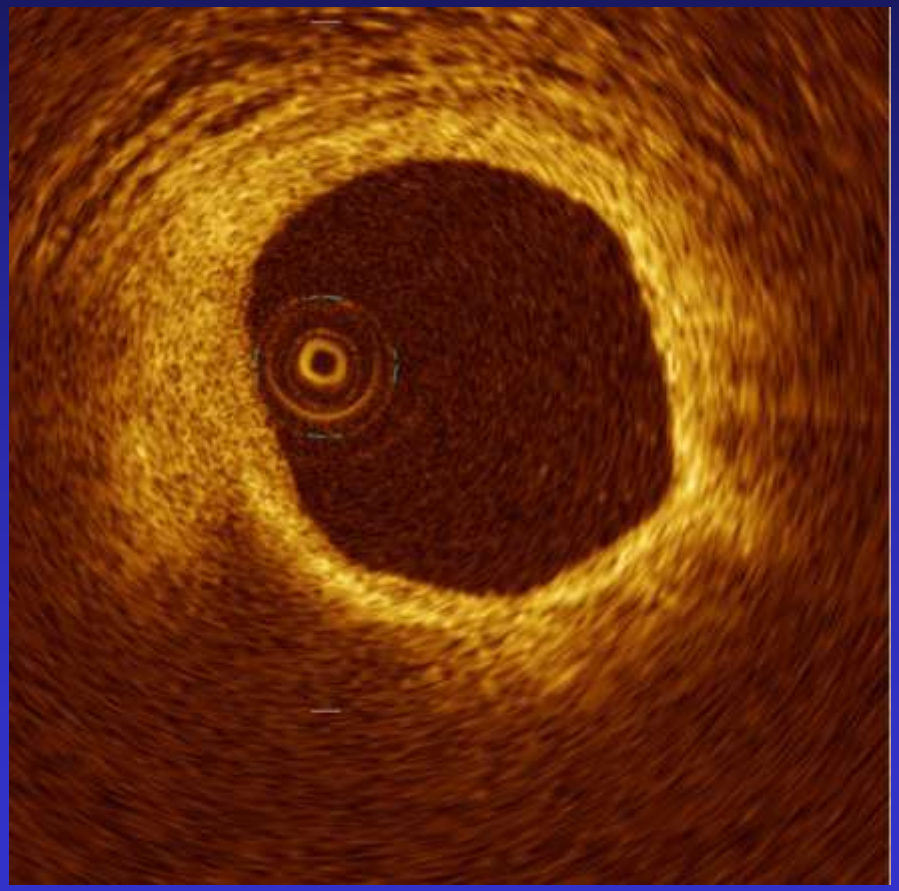


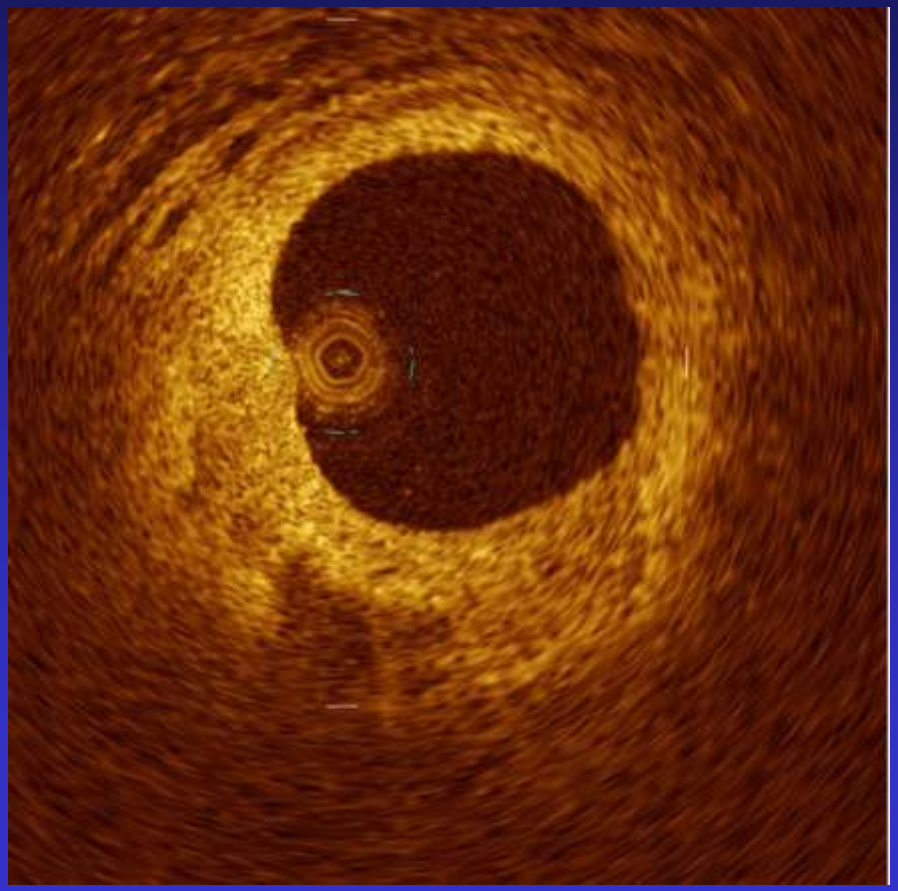
Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

Decrease of macrophage density during 20mg/day of Atorvastatin

Baseline

12-month follow-up





Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

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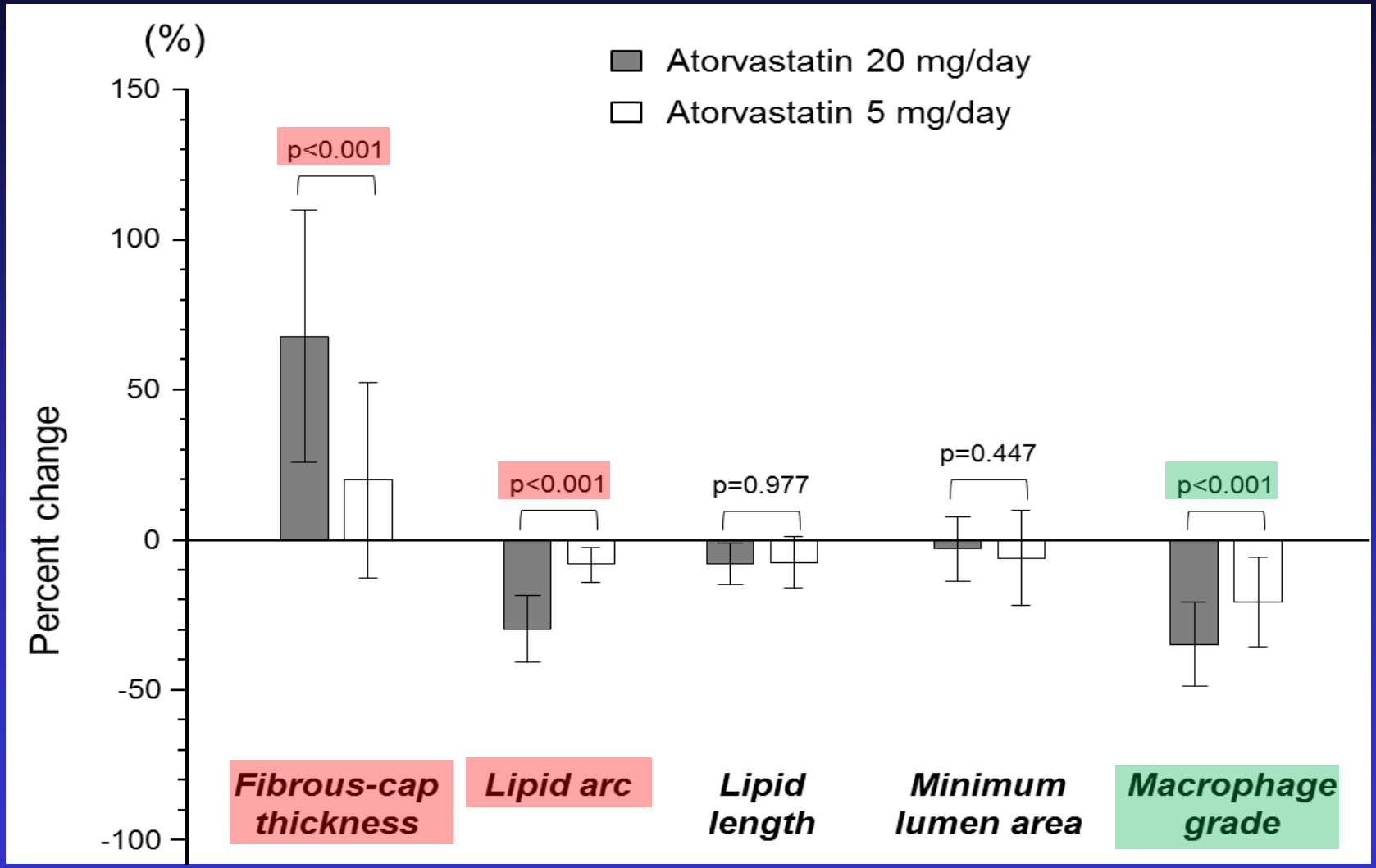
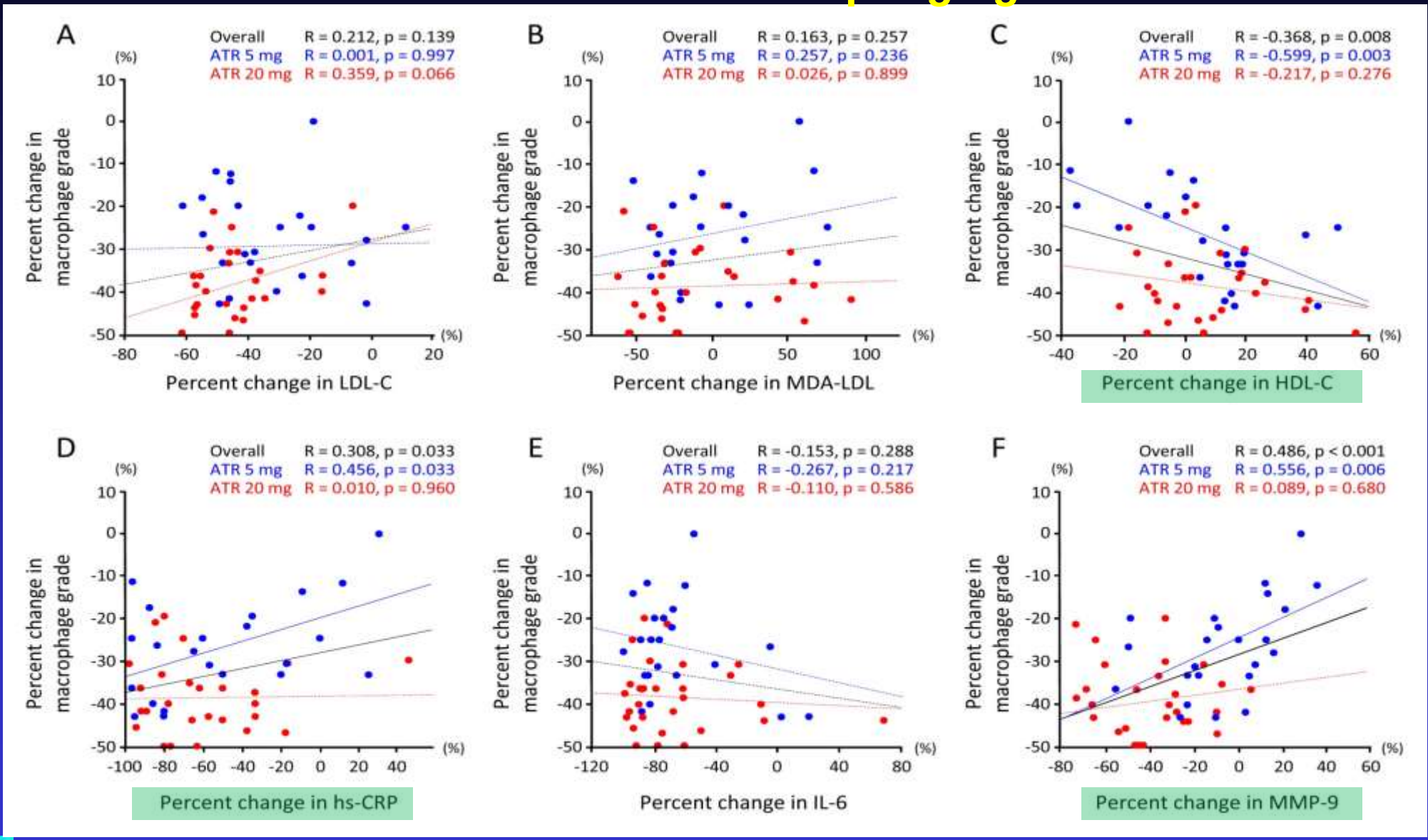
Percent change in OCT measurements between baseline and 12-month follow-up



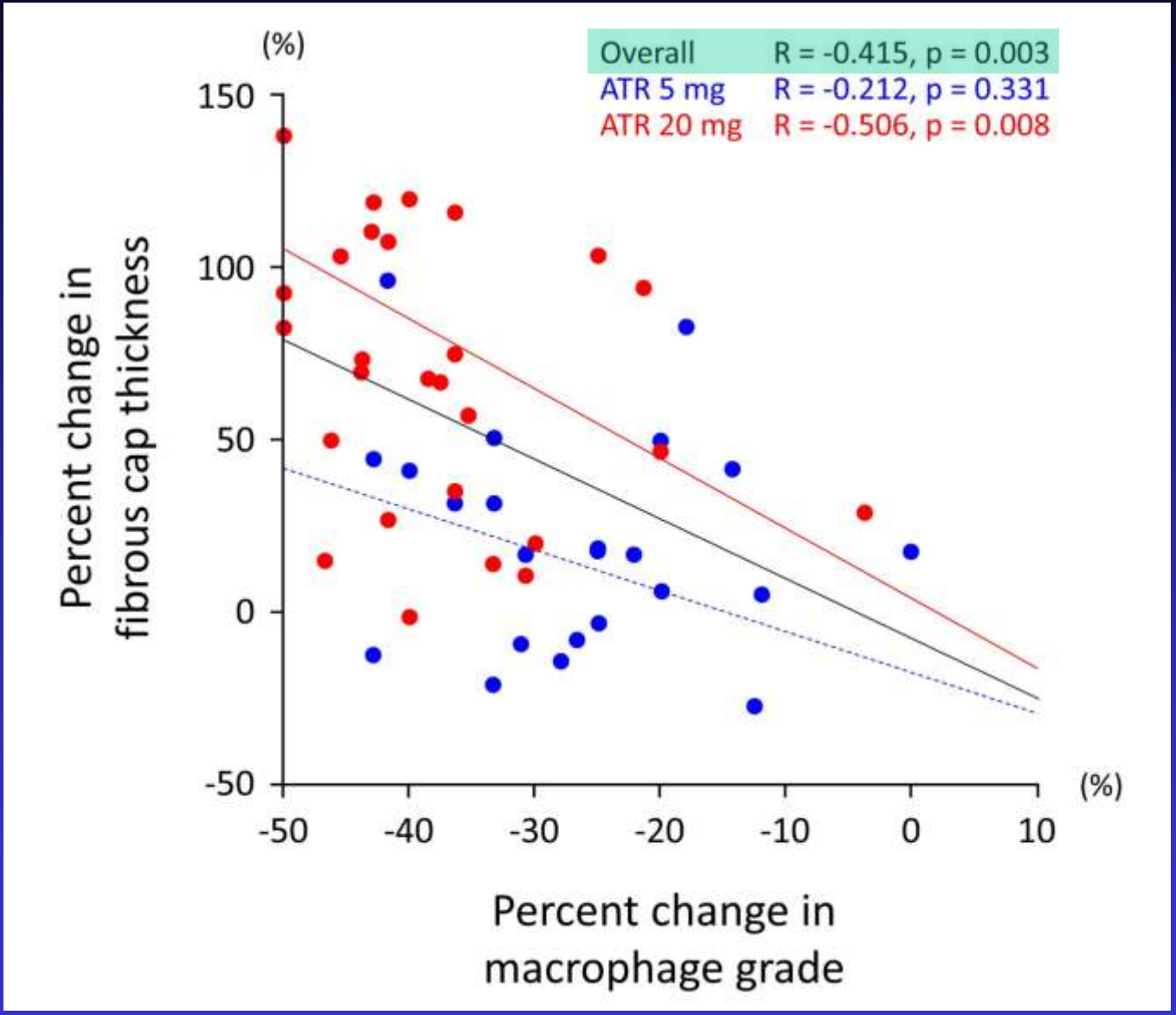
Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

Relationships between percent changes in biomarkers and macrophage grade



Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

Relationship between percent changes in macrophage grade and fibrous cap thickness



Komukai K, et al. J Am Coll Cardiol 2014;64:2207-2217

Elevated Levels of Systemic Pentraxin 3 Are Associated With Thin-Cap Fibroatheroma in Coronary Culprit Lesions

Assessment by Optical Coherence Tomography and Intravascular Ultrasound

Seiji Koga, MD,* Satoshi
Masayoshi Takeno, MD,*
Hiroaki Kawano, MD,* K

Nagasaki and Tokyo, Japan

Objectives This study sought to determine whether systemic levels of pentraxin 3 (PTX3), a novel inflammatory marker, are associated with thin-cap fibroatheroma (TCFA).

Background Biomarkers predicting the presence of TCFA in vivo have not been established.

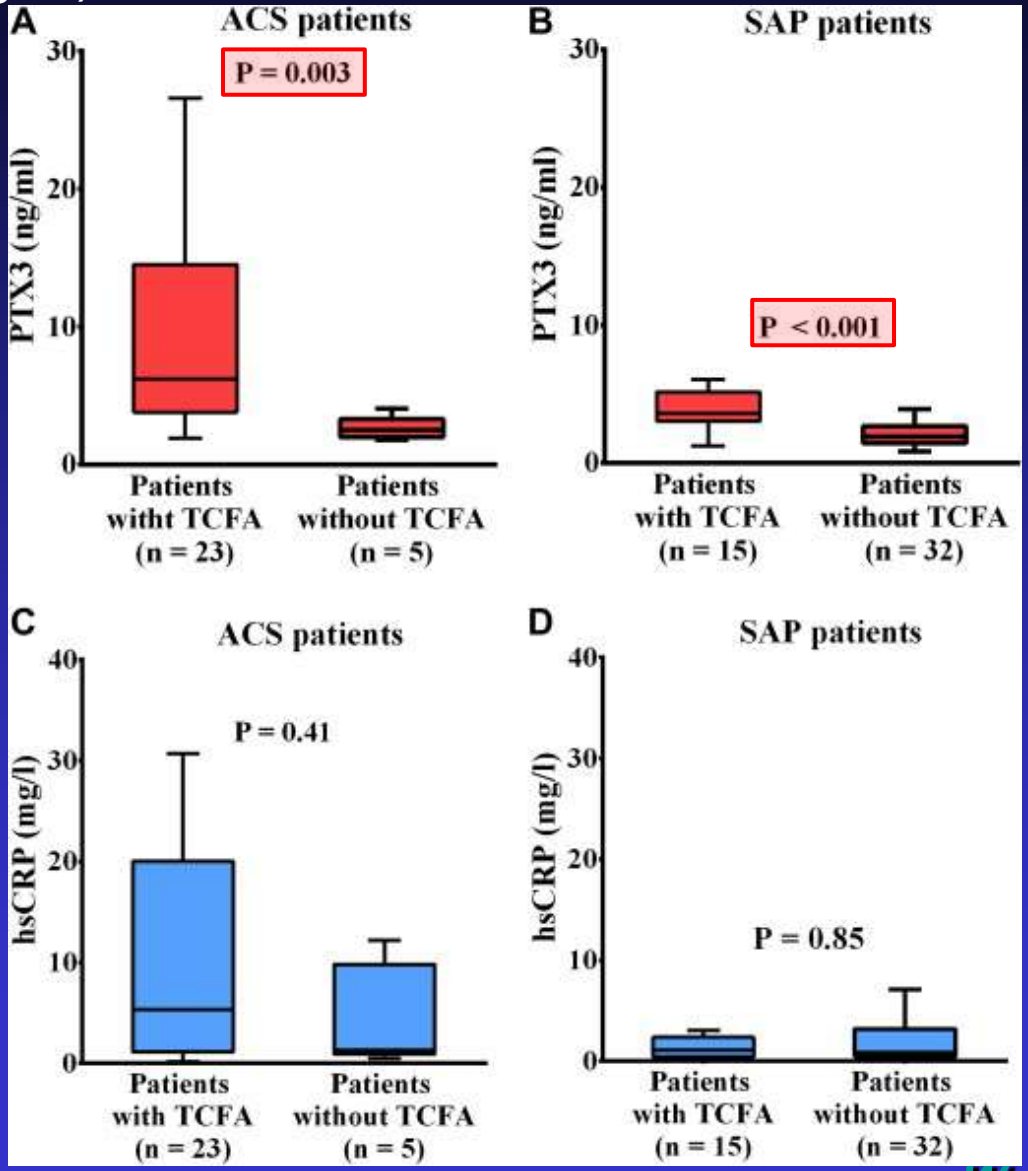
Methods We evaluated 75 patients (stable angina pectoris, n = 47; acute coronary syndrome, n = 28) with de novo culprit lesions who were examined by optical coherence tomography and intravascular ultrasound. We defined TCFA as lipid-rich plaque with a fibrous cap <65 μm thick. Systemic levels of PTX3 were compared between patients with and without TCFA.

Results Thirty-eight and 37 patients with and without TCFA, respectively, were identified. Levels of PTX3 were significantly higher in patients with than in those without TCFA ($p < 0.001$) and correlated inversely with fibrous cap thickness ($r = -0.71$, $p = 0.001$) and positively with the remodeling index ($r = 0.25$, $p = 0.037$). Multivariate logistic regression analysis showed that a higher PTX3 level was the most powerful predictor of TCFA (odds ratio: 3.26, 95% confidence interval: 1.75 to 6.05, $p < 0.001$). Receiver-operating characteristic curve analysis showed that >3.24 ng/ml of PTX3 could predict TCFA with 84% sensitivity and 86% specificity.

Conclusions Higher levels of systemic PTX3 are associated with TCFA. Systemic PTX3 levels comprise a useful inflammatory marker that reflects coronary plaque vulnerability. (J Am Coll Cardiol Intv 2013;6:945–54)

Comparisons of PTX3 and hs-CRP Levels Based on the Presence of TCFA in Patients With ACS and SAP

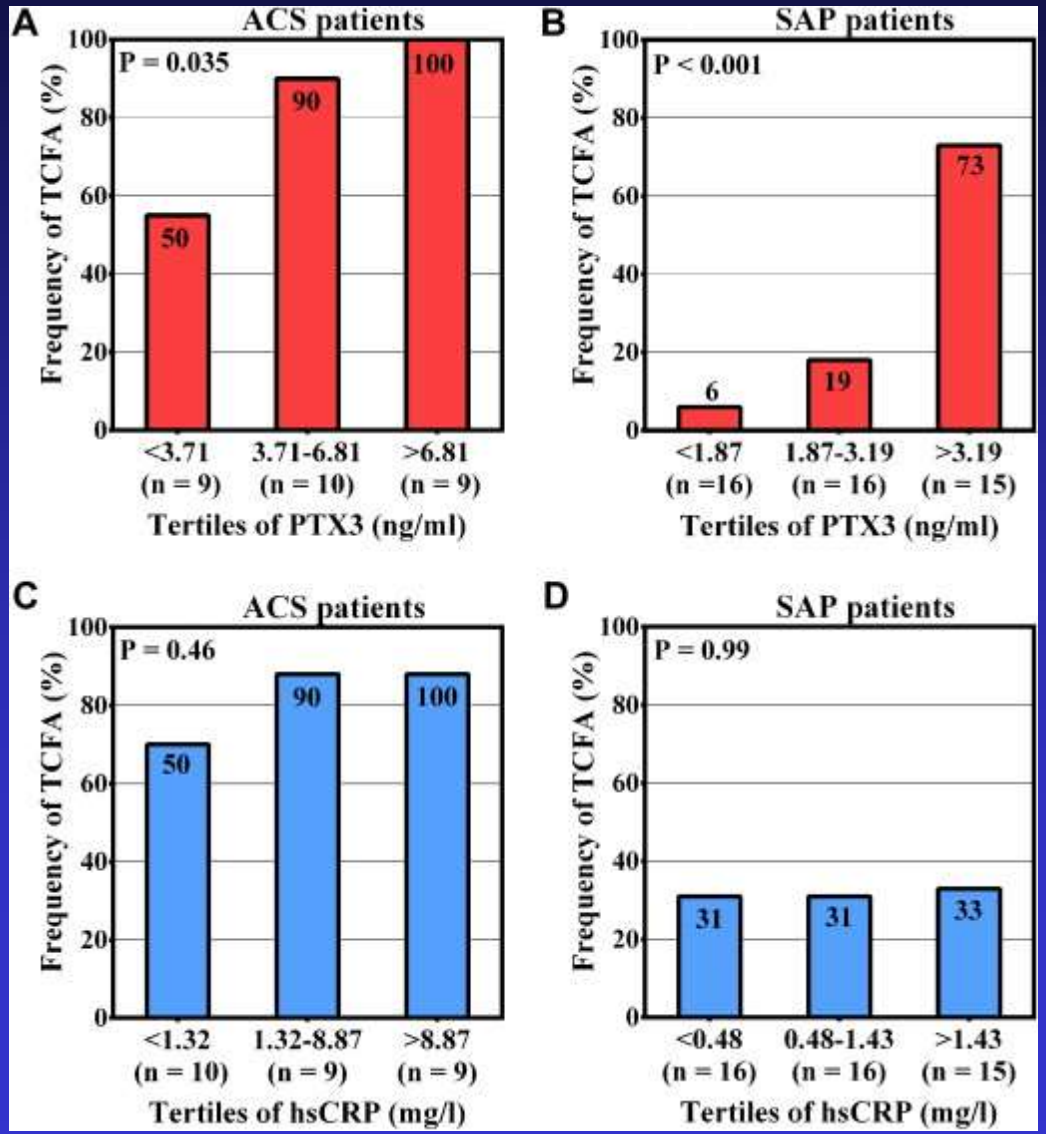
Koga S, et al. J Am Coll Cardiol Cardiovasc Interv. 2013;6:945 - 954



Frequency of TCFA According to PTX3 & hs-CRP Levels

Comparison of TCFA frequency among PTX3 tertiles (A, B) or hs-CRP levels (C, D) in patients with ACS and SAP

Koga S, et al. J Am Coll Cardiol Cardiovasc Interv. 2013;6:945 - 954



ROC of PTX3 Levels for Predicting TCFA

Koga S, et al. J Am Coll Cardiol Cardiovasc Interv. 2013;6:945 - 954

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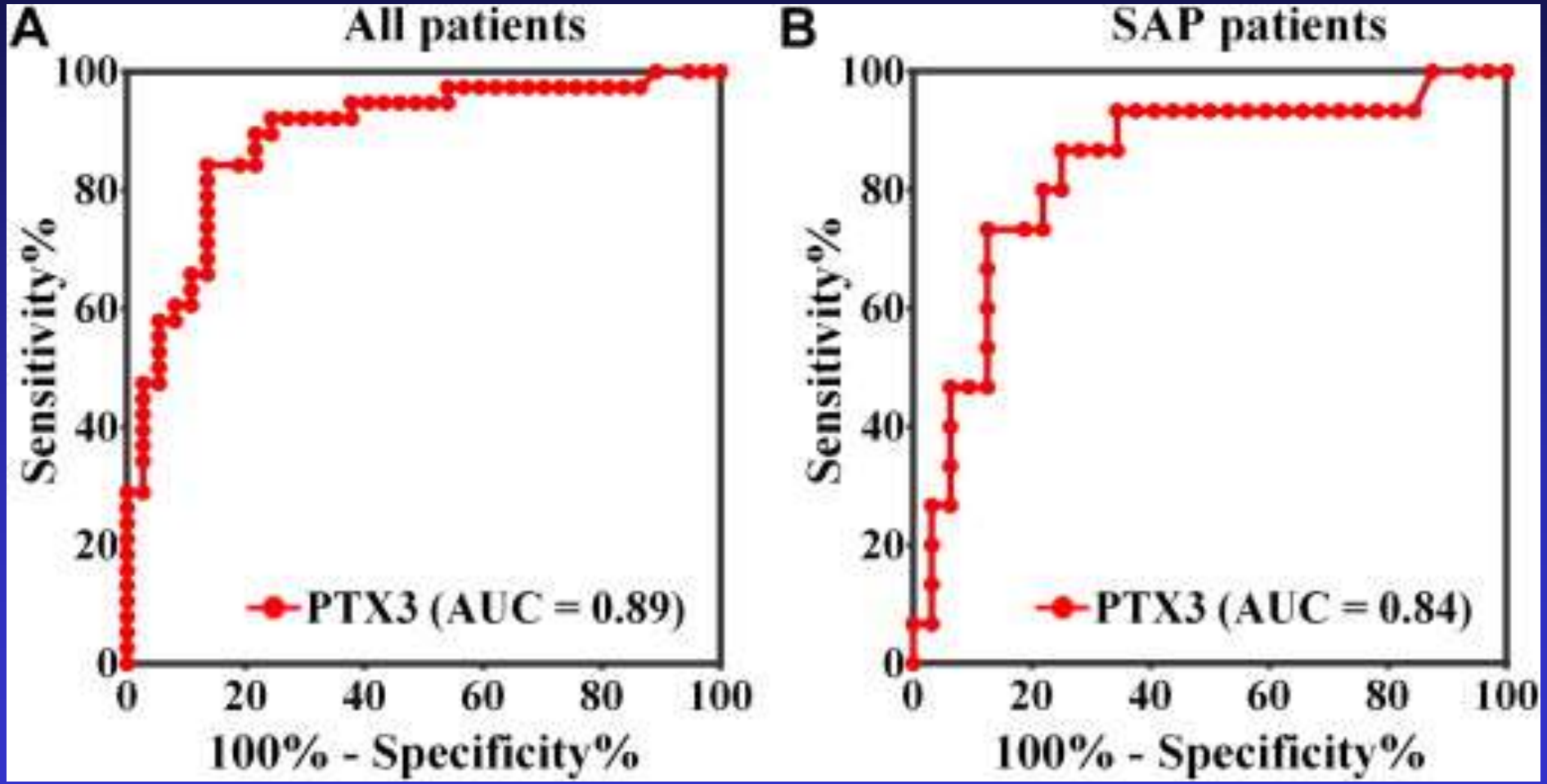

Effect of EPA & statin on TCFA

Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma

Ryo Nishio, Toshiro Shinke*, Hiromasa Otake, Masayuki Nakagawa, Ryoji Nagoshi, Takumi Inoue, Amane Kozuki, Hirotoshi Hariki, Tsuyoshi Osue, Yu Taniguchi, Masamichi Iwasaki, Noritoshi Hiranuma, Akihide Konishi, Hiroto Kinutani, Junya Shite, Ken-ichi Hirata

Kobe University Graduate School of Medicine, Division of Cardiovascular Medicine, Department of Internal Medicine, Japan

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Pentraxin-3

ABSTRACT

Background: The addition of highly purified eicosapentaenoic acid (EPA) to statin therapy prevents cardiovascular events. However, the impact of this treatment on vulnerable plaques remains unclear. The aim of this study was to assess the impact of adding EPA to a standard statin therapy on vulnerable plaques by serial optical coherence tomography (OCT).

Methods: Forty-nine non-culprit thin-cap fibroatheroma (TCFA) lesions in 30 patients with untreated dyslipidemia were included. Patients were randomly assigned to EPA (1800 mg/day) + statin (23 TCFA, 15 patients) or statin only (26 TCFA, 15 patients) treatment. The statin (rosuvastatin) dose was adjusted to achieve a target low-density lipoprotein (LDL) level of <70 mg/dL. Post-percutaneous intervention and 9-month follow-up OCT were performed to evaluate morphological changes of TCFAs. The EPA/arachidonic acid (EPA/AA) ratio and pentraxin-3 (PTX3) levels were also evaluated.

Results: Despite similar follow-up LDL levels, the EPA + statin group had higher EPA/AA ratios and lower PTX3 levels than the statin group. OCT analysis showed that the EPA + statin group had a greater increase in fibrous-cap thickness, with a greater decrease in lipid arc and lipid length. Macrophage accumulation was less frequently detected in the EPA + statin group than in the statin group at follow-up. When the patients were categorized according to their follow-up PTX3 tertiles, fibrous-cap thickness showed significant increase, and the incidence of macrophages accumulation decreased with lower PTX3 levels.

Conclusion: The concomitant use of EPA and rosuvastatin may stabilize vulnerable plaques better than the statin alone, possibly by suppressing arterial inflammation.

Effect of EPA & statin on TCFA

Table 2
Blood tests and OCT[a] measurements at baseline and at the 9-month follow-up.

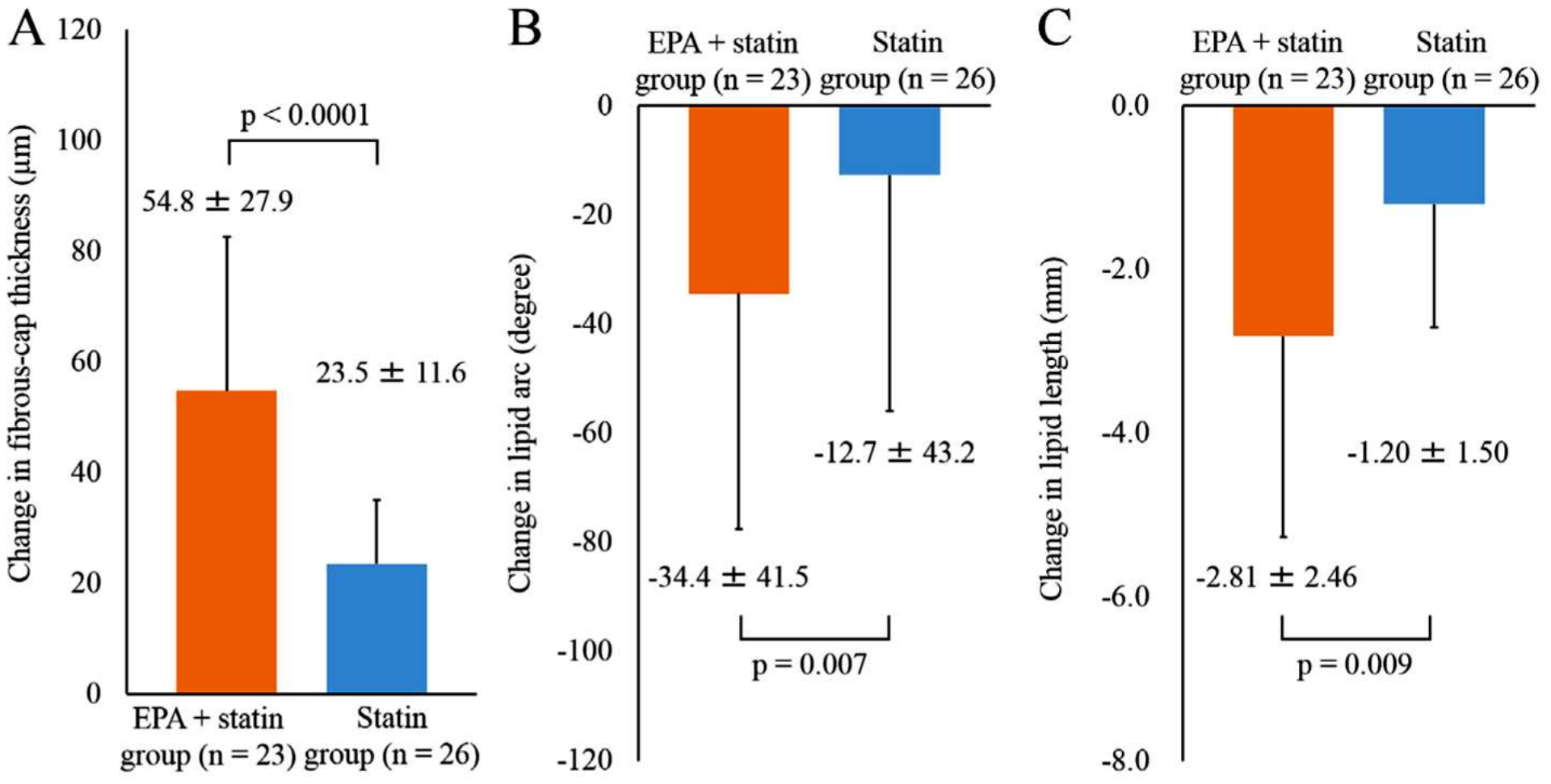
Variables	Baseline			Follow-up		
	EPA + statin group	Statin group	*p*-value	EPA + statin group	Statin group	*p*-value
Blood test						
EPA/AA[b]	0.32 ± 0.15	0.27 ± 0.13	0.37	1.11 ± 0.53	0.42 ± 0.31	0.0001
TC[c] (mg/dL)	207.3 ± 39.1	196.3 ± 40.3	0.34	144.4 ± 36.5	146.3 ± 20.5	0.62
HDL[d] (mg/dL)	40.9 ± 12.0	41.5 ± 7.4	0.97	44.9 ± 9.9	43.6 ± 9.4	0.72
LDL[e] (mg/dL)	138.0 ± 35.3	130.3 ± 34.8	0.41	80.1 ± 29.7	83.2 ± 19.6	0.58
TG[f] (mg/dL)	161.4 ± 50.4	146.8 ± 37.4	0.30	123.5 ± 42.6	131.4 ± 47.9	0.72
hs-CRP[g] (mg/dL)	0.24 ± 0.18	0.22 ± 0.15	0.95	0.06 ± 0.05	0.12 ± 0.11	0.07
PTX3[h] (ng/mL)	4.49 ± 2.25	4.75 ± 2.22	0.60	2.79 ± 0.96	3.84 ± 1.17	0.01
OCT measurements						
Fibrous-cap thickness (μm)	47.5 ± 7.4	46.5 ± 10.9	0.94	102.2 ± 28.8	70.0 ± 10.6	<0.0001
Lipid arc (degree)	159.0 ± 62.0	158.3 ± 63.5	0.98	127.7 ± 44.8	145.6 ± 50.6	0.27
Lipid length (mm)	6.52 ± 3.47	6.17 ± 2.84	0.85	3.87 ± 2.02	4.97 ± 2.39	0.13
The incidence of macrophages accumulation (*n*; %)	16 (69.6)	18 (69.2)	0.99	3 (13.0)	12 (46.2)	0.02
The presence of intimal microvessels (*n*; %)	13 (56.5)	16 (61.5)	0.78	7 (30.4)	15 (57.7)	0.08

Nishio R, et al. Atherosclerosis 2014;234:114 - 119

Wakayama Medical University

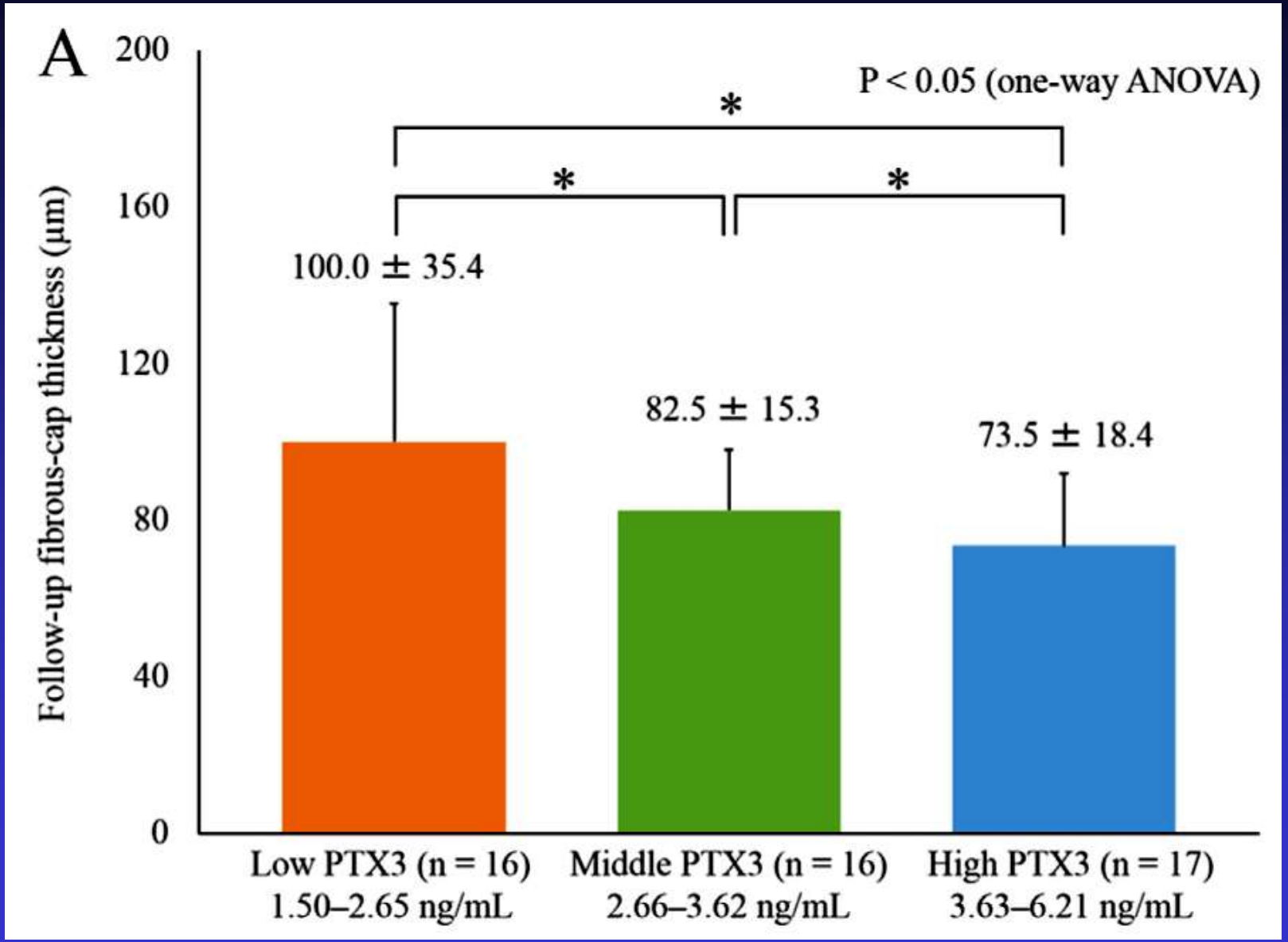
Effect of EPA & statin on TCFA

Change in Cap Thickness **Change in Lipid Arc** **Change in Lipid Length**



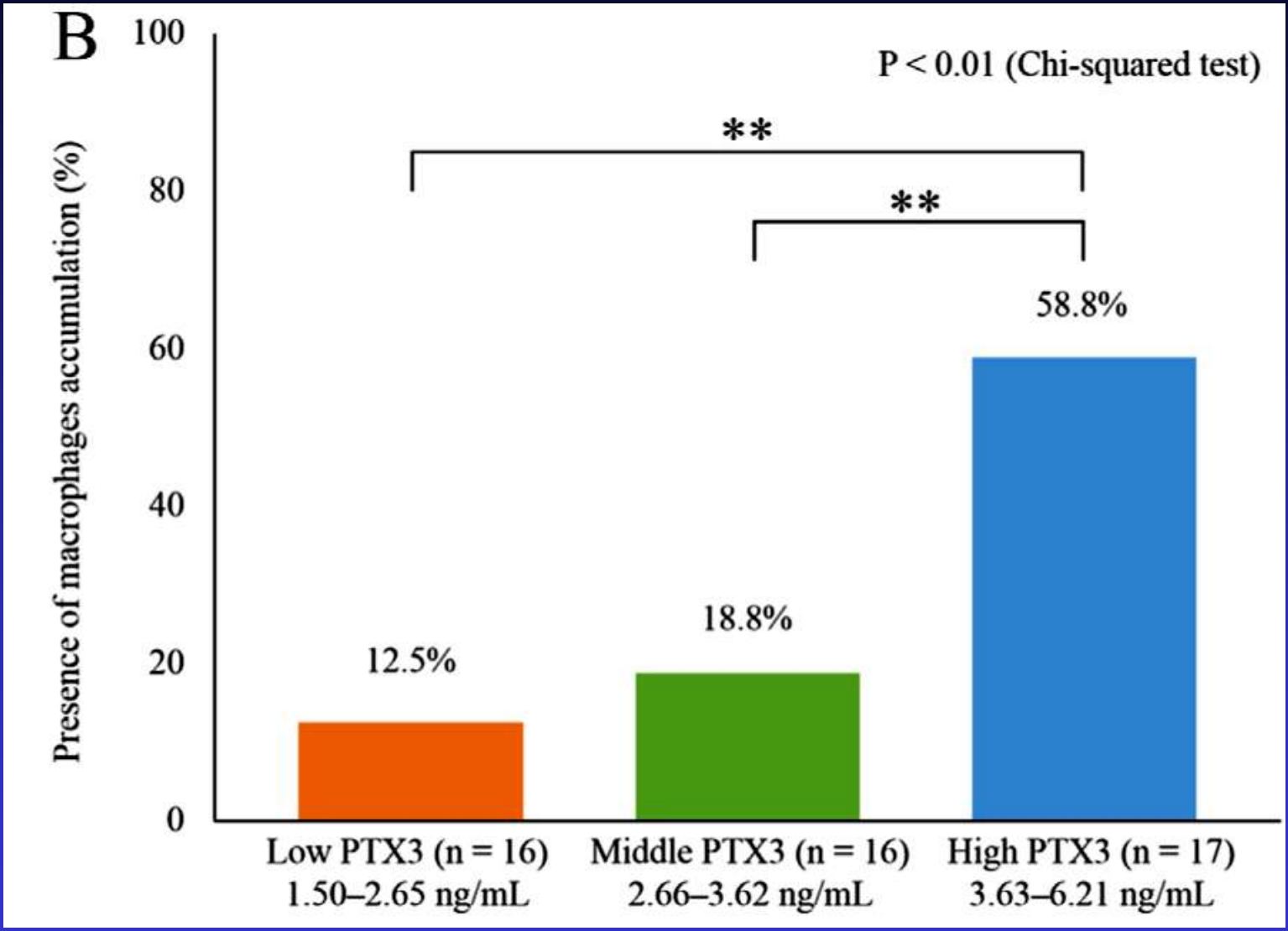
Nishio R, et al. Atherosclerosis 2014;234:114 - 119

Effect of EPA & statin on TCFA



Nishio R, et al. Atherosclerosis 2014;234:114 - 119

Effect of EPA & statin on Macrophage Accumulation



Nishio R, et al. Atherosclerosis 2014;234:114 - 119

Impact of Statin Therapy on Plaque Characteristics as Assessed by Serial OCT, Grayscale and Integrated Backscatter–IVUS

Kousuke Hattori, MD,* Yukio Ozaki,
Masanori Okumura, MD,* Hiroyuki N
Tomoko Kawai, MD,* Masaya Ohta, I
Yasushi Takagi, MD,* Junichi Ishii, M
Toyoake, Japan; London, United Kingdom;

OBJECTIVES The purpose of this study was to evaluate the effect of statin treatment on coronary plaque composition and morphology by optical coherence tomography (OCT), grayscale and integrated backscatter (IB) intravascular ultrasound (IVUS) imaging.

BACKGROUND Although previous studies have demonstrated that statins substantially improve cardiac mortality, their precise effect on the lipid content and fibrous cap thickness of atherosclerotic coronary lesions is less clear. While IVUS lacks the spatial resolution to accurately assess fibrous cap thickness, OCT lacks the penetration of IVUS. We used a combination of OCT, grayscale and IB-IVUS to comprehensively assess the impact of pitavastatin on plaque characteristics.

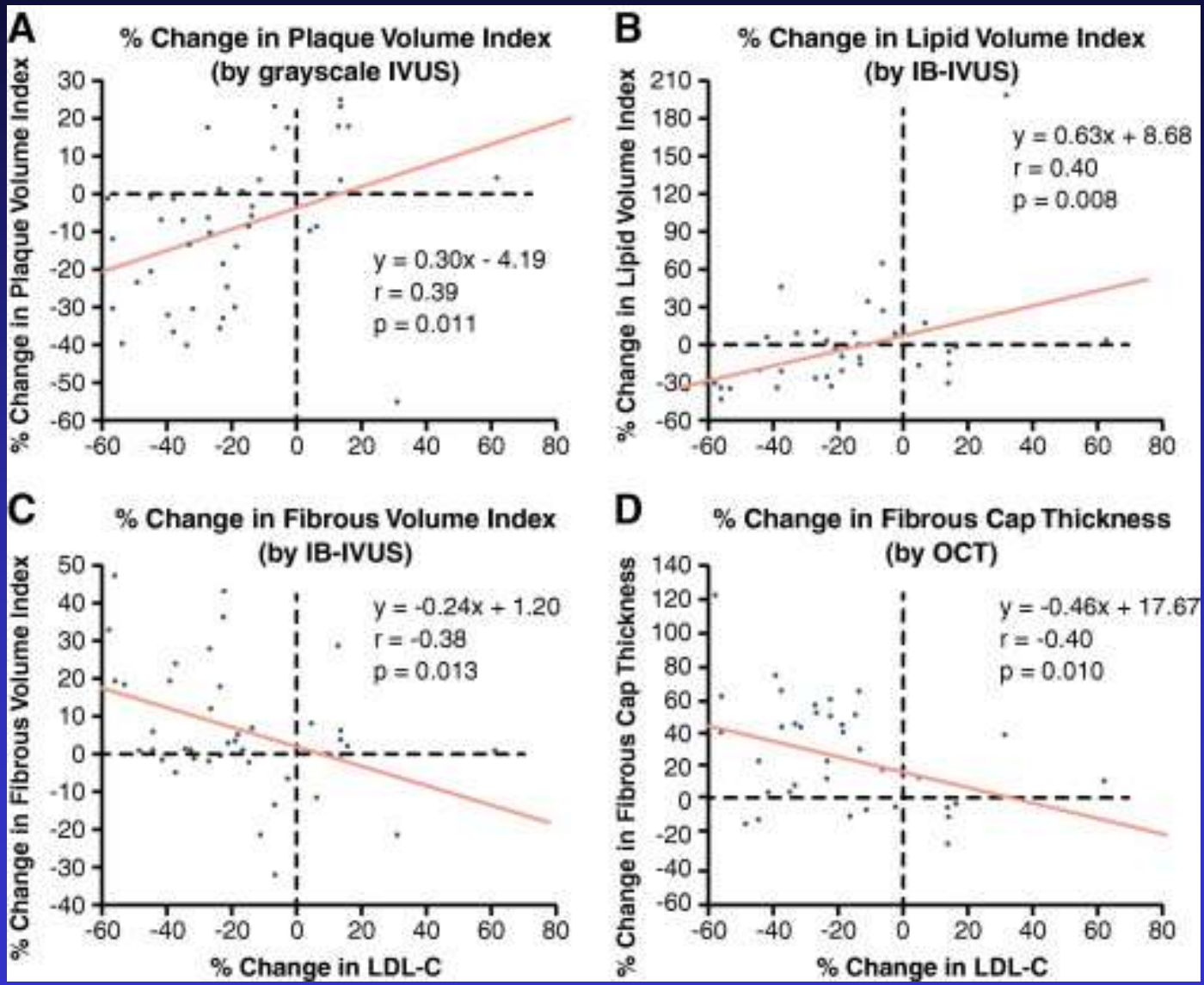
METHODS Prospective serial OCT, grayscale and IB-IVUS of nontarget lesions was performed in 42 stable angina patients undergoing elective coronary intervention. Of these, 26 received 4 mg pitavastatin after the baseline study; 16 subjects who refused statin treatment were followed with dietary modification alone. Follow-up imaging was performed after a median interval of 9 months.

RESULTS Grayscale IVUS revealed that in the statin-treated patients, percent plaque volume index was significantly reduced over time (48.5 ± 10.4%, 42.0 ± 11.1%; $p = 0.033$), whereas no change was observed in the diet-only patients (48.7 ± 10.4%, 50.4 ± 11.8%; p = NS). IB-IVUS identified significant reductions in the percentage lipid volume index over time (34.9 ± 12.2%, 28.2 ± 7.5%; $p = 0.020$); no change was observed in the diet-treated group (31.0 ± 10.7%, 33.8 ± 12.4%; p = NS). While OCT demonstrated a significant increase in fibrous cap thickness (140 ± 42 μm, 189 ± 46 μm; $p = 0.001$), such changes were not observed in the diet-only group (140 ± 35 μm, 142 ± 36 μm; p = NS). Differences in the changes in the percentage lipid volume index (−6.8 ± 8.0% vs. 2.8 ± 9.9%, $p = 0.031$) and fibrous cap thickness (52 ± 32 μm vs. 2 ± 22 μm, $p < 0.001$) over time between the pitavastatin and diet groups were highly significant.

CONCLUSIONS Statin treatment induces favorable plaque morphologic changes with an increase in fibrous cap thickness, and decreases in both percentage plaque and lipid volume indexes. (J Am Coll Cardiol Img 2012;5:169–77) © 2012 by the American College of Cardiology Foundation

Relationship Between %Change in LDL-C and %Change of Grayscale IB-IVUS, and OCT Parameters

Hattori K, et al. J Am Coll Cardiol Cardiovasc Img, 2012:5;169 - 177



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

Yuichi Ozaki, MD; Atsushi Tanaka, MD, PhD; Kenichi Komukai, MD; Kohei Ishibashi, MD; Takashi Tanimoto, MD, PhD; Hironori Kitabata, MD, PhD; Yasushi Ino, MD; Takashi Kubo, MD, PhD; Toshio Imanishi, MD, PhD; Takashi Akasaka, MD, PhD

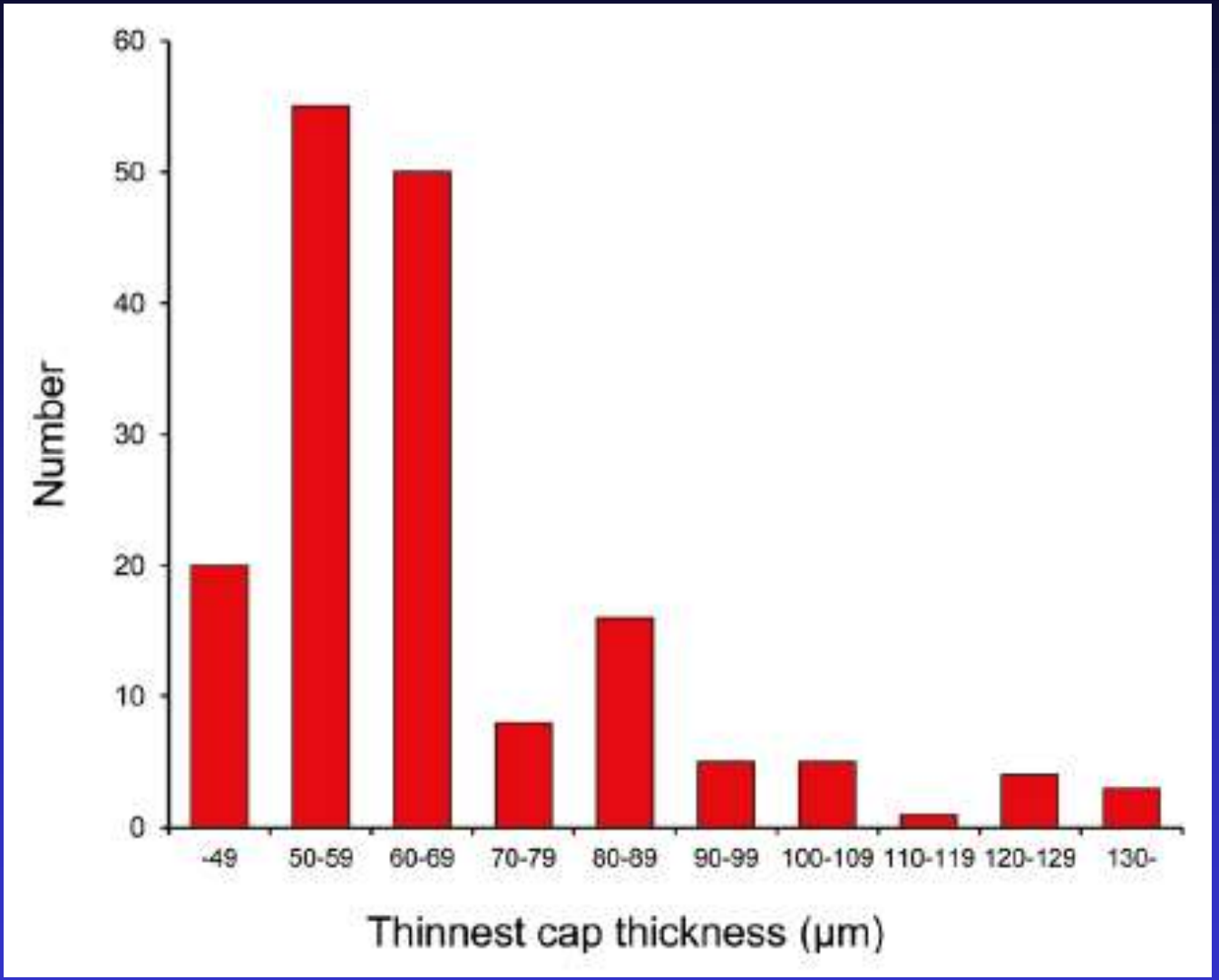
Background: Although low high-density lipoprotein cholesterol (HDL-C) level has been reported as an independent risk factor for coronary artery disease, few studies addressed the direct relationship between the presence of thin-cap fibroatheroma (TCFA) that is considered as vulnerable plaque in pathology 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 μm-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)

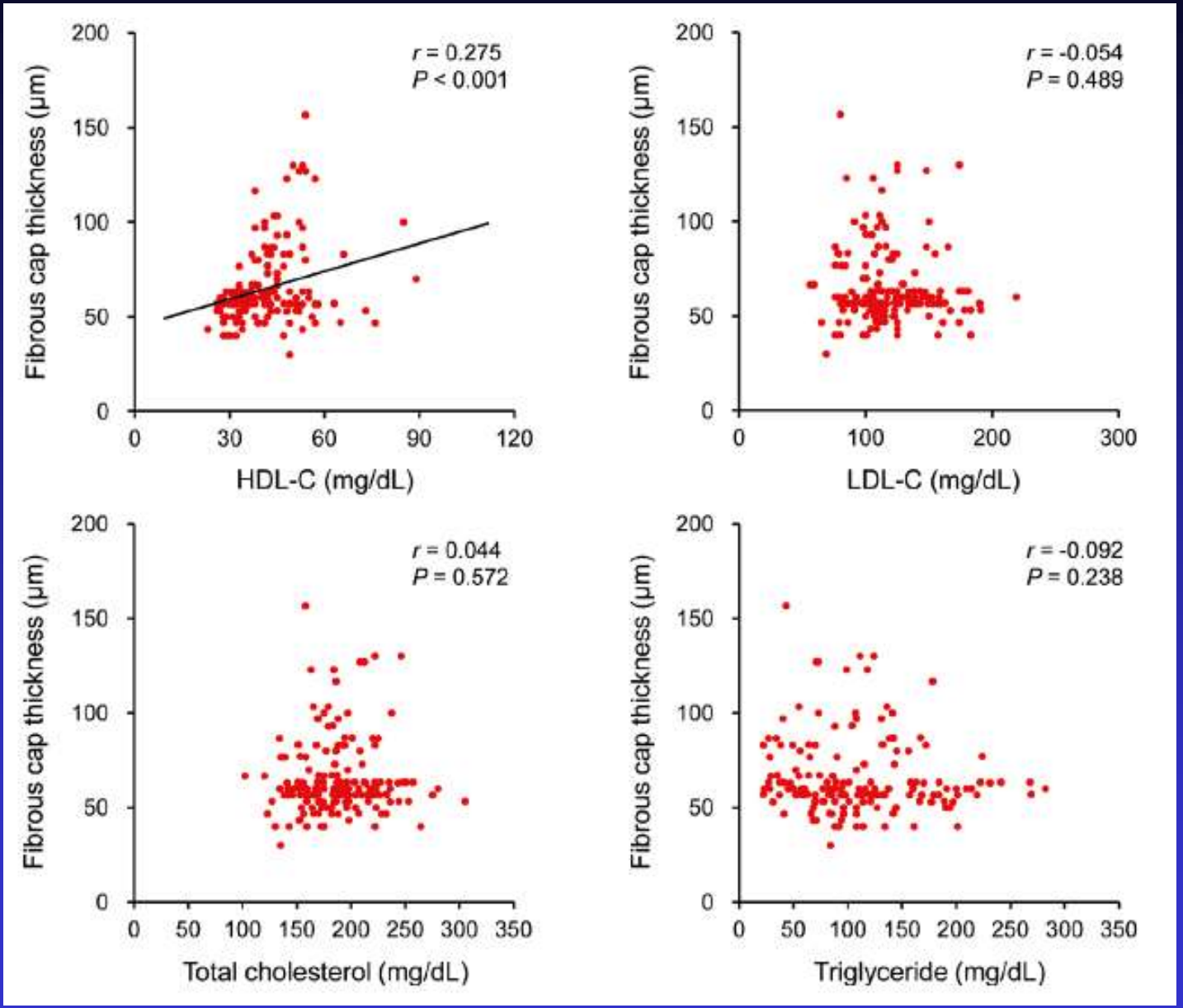
Frequency of thinnest cap thickness

Ozaki Y, et al. Circ J 2013;77:2982 - 2989



Fibrous cap thickness vs HDL-C, LDL-C, Total-C and TG level

Ozaki Y, et al. Circ J 2013;77:2982 - 2989



Impact of Cholesterol Metabolism on Coronary Plaque Vulnerability of Target Vessels

A Combined Analysis of Virtual Histology Intravascular Ultrasound and Optical Coherence Tomography

Kenya Nasu, MD, Mitsuyasu Terashima, M
Tsuyoshi Ito, MD, Daisuke Yokota, MD, S
Masashi Kimura, MD, Yoshihisa Kinoshita,
Etsuo Tsuchikane, MD, PhD, Osamu Kato

Toyohashi, Japan

Objectives The aim of this study was to evaluate the relationship between cholesterol metabolism and coronary plaque vulnerability.

Background Cholesterol homeostasis, defined as the balance between absorption and synthesis, influences the progression of coronary atherosclerosis.

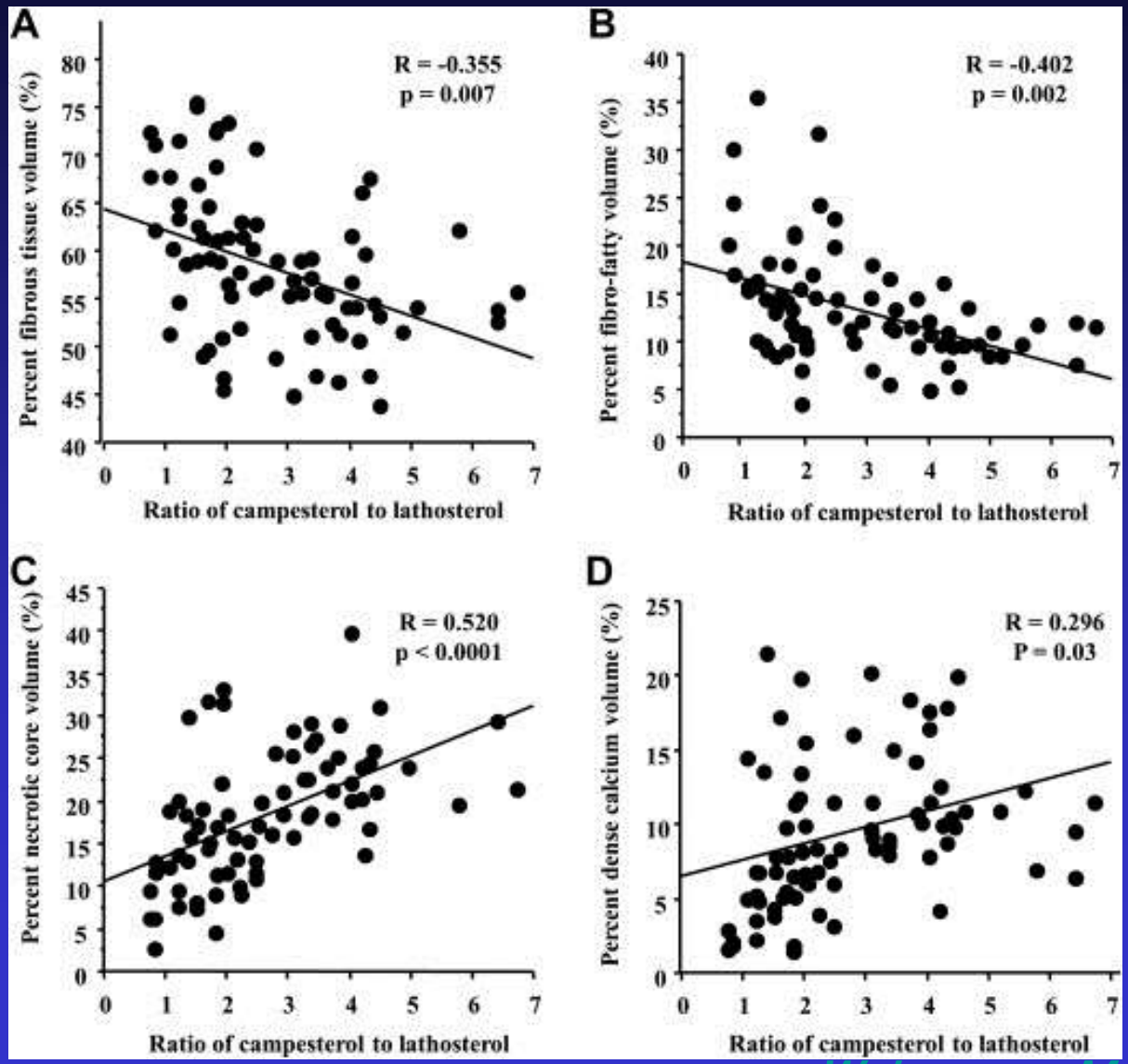
Methods Consecutive stable angina pectoris patients (N = 80) not receiving any lipid-lowering therapy were divided into 2 groups based on the presence of in vivo thin cap fibroatheroma (TCFA) in de novo target vessels assessed by the combined use of virtual histology intravascular ultrasound and optical coherence tomography.

Results Patients with in vivo TCFA (n = 42) showed a higher campesterol-to-lathosterol ratio (3.36 [interquartile range, 2.10 to 4.26] vs. 1.50 [1.20 to 2.50], $p < 0.0001$). The campesterol-to-lathosterol ratio, low-density lipoprotein (LDL) cholesterol, and high-sensitivity C-reactive protein (hsCRP) were positively correlated with the percentage of necrotic core volume ($r = 0.520$, $p < 0.0001$; $r = 0.520$, $p < 0.0001$; and $r = 0.539$, $p < 0.0001$, respectively) and negatively correlated with thinnest fibrous cap thickness ($r = -0.566$, $p < 0.0001$; $r = -0.530$, $p < 0.0001$; and $r = -0.358$, $p = 0.007$, respectively) . The independent predictors of the incidence of TCFA were the campesterol-to-lathosterol ratio (odds ratio: 3.989, 95% confidence interval: 1.688 to 9.428; $p = 0.002$), LDL cholesterol (odds ratio: 1.425, 95% confidence interval: 1.023 to 1.985; $p = 0.03$), hsCRP (odds ratio: 1.025, 95% confidence interval: 1.003 to 1.047; $p = 0.02$), and the percentage of necrotic core volume (odds ratio:1.084, 95% confidence interval: 1.012 to 1.161; $p = 0.02$).

Conclusions Enhanced absorption and reduced synthesis of cholesterol may be related to coronary plaque vulnerability. (J Am Coll Cardiol Intv 2013;6:746–55)

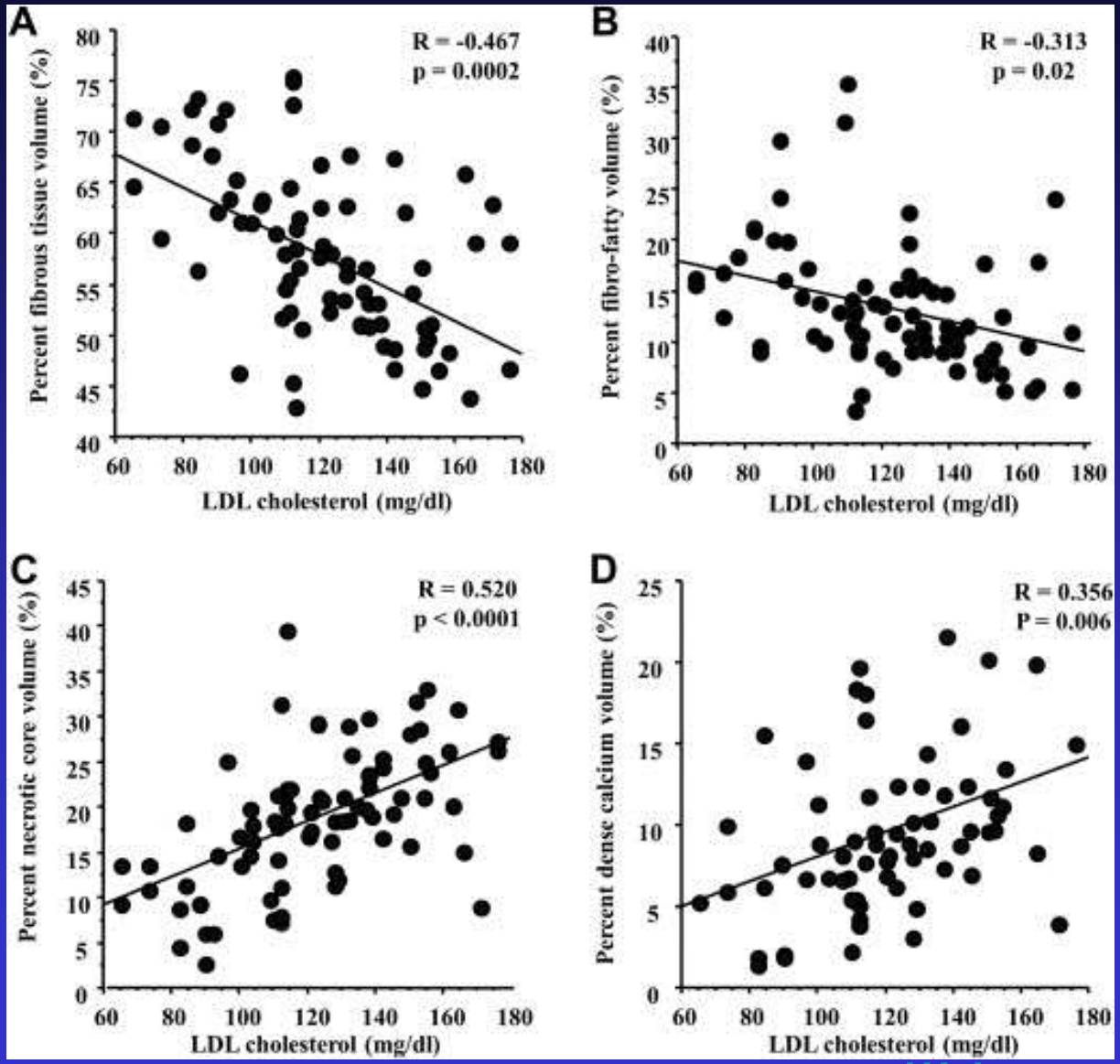
Correlation Between Relative Value of Each Plaque Component Volume and Ratio of Campesterol to Lathosterol

Nasu K, et al. J Am Coll Cardiol Cardiovasc Interv 2013;6:746 - 755



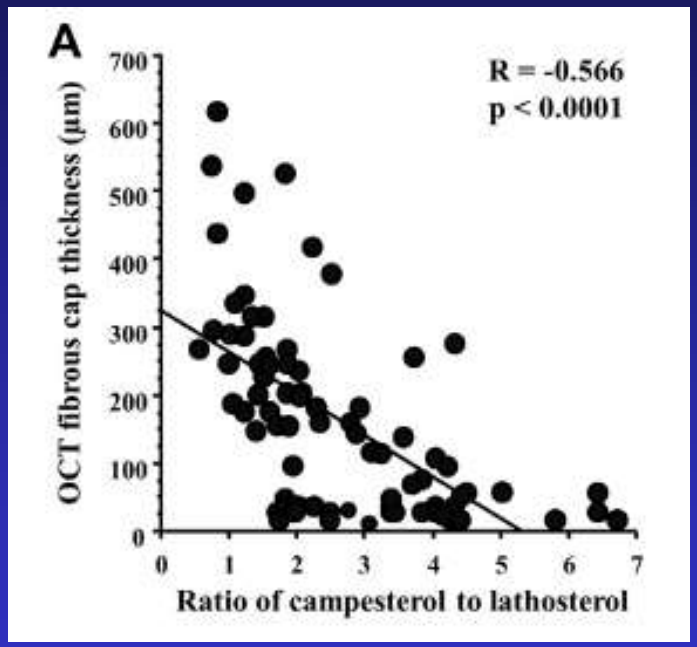
Correlation Between Relative Value of Each Plaque Component Volume and LDL-Cholesterol Level

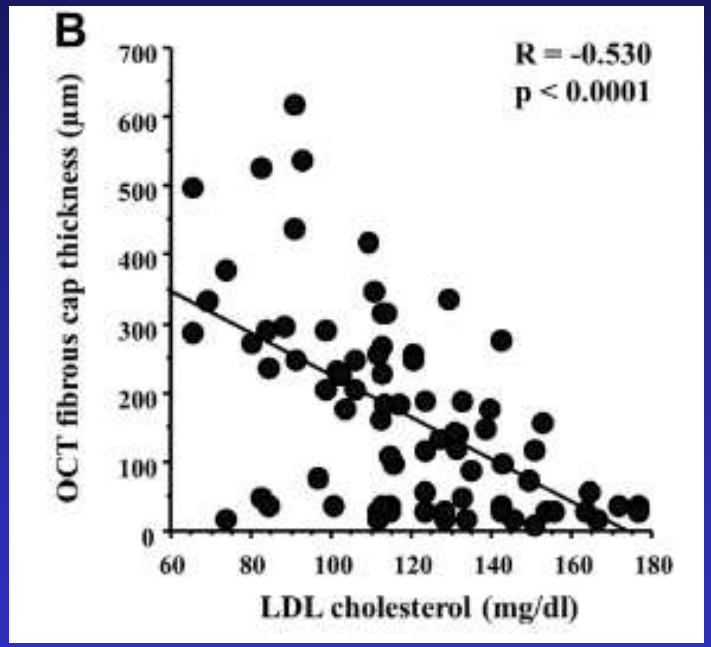
Nasu K, et al. J Am Coll Cardiol Cardiovasc Interv 2013;6:746 - 755

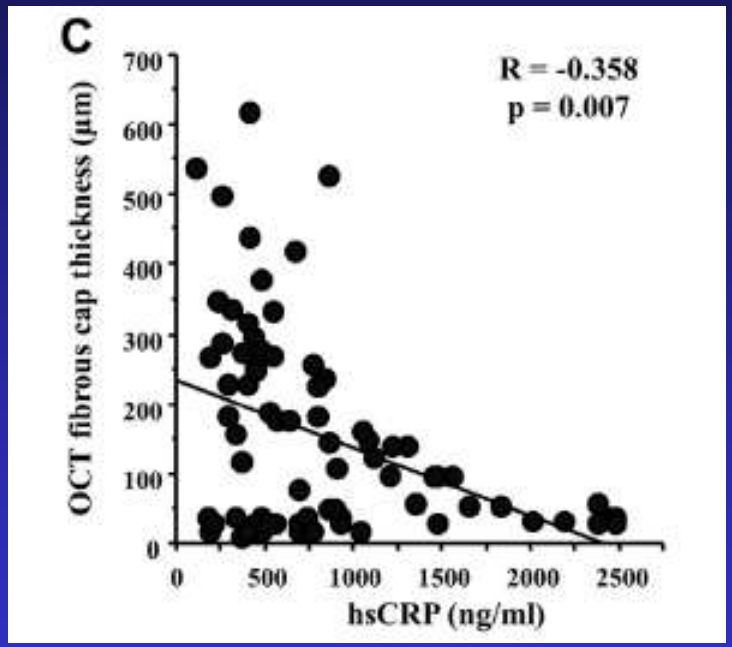


Correlation Between Thinnest Fibrous Cap Thickness Assessed by OCT and Laboratory Data

Nasu K, et al. J Am Coll Cardiol Cardiovasc Interv 2013;6:746 - 755







Summery

Vulnerable Plaque Detection:
Between Biological & Morphological (OCT) Approach

- Not only the presence of TCFA but also the amount of plaque burden, MLD, MLA, the presence of thrombus, etc. would improve to detect vulnerable plaque.
- Biological inflammatory markers, such as hs-CRP, various type of cytokines, etc. may allow us to support in identifing VP more correctly in addition to plaque characteristics.
- Making score by using several biological inflammatory markers in addition to plaque characteristics may lead us identification of vulnerable plaque much more correct and easier.