

シンポジウム②

無症候性冠動脈疾患の重症化予防(急性冠症候群の発症予防)と不安定プラーク

冠動脈CT検査の進歩と不安定プラーク

元山貞子

藤田医科大学 循環器内科



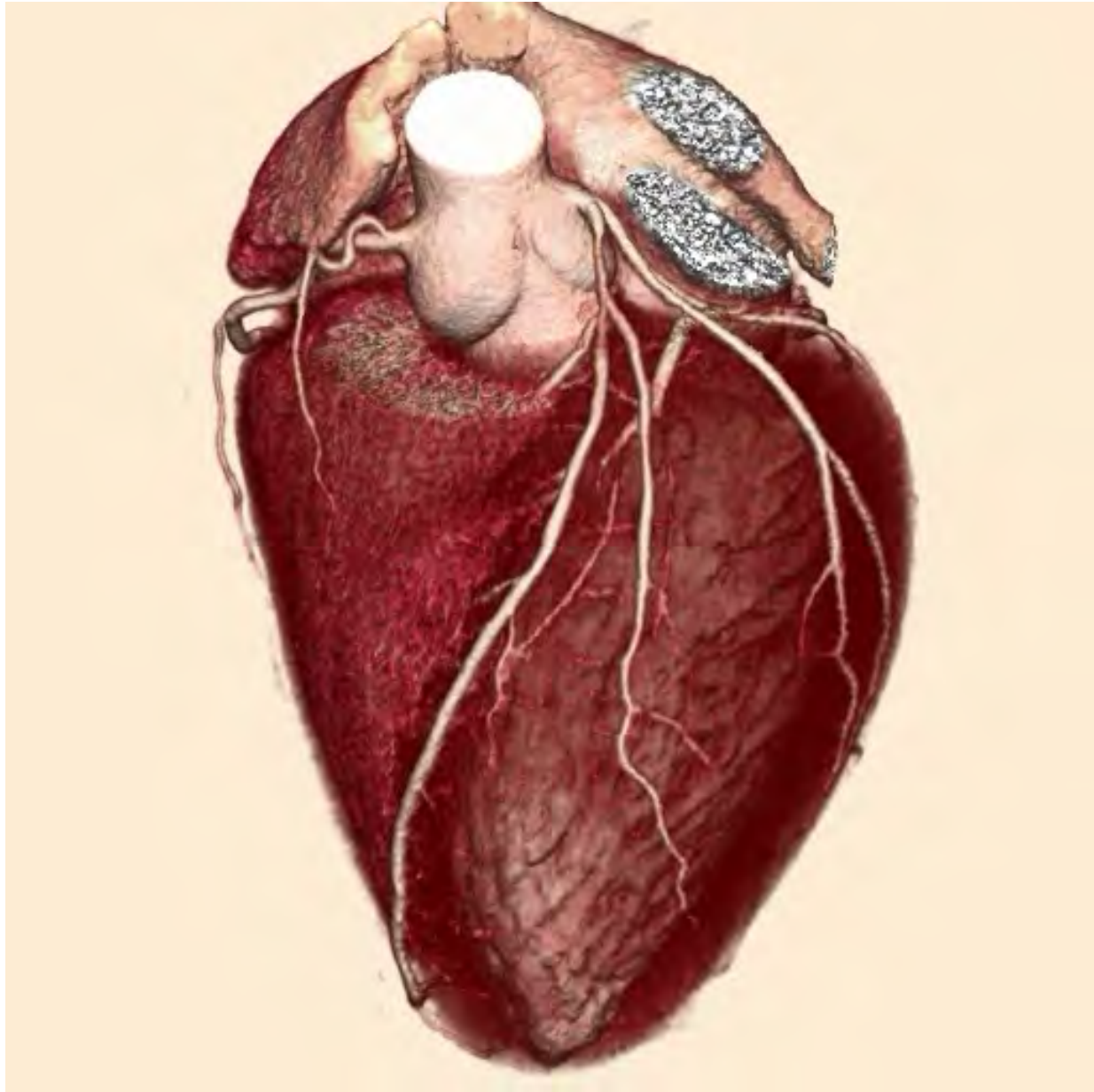
藤田保健衛生大学
FUJITA HEALTH UNIVERSITY

不安定プラークの検出

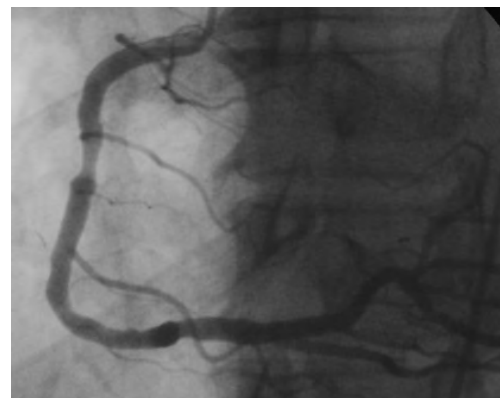
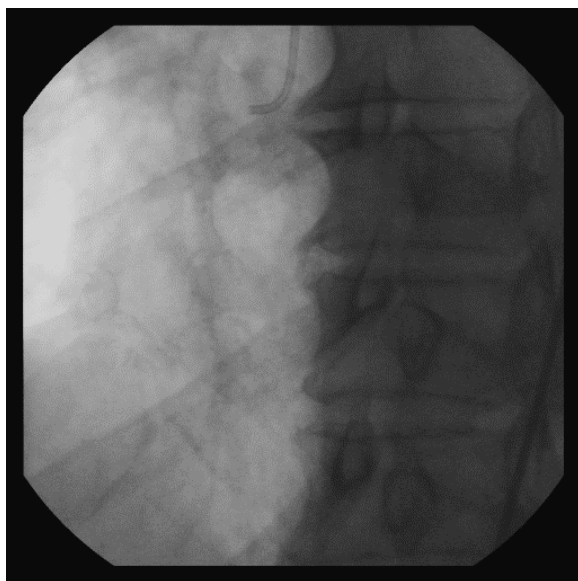
不安定プラークの治療

不安定プラークの検出

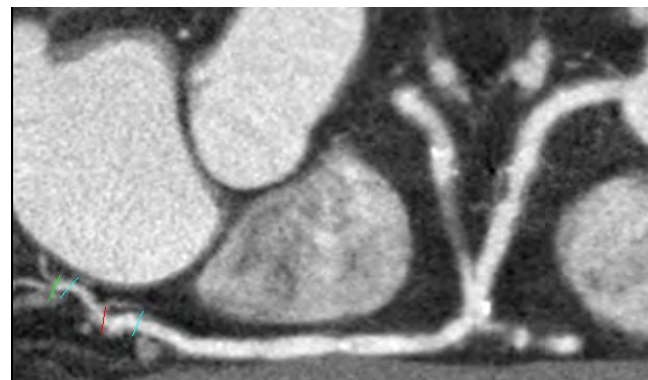
不安定プラークの治療

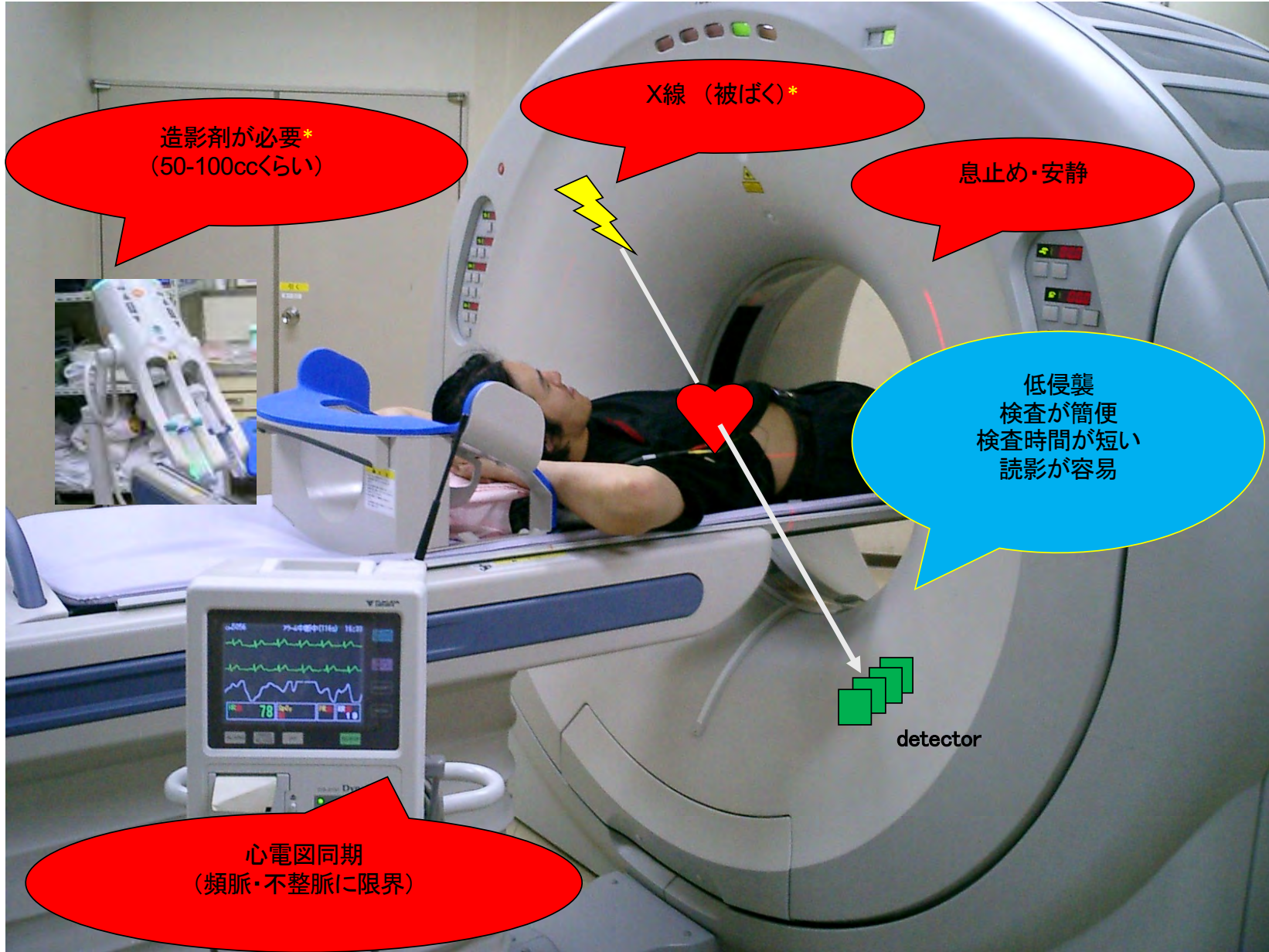


心臓カテーテル検査を用いた
冠動脈造影 (CAG)



冠動脈のCTA画像





造影剤が必要*
(50-100ccくらい)

X線 (被ばく)*

息止め・安静

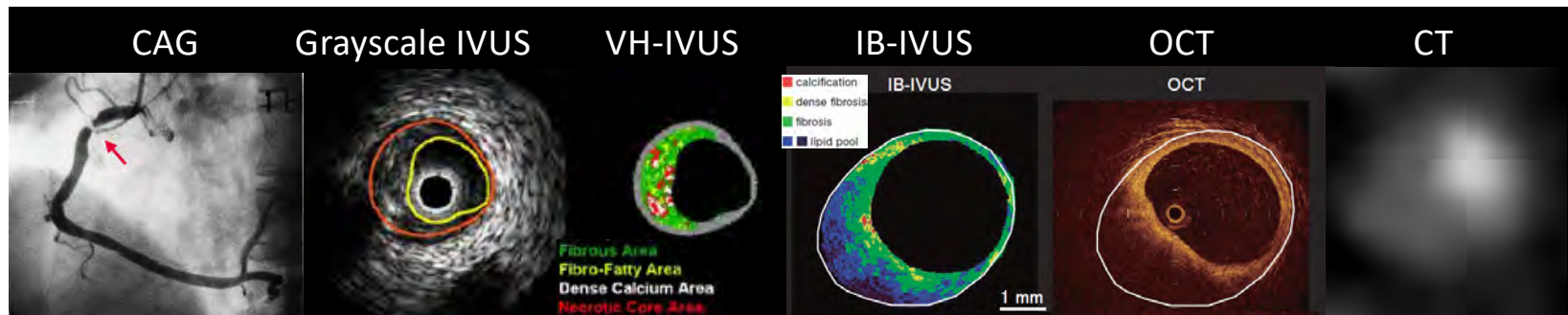
低侵襲
検査が簡便
検査時間が短い
読影が容易

心電図同期
(頻脈・不整脈に限界)

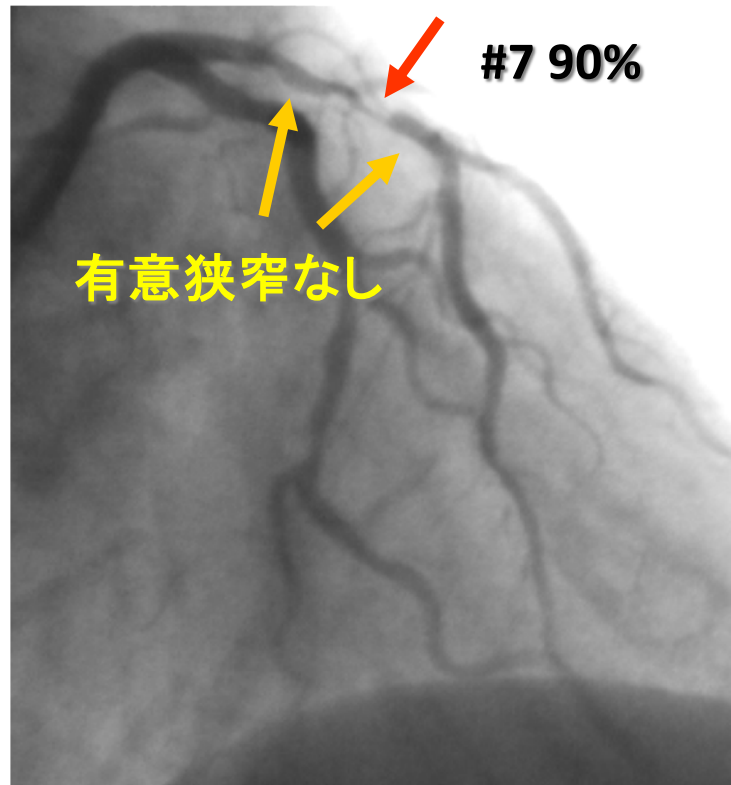
detector

CAG vs. CCTA

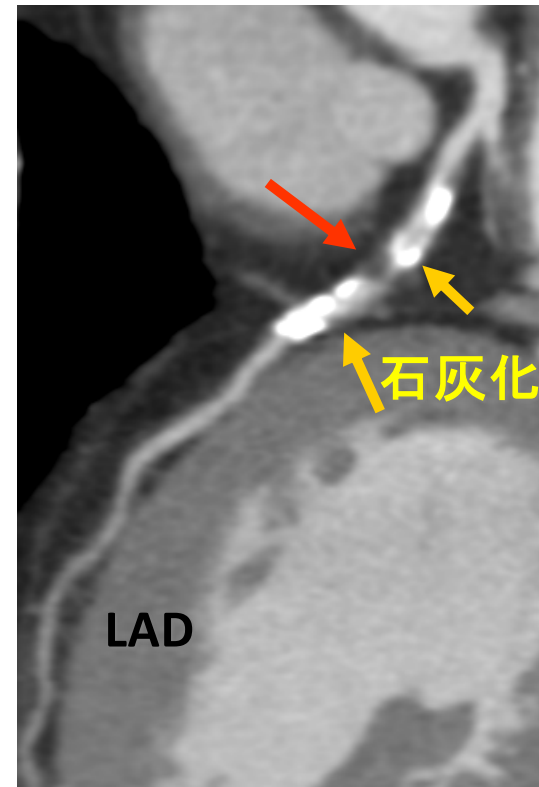
	CAG	CCTA
invasiveness	invasive	Less invasive
Contrast media	Intra coronary injection	Intra venous injection
Radiation dose	3-15 mSv	3-8 mSv
Spatial resolution	0.22mm/pixel	0.3~0.5mm/pixel
Temporal resolution	3 ~ 4 msec	35~150 msec
Arrhythmia / tachycardia	-	limitation
Plaque assessment	No Culprit lesion: IVUS: 100-250 μ m OCT: 10-20 μ m	Yes Culprit and non-culprit lesions (whole heart): 300-500 μ m

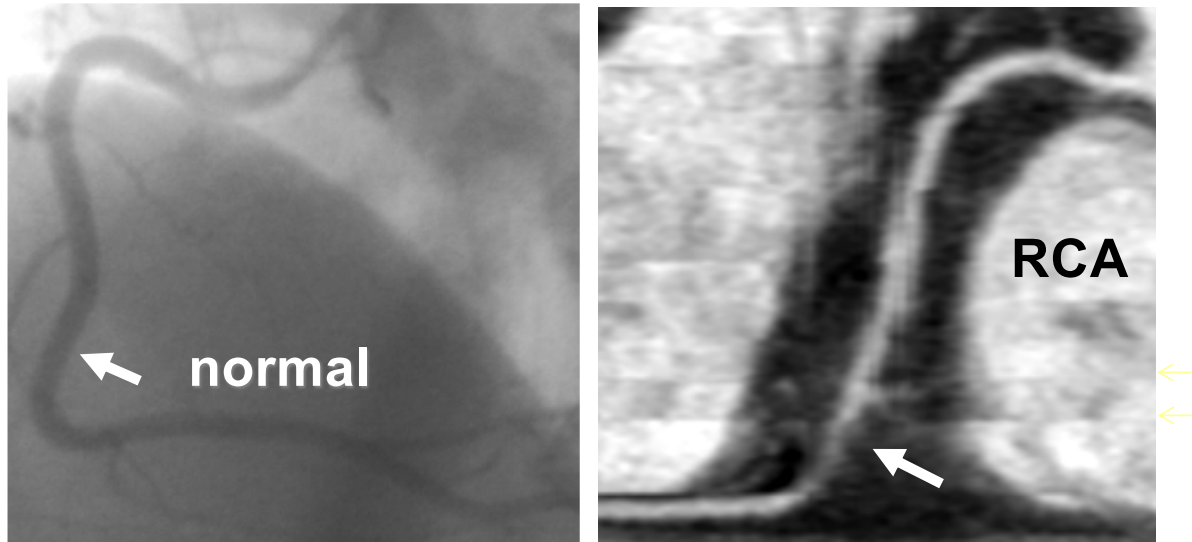


冠動脈造影 (CAG)



CT angiography (CTA)





Diagnostic performance of 64-slice CT to detect obstructive stenosis - meta-analysis of comparison with ICA -

Peach and Weston *BMC Cardiovascular Disorders* 2011, 11:32
<http://www.biomedcentral.com/1471-2261/11/32>



RESEARCH ARTICLE

Open Access

A systematic review of the clinical effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of suspected coronary artery disease

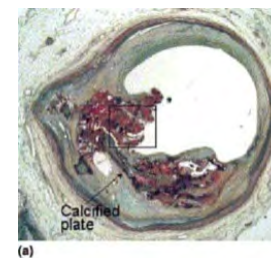
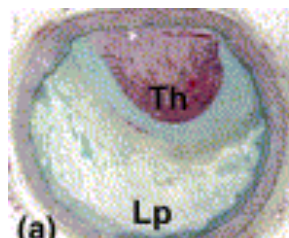
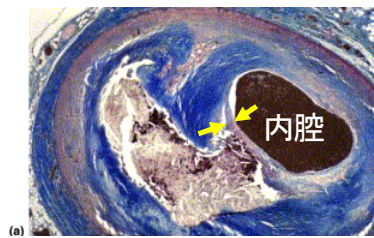
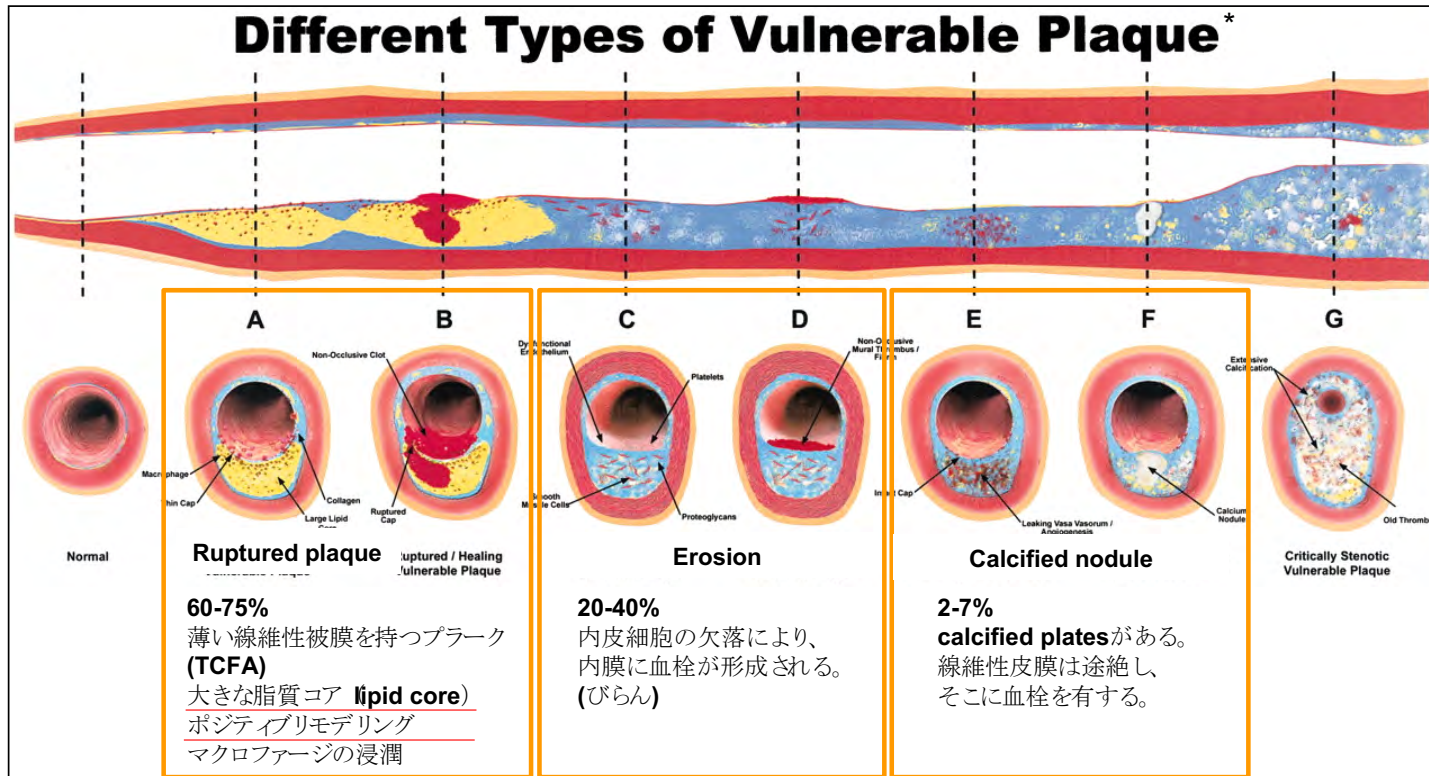
Daniel C Peach* and Adèle R Weston

Coronary Arteries: Diagnostic Performance of 16- versus 64-Section Spiral CT Compared with Invasive Coronary Angiography—Meta-Analysis¹

Vessel based analysis

	Peach, et al.	Hamon, et al.
No. of included studies	17	13
Sensitivity %	94.9	88
Specificity %	89.5	96
PPV	75	79
NPV	99	98
Diagnostic accuracy	91.5	

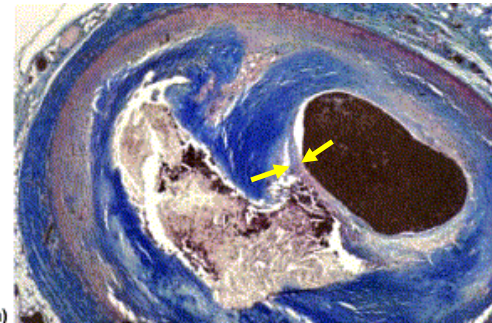
Vulnerable plaqueの病理



*Circulation 2003;108:1664, ** Ebara et al. Circulation. 2004;110:3424-3429, ***Wilson et al. Circulation 2002;105:415-41

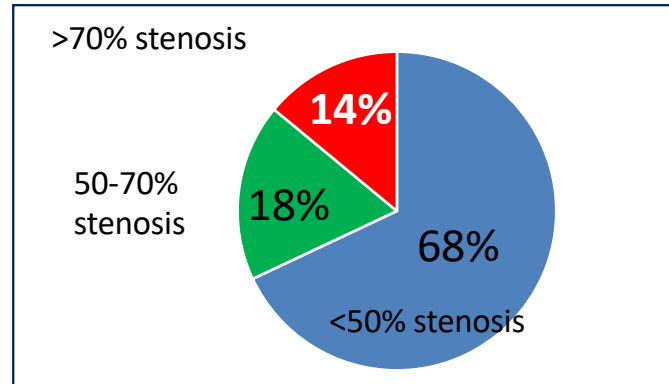
Rupture Plaque and TCFA

Plaque type	Rupture (n=25)	TCFA (n=15)	p value
Necrotic Core %	34±17	23±17	26±20
Fibrous Cap Thickness μm	<u>23±19</u>	<u>≤65</u>	-
Macrophages %	26±20	14±10	0.05



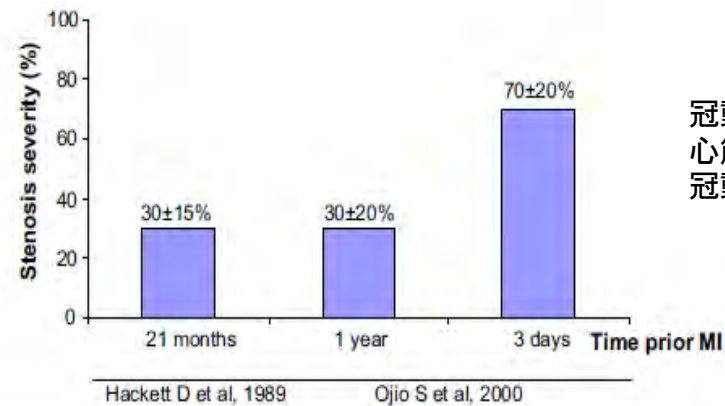
より大きな脂質コア
より薄い線維性被膜

冠動脈造影での冠動脈狭窄度



心筋梗塞前の冠動脈造影では、責任病変の2/3が<50%狭窄

Falk E, et al. *Eur Heart J* 2013;34:719–28.
 Ambrose JA, et al. *J Am Coll Cardiol* 1988;12:56–62.
 Little WC et al. *Circulation* 1988;78:1157–1166.
 Giroud D, et al. *Am J Cardiol* 1992;69:729–732.



冠動脈造影から心筋梗塞までの期間：心筋梗塞発症直前の冠動脈造影では冠動脈の高度狭窄を認めた

Niccoli G, et al. *JACC Cardiovasc Imaging*. 2013 ; 10)1108-1114.
 Ojio S, et al. *Circulation* 2000;102:2063–9. Hackett D, et al. *Am J Cardiol* 1989;63:1517–1518.

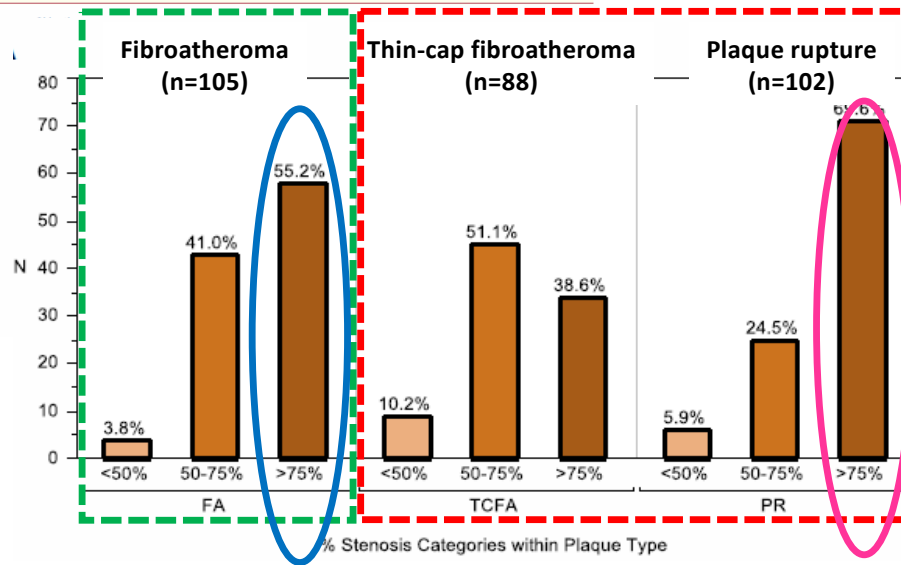
Histopathologic Characteristics of Atherosclerotic Coronary Disease and Implications of the Findings for the Invasive and Noninvasive Detection of Vulnerable Plaques

Jagat Narula, MD, PhD,* Masataka Nakano, MD, PhD,† Renu Virmani, MD,† Frank D. Kolodgie, PhD,‡ Rita Petersen, MS,‡ Robert Newcomb, PhD,‡ Shaista Malik, MD, PhD,‡ Valentin Fuster, MD, PhD,§ Aloke V. Finn, MD||
New York, New York; Gaithersburg, Maryland; Irvine, California; Madrid, Spain; and Atlanta, Georgia

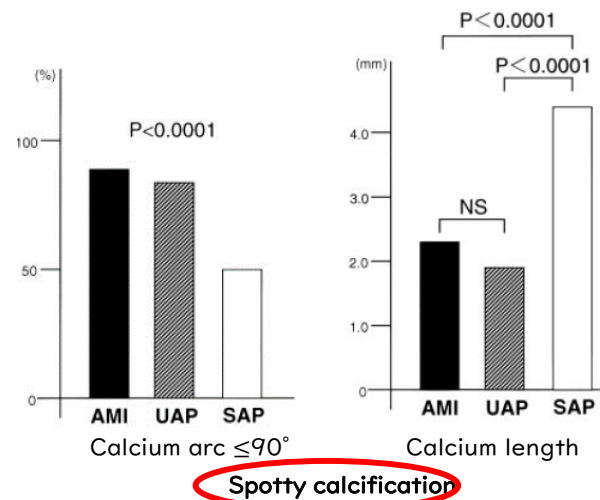
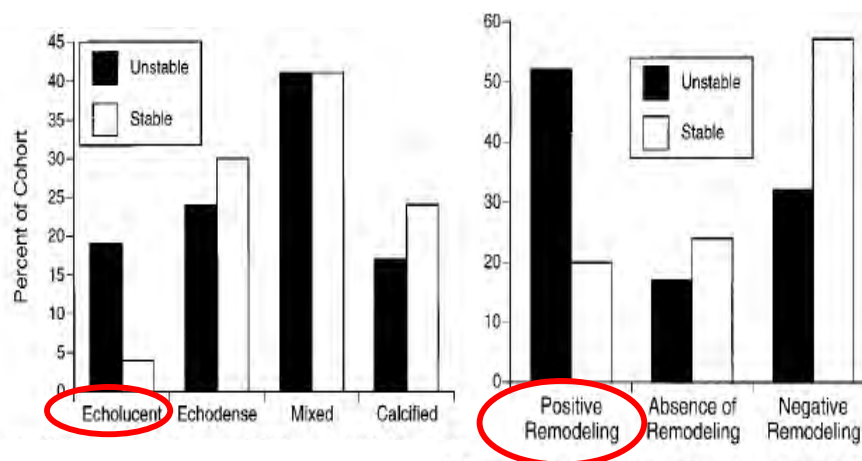
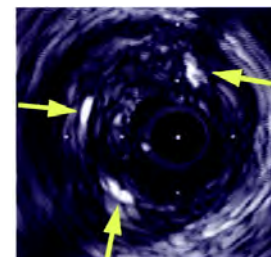
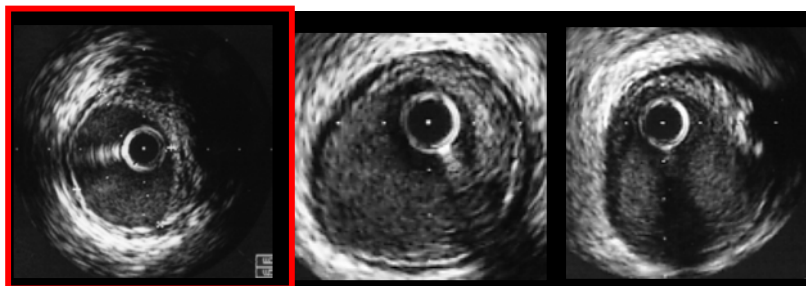
プラーク性状と血管内腔狭窄度

Vulnerable plaqueは
Plaque ruptureの直前には、内腔が狭くなる

Stable plaqueとの区別は、狭窄度だけでは困難
狭窄度だけでは、プラーク性状はわからない



IVUSでのACS責任病変の特徴



Schoenhagen P, et al. *Circulation*. 2000;101:598-603.

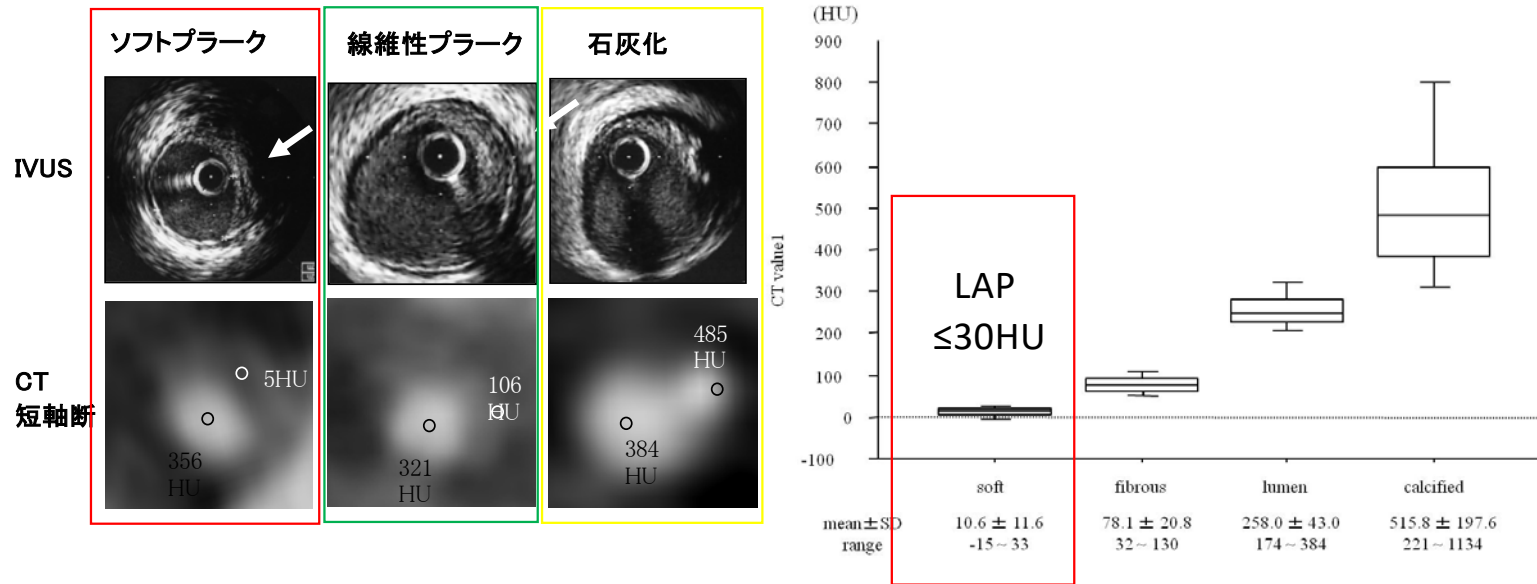
Ehara et al. *Circulation*. 2004;110:3424-3429

CTAでの冠動脈プラーク評価

CT plaque characteristics compared with histology or IVUS

Study	slice thickness	rotation speed(ms)	slice	reference	CT attenuation (mean±SD [HU])		
					soft	fibrous	calcification
Becker et al	0.6mm	500	4	histology	47±9	104±28	
Schroeder et al.	1.0mm	500	4	histology	42±22	70±21	715±328
Schroeder et al.	1.0mm	500	4	IVUS	14±26	91±21	419±194
Leber et al.	0.75mm	420	12	IVUS	49±22	91±22	391±156
Pohle et al	0.75mm	375/420	16	IVUS	58±43	121±39	
<i>Motoyama et al.</i>	0.5mm	400	16	IVUS	11±12	78±21	516±198
Hur et al.	1.0mm	330	64	IVUS	54±13	82±17	392 ±155

CT= computed tomography, IVUS= intravascular ultrasound, SD=standard deviation, HU=Hounsfield unit

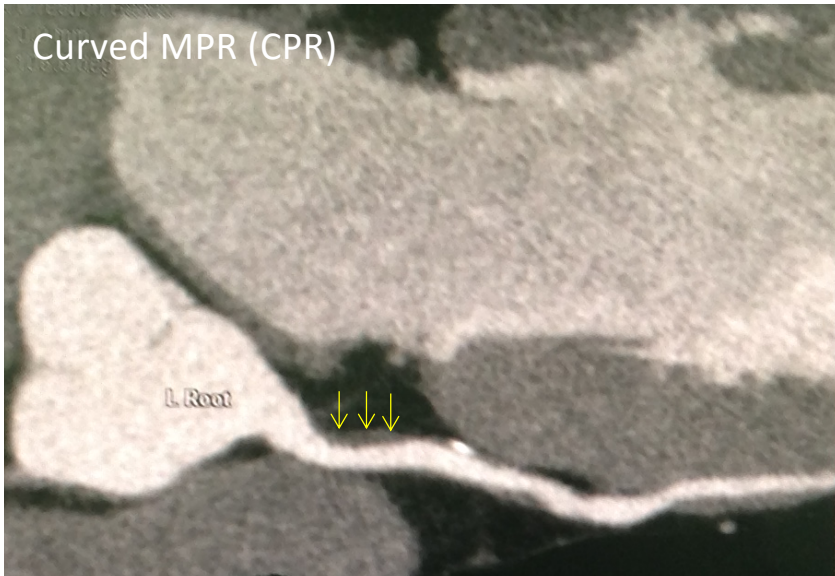


Motoyama et al. Circ J 2007;71:363-366

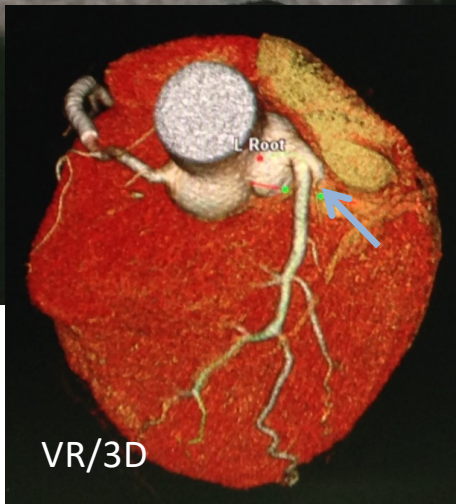
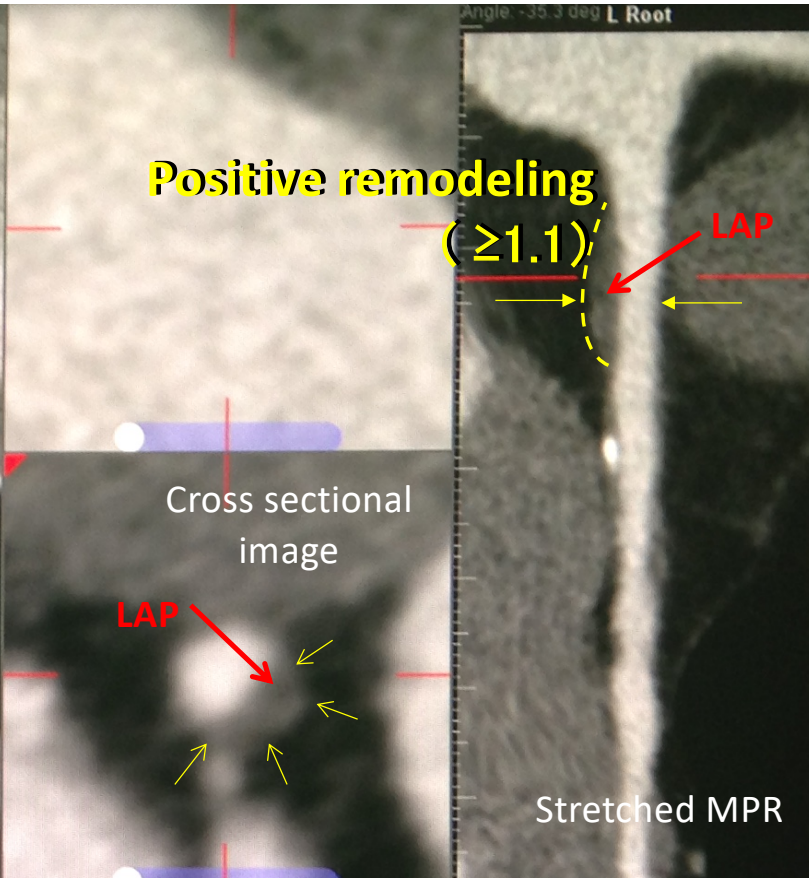
Fig. 2

p < 0.0001, Nonparametric Kruskal-Wallis test

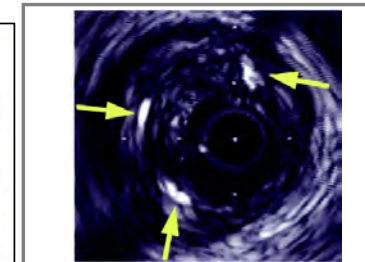
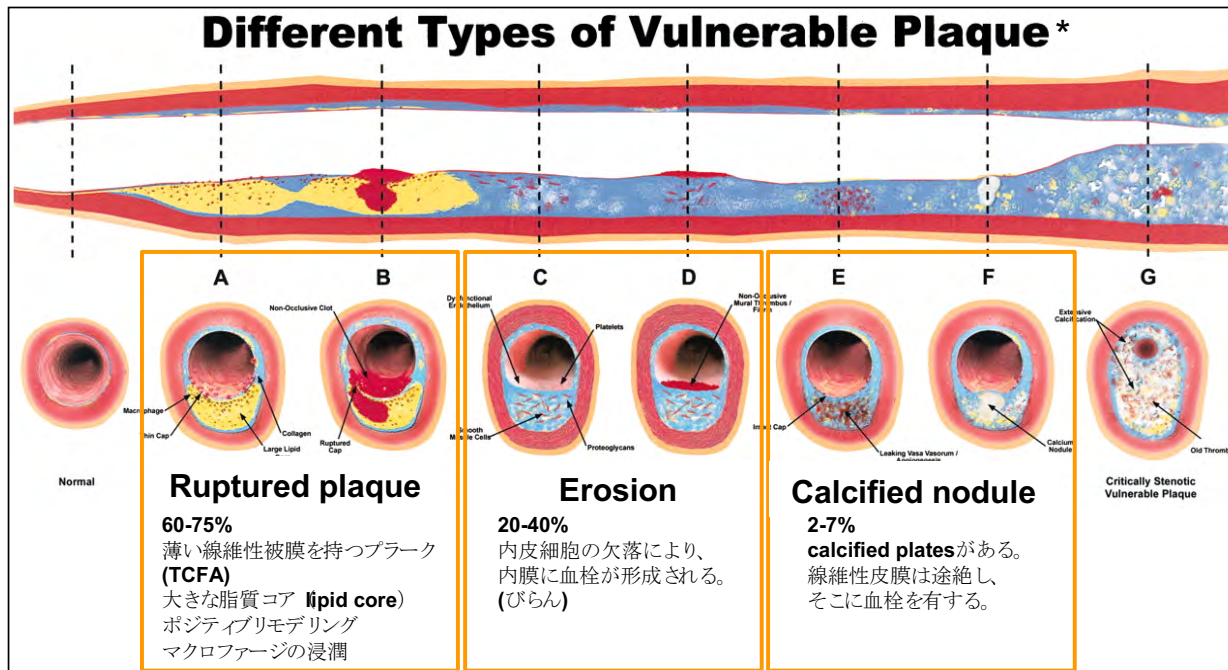
Curved MPR (CPR)



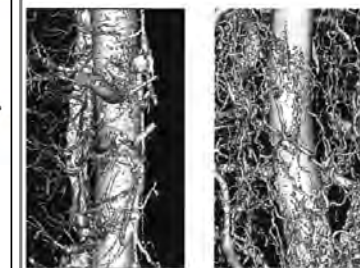
Positive remodeling
(≥ 1.1)



不安定プラークの特徴



Spotty calcification on IVUS**



N HC
Vasa Vasorum***

Thin-cap fibroatheroma (TCFA)	x
large lipid core:	○ : LAP with <30HU
positive remodeling:	○ : >110% in diameter
macrophage infiltration:	x
spotty calcification:	○ : one-sided / the length of <3mm
vasa varorum:	x

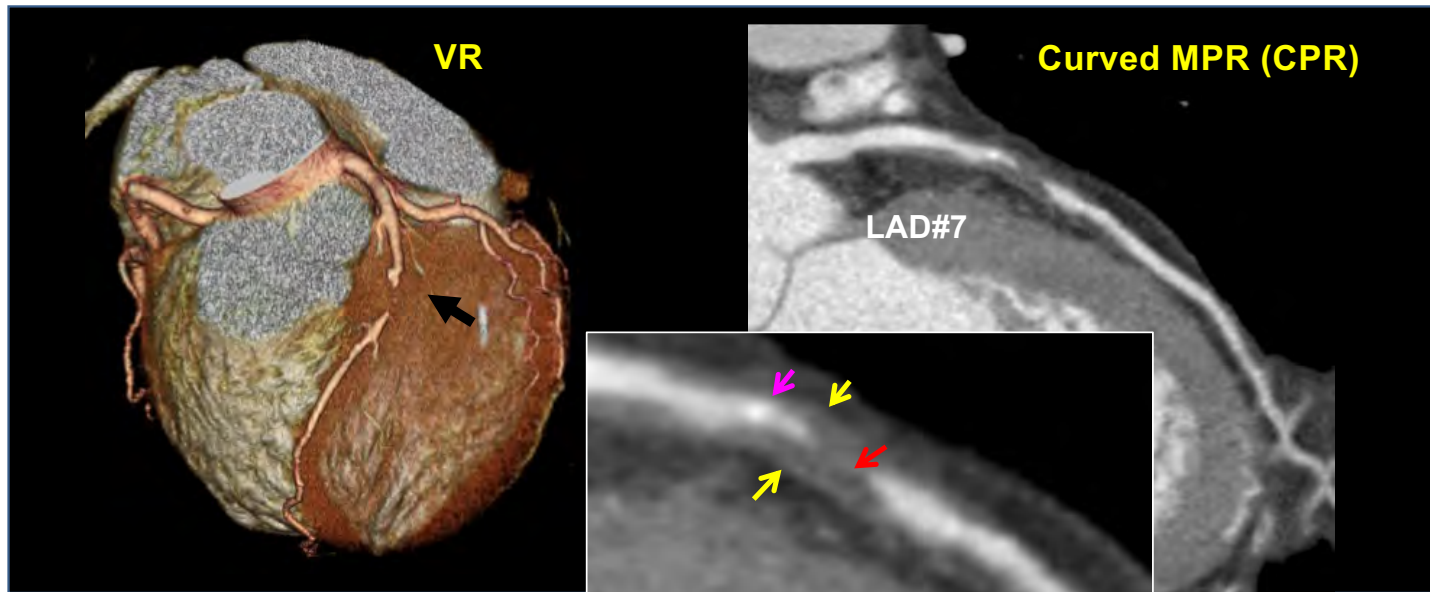
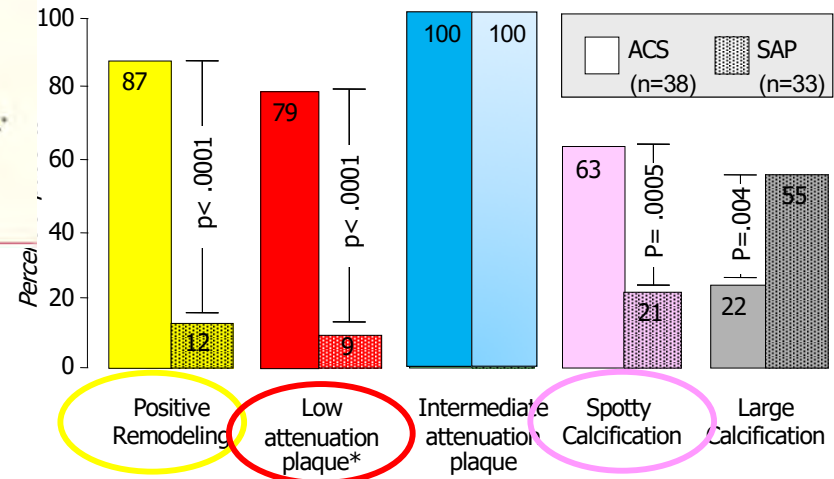
*Circulation 2003;108:1664, ** Ehara et al. Circulation. 2004;110:3424-3429 , ***Wilson et al. Circulation 2002;105:415-41

Multislice Computed Tomographic Characteristics of Coronary Lesions in Acute Coronary Syndromes

Sadako Motoyama, MD, PhD,* Takeshi Kondo, MD, PhD,† Masayoshi Sarai, MD, PhD,* Atsushi Sugiura, MD, PhD,* Hiroto Harigaya, MD,* Takahisa Sato, MD, PhD,* Kaori Inoue, MD,* Masanori Okumura, MD,* Junichi Ishii, MD, PhD,* Hirofumi Anno, MD, PhD,‡ Renu Virmani, MD, FACC,§ Yukio Ozaki, MD, PhD,* Hitoshi Hishida, MD, PhD,* Jagat Narula, MD, PhD, FACC¶

Toyoake and Takasaki, Japan; Gaithersburg, Maryland; and Irvine, California

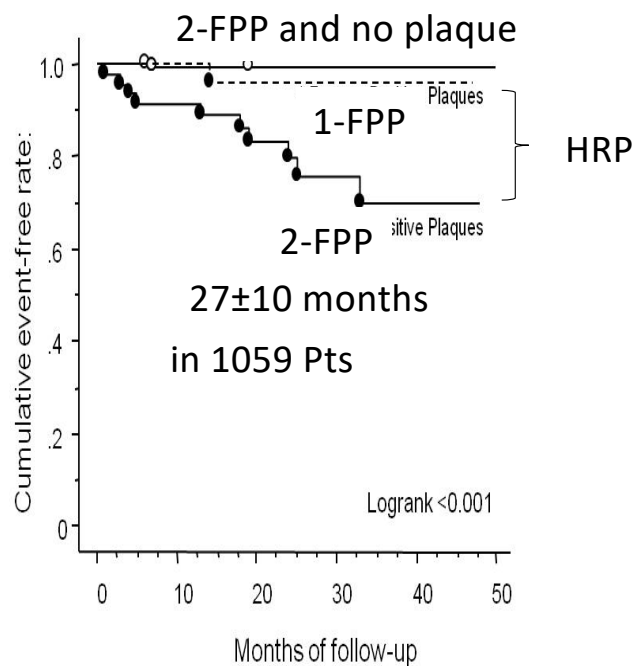
Culprit lesions of ACS



Motoyama et al. J Am Coll Cardiol 2007;50:319-326,

**Computed Tomographic Angiography
Characteristics of Atherosclerotic Plaques
Subsequently Resulting in Acute Coronary Syndrome**

Sadako Motoyama, MD, PhD,*‡ Masayoshi Sarai, MD, PhD,* Hiroto Harigaya, MD,* Hirofumi Anno, MD, PhD,† Kaori Inoue, MD,* Tomonori Hara, MD,* Hiroyuki Naruse, MD, PhD,* Junichi Ishii, MD, PhD,* Hitoshi Hishida, MD, PhD,* Nathan D. Wong, PhD,‡ Renu Virmani, MD,§ Takeshi Kondo, MD, PhD,|| Yukio Ozaki, MD, PhD,* Jagat Narula, MD, PhD‡
Toyoake and Takasaki, Japan; Irvine, California; and Gaithersburg, Maryland

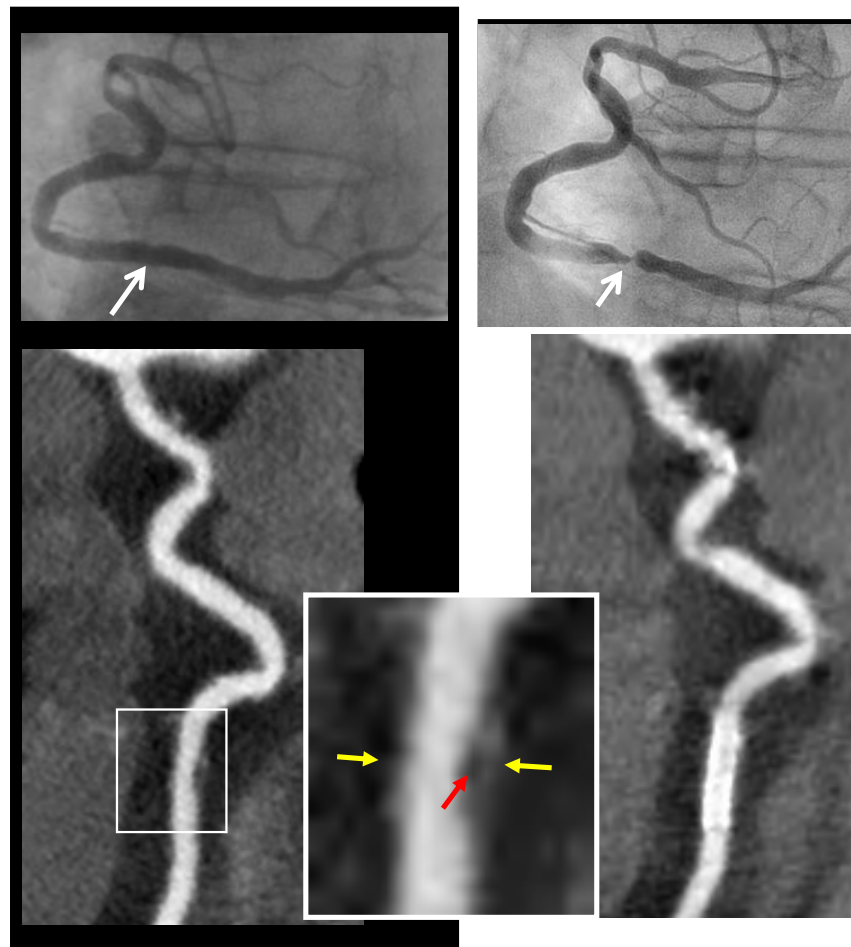


- Non-culprit lesions with **PR** or **LAP** had higher risk of ACS with follow-up of **27 months** in **1059 pts**.
- **Sp-Ca** was not significantly different (27 vs. 13%, p=0.31) between ACS(+) and ACS(-).

ACSの発症率が高いHRP

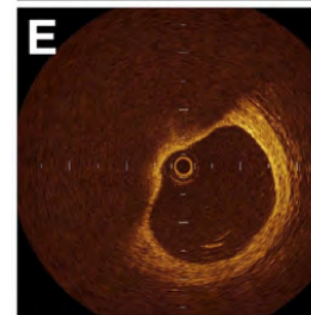
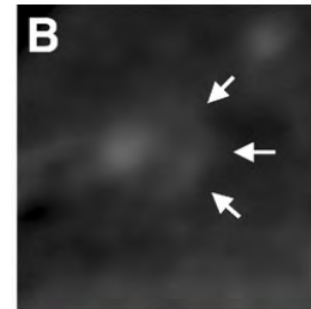
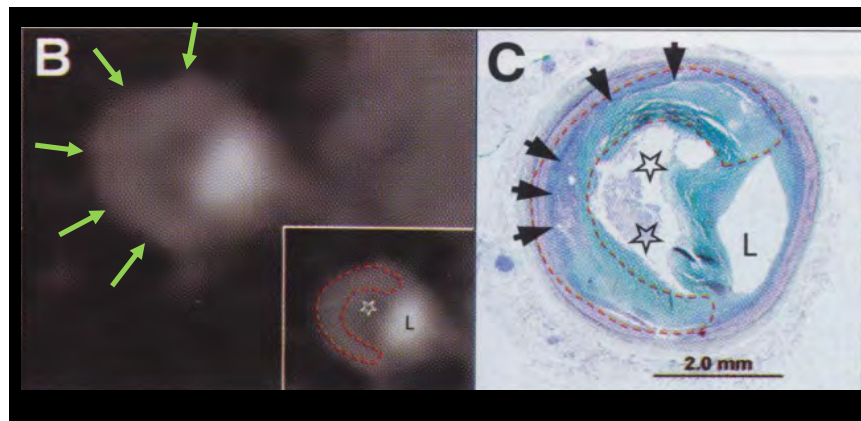
High risk plaque

ACS in 20 months



Motoyama et al. J Am Coll Cardiol 2009

Napkin-ring sign (Ring-like sign)

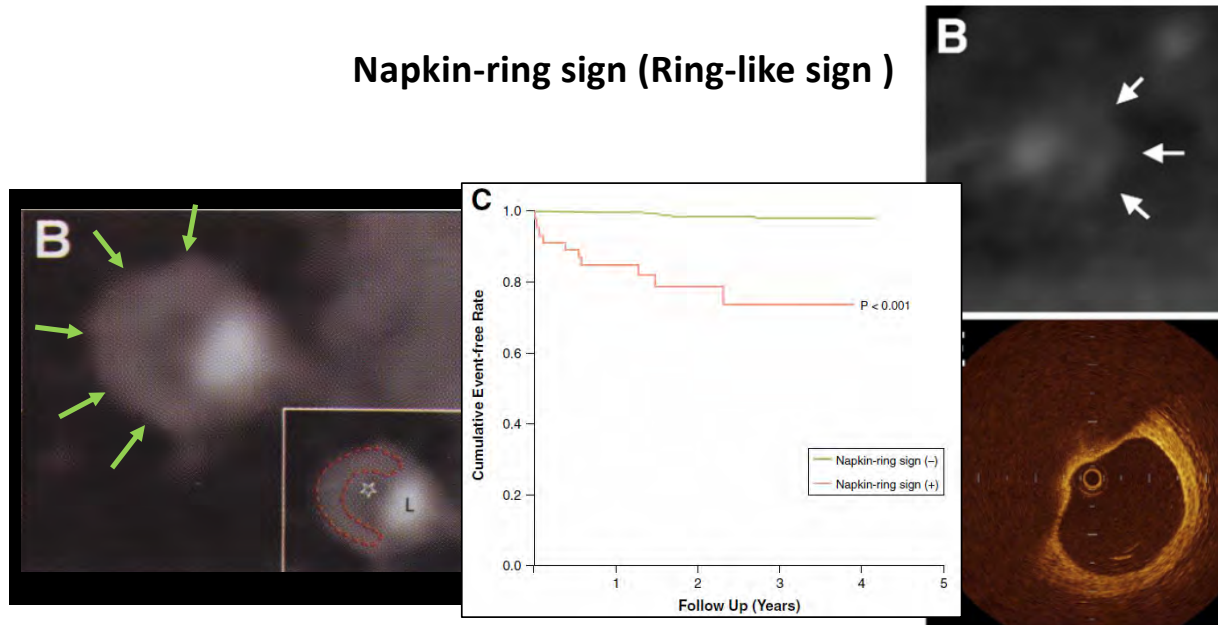


a hyperdense ring-like structure surrounding a hypodense center

Delineation of NRS in CCTA is independently linked to the size of the necrotic/lipid core, the size of the non-core plaque and to the vessel area

JACC Cardiovasc Imaging
2010;3:440-4,
JACC Cardiovasc Imaging
2012;5:1243-52
Atherosclerosis 2012;224:90-96
JACC Cardiovasc Imaging
2009;2:1412-9
JACC Cardiovasc Imaging
2013;6:448-57

Napkin-ring sign (Ring-like sign)



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Delineation of NRS in CCTA is independently linked to
the size of the necrotic/lipid core,
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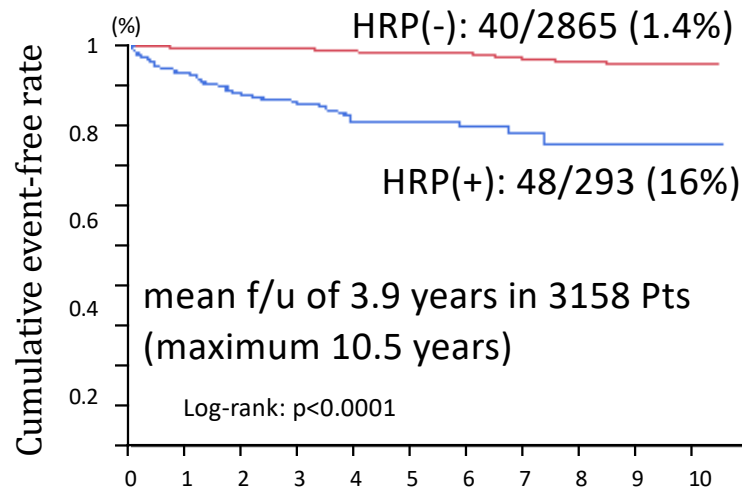
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JACC Cardiovasc Imaging
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Plaque Characterization by Coronary Computed Tomography Angiography and the Likelihood of Acute Coronary Events in Mid-Term Follow-Up

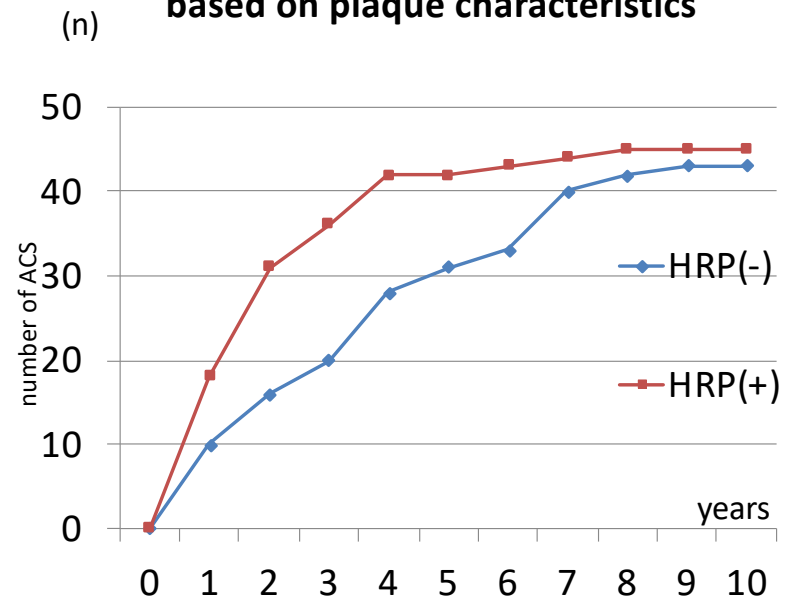


Sadako Motoyama, MD, PhD,*¹ Hajime Ito, MD, PhD,*² Masayoshi Sarai, MD, PhD,*³ Takeshi Kondo, MD, PhD,*⁴ Hideki Kawai, MD, PhD,*⁵ Yasuomi Nagahara, MD,*⁶ Hiroto Harigaya, MD, PhD,*¹ Shino Kan, MD,*¹ Hirofumi Anno, MD, PhD,⁷ Hiroshi Takahashi, BSc,⁸ Hiroyuki Naruse, MD, PhD,*⁹ Junichi Ishii, MD, PhD,*¹⁰ Harvey Hecht, MD,¹¹ Leslee J. Shaw, PhD,*¹² Yukio Ozaki, MD, PhD,¹³ Jagat Narula, MD, PhD¹⁴

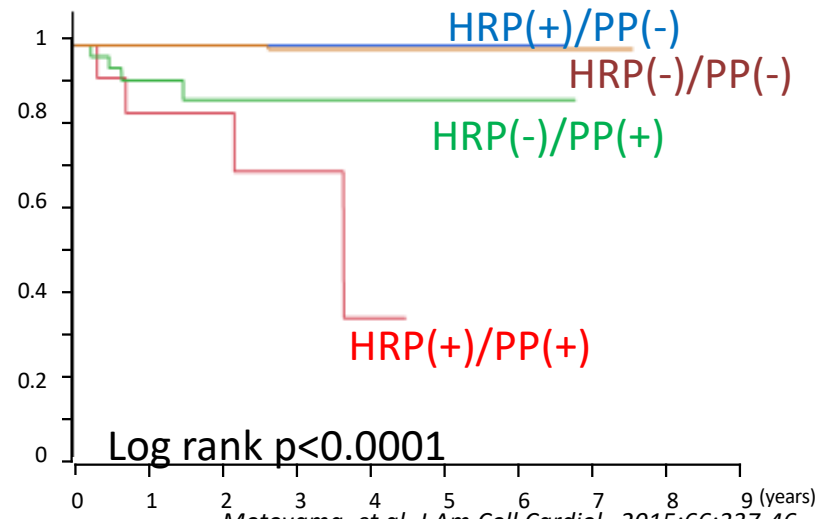
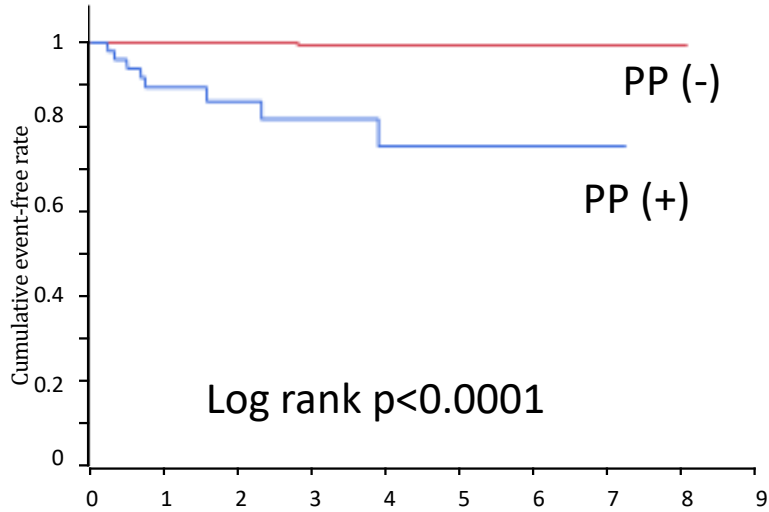
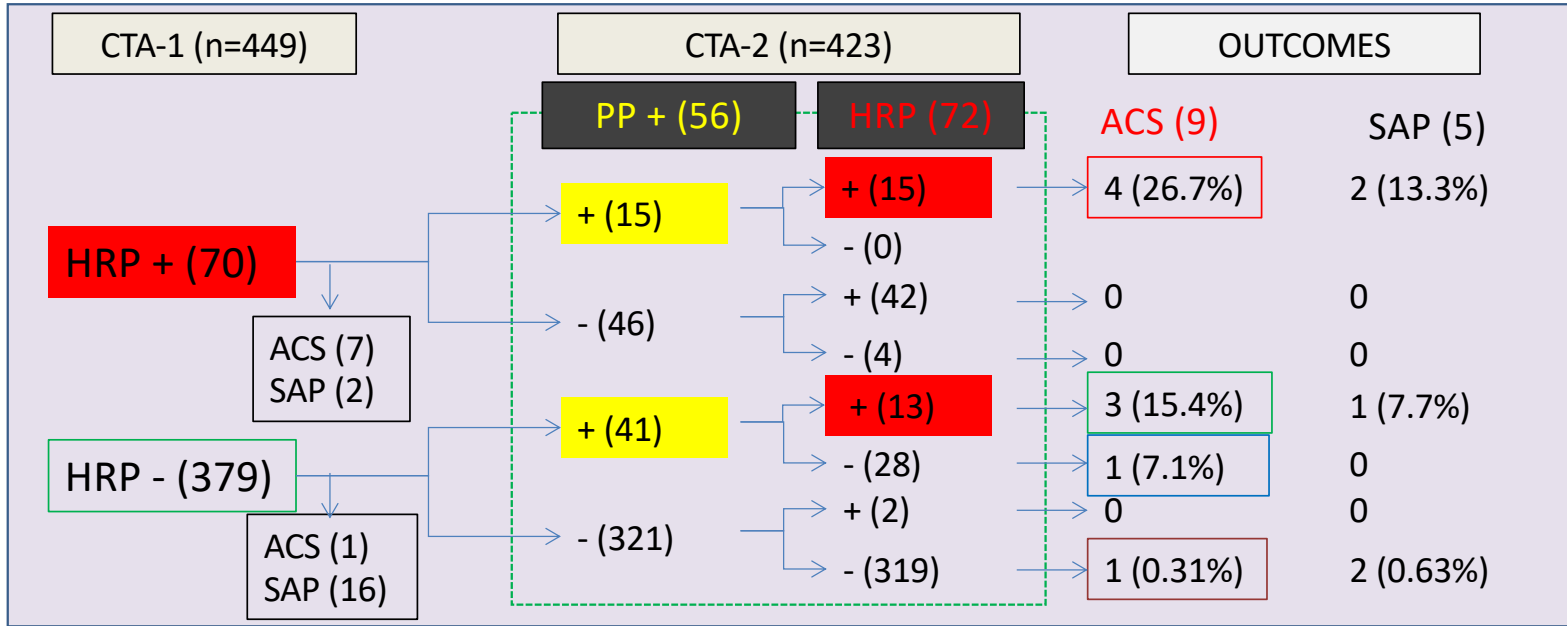
Patient based analysis: Event **rate** based on plaque characteristics



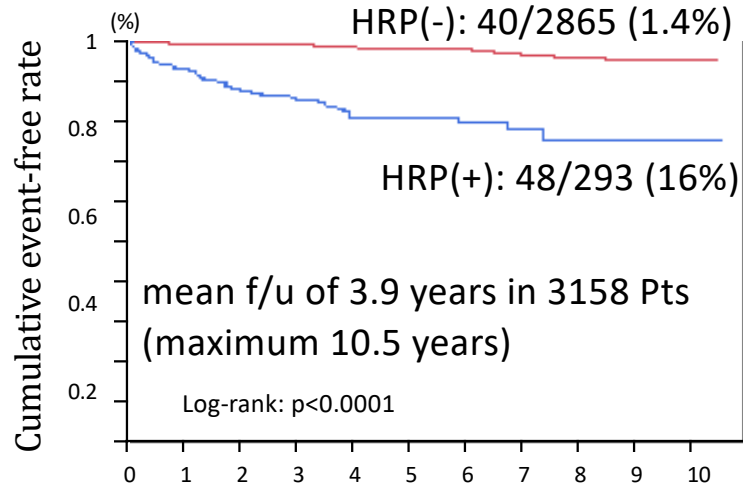
Lesion based analysis: cumulative number of ACS patients based on plaque characteristics



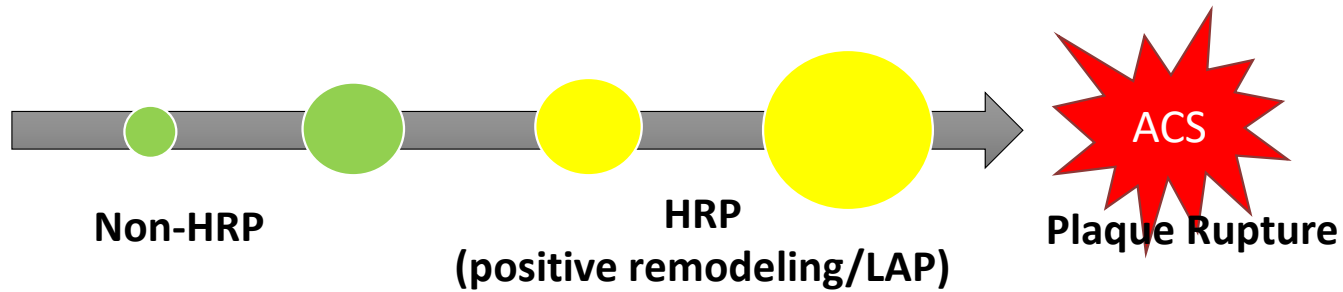
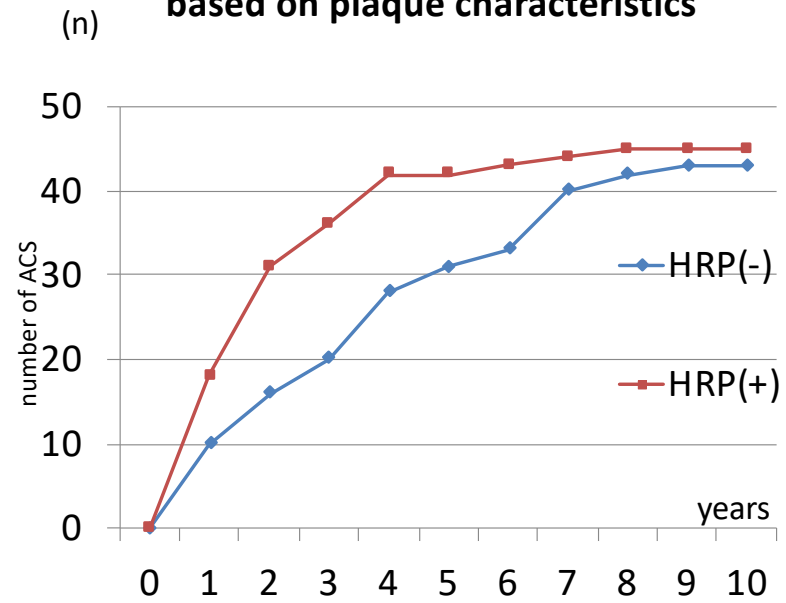
Serial CTA analysis (f/u 4.1 years: CTA1-2 1 year)



**Patient based analysis:
Event rate based on
plaque characteristics**



**Lesion based analysis:
cumulative number of ACS patients
based on plaque characteristics**



Comparison of *pathology* between ruptured plaque and un-ruptured TCFA

<病理>

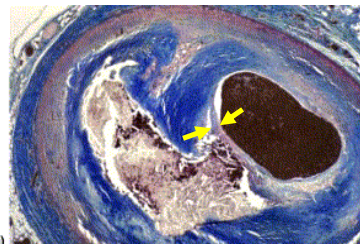
Plaque type	Rupture (n=25)	TCFA (n=15)	p value
Necrotic Core %	34±17	23±17	26±20
Fibrous Cap Thickness μm	<u>23±19</u>	<u><65</u>	-
Macrophages %	26±20	14±10	0.05

Comparison of *CT characteristics* of HRP which subsequently developed or did not develop ACS

<CT>

	ACS n=11	No ACS n=63	<i>p</i>
	Mean±SE (95%CI)		
Remodeling index (%)	126.7±3.9 (118.9–134.5)	113.4±1.6 (110.2–116.6)	0.003
total plaque volume (mm ³)	134.9±14.1 (106.8–162.9)	57.8±5.7 (46.3–69.2)	<0.001
LAP volume (mm ³)	20.4±3.4 (13.58–27.21)	1.1±1.4 (-1.7–3.9)	<0.001

*TICFA: plaque at the other site resemble the rupture plaque bu



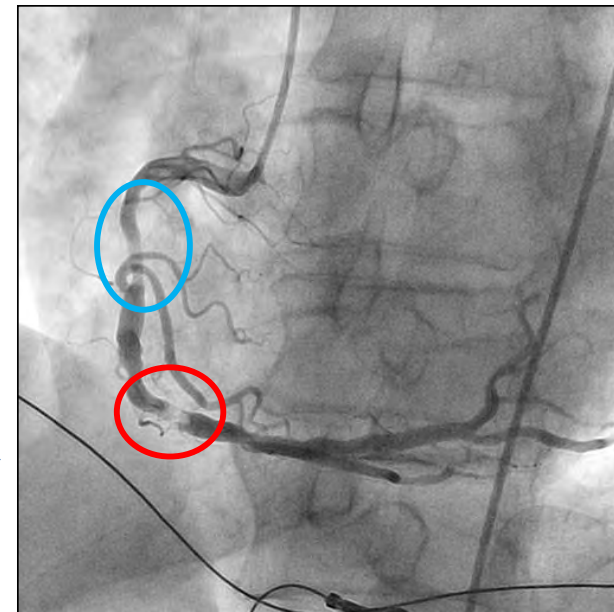
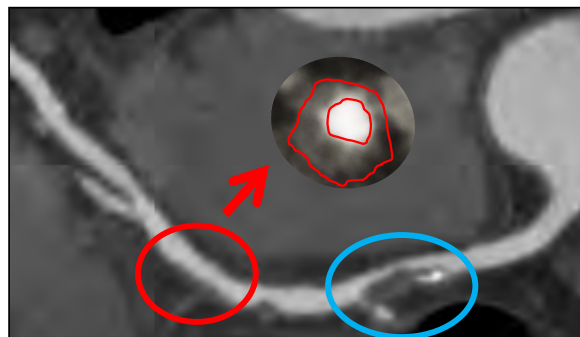
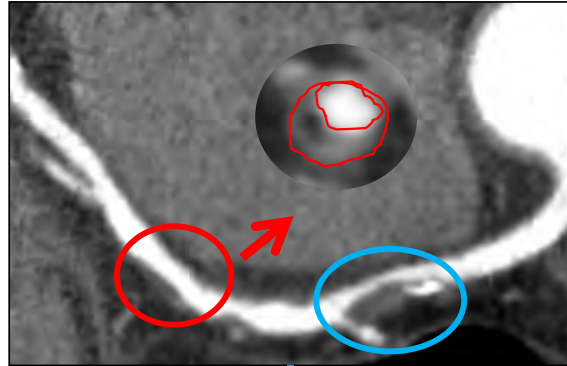
Virmani, JACC 2006;47:C13-18

ANCOVA adjusted for age, hypertension, hyperlipidemia, prior myocardial infarction. NCP=non-calcified plaque

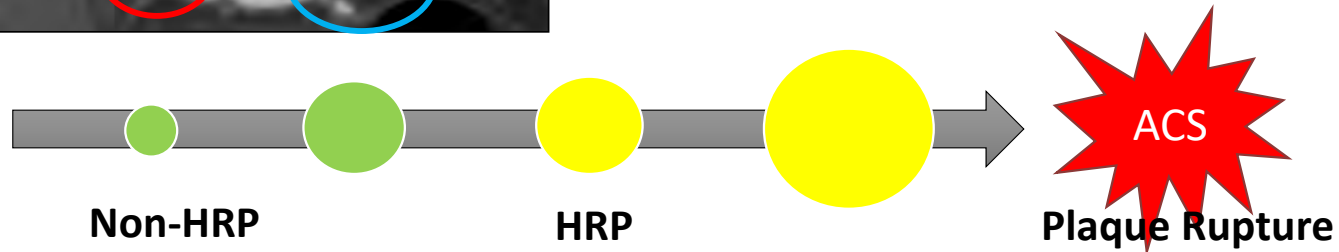
Motoyama Narula, et al. J Am Coll Cardiol 2009

Serial change of HRP

RCA



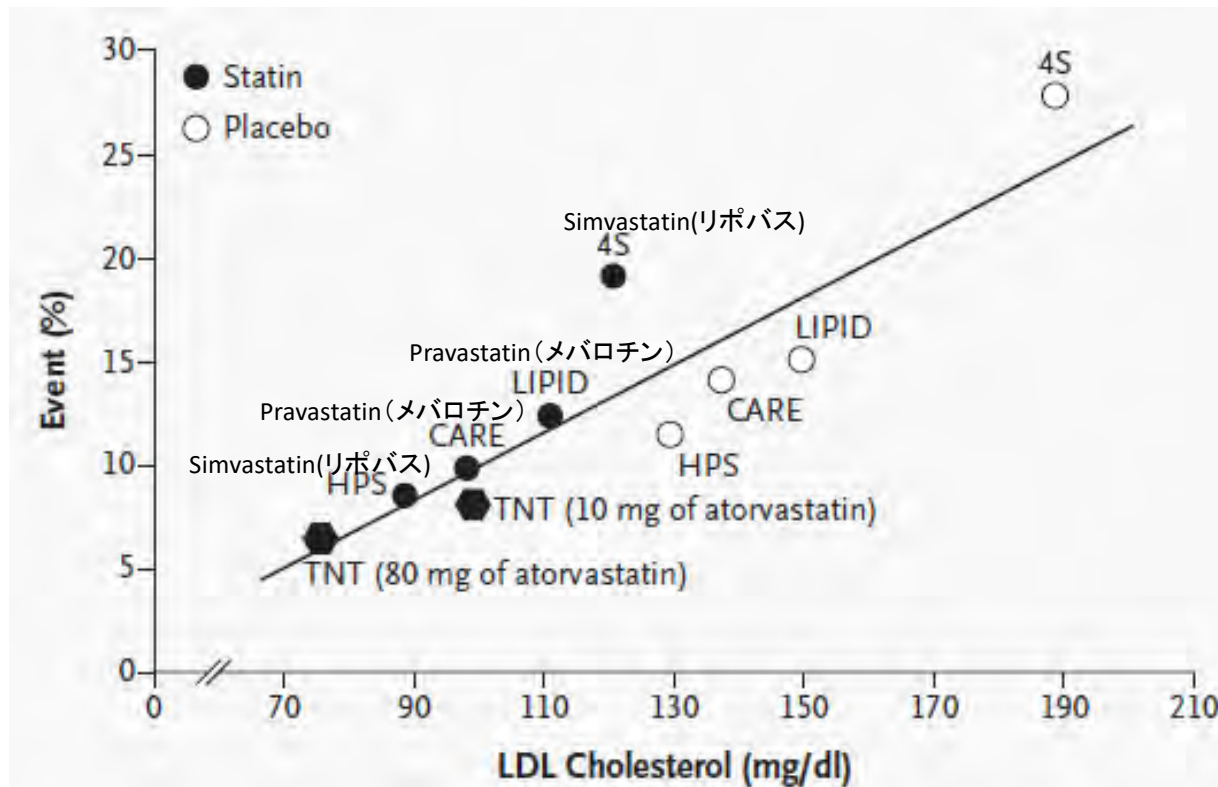
ACS at 3 years after 1st CTA



- 不安定プラークの検出
 - ハイリスクプラーク: PR、LAP
 - プラーク進展 (plaque progression)
- 不安定プラークの治療

- 不安定プラークの検出
 - ハイリスクプラーク: PR、LAP
 - プラーク進展 (plaque progression)
- 不安定プラークの治療

LDL-C値と心血管イベント



Serial Coronary CT Angiography–Verified Changes in Plaque Characteristics as an End Point

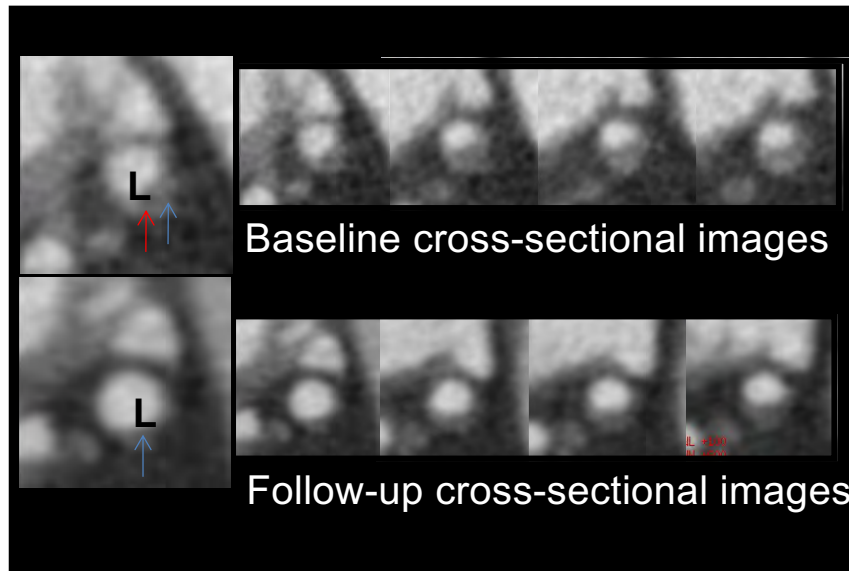
Evaluation of Effect of Statin Intervention

Kaori Inoue, MD,* Sadako Motoyama, MD, PhD,* Masayoshi Sarai, MD, PhD,*
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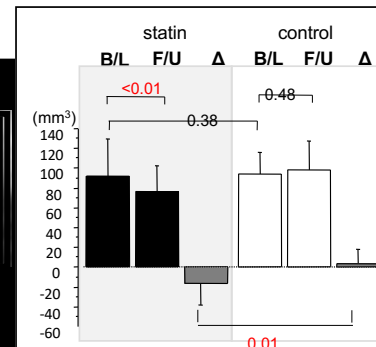
Toyoake and Takasaki, Japan; and Irvine, California



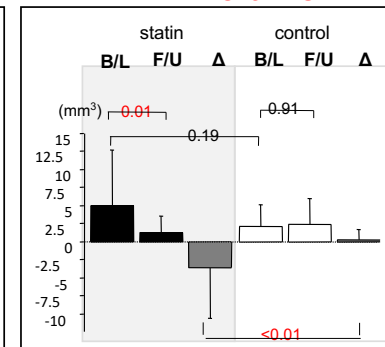
スタチンによるプラーク変化



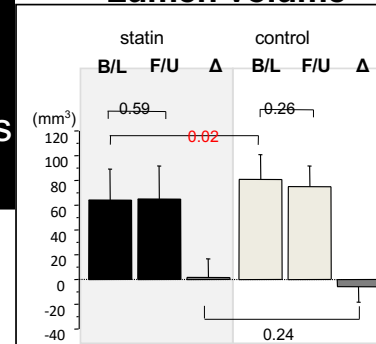
Total plaque volume



LAP volume



Lumen volume



Remodeling index

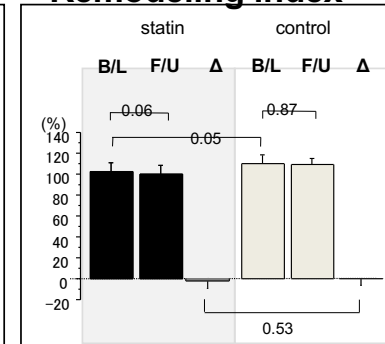
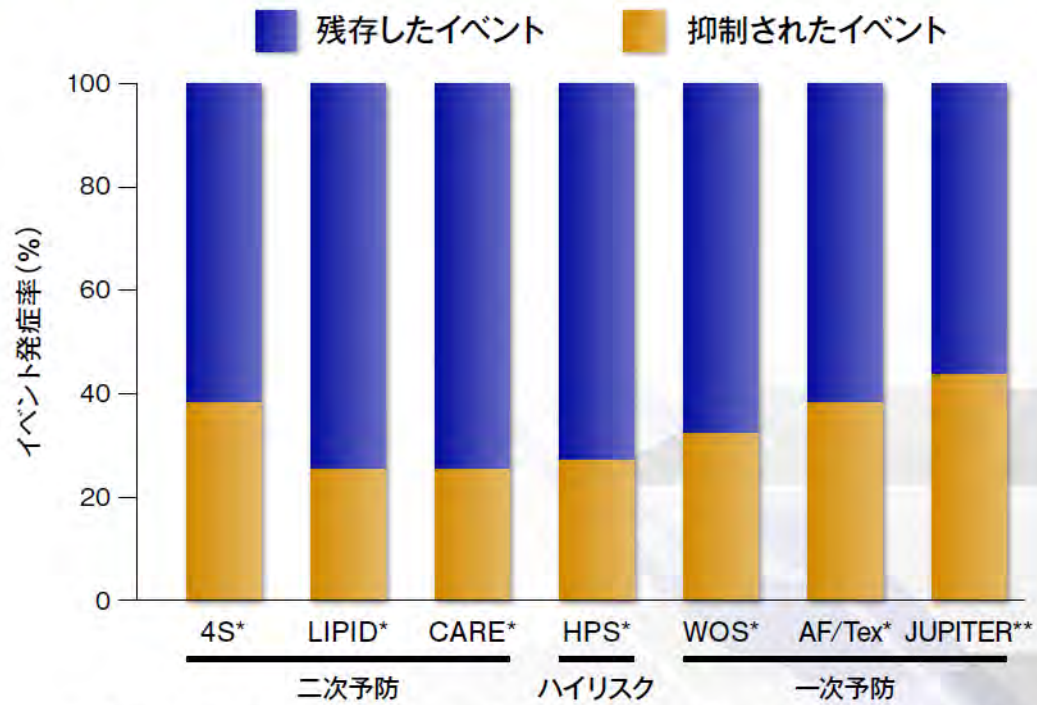


図1 スタチン投与後の残存リスク



* LaRosa JC, et al; Treating to New Targets (TNT) Investigators. *N Engl J Med* 2005; 352: 1425-35. より作図

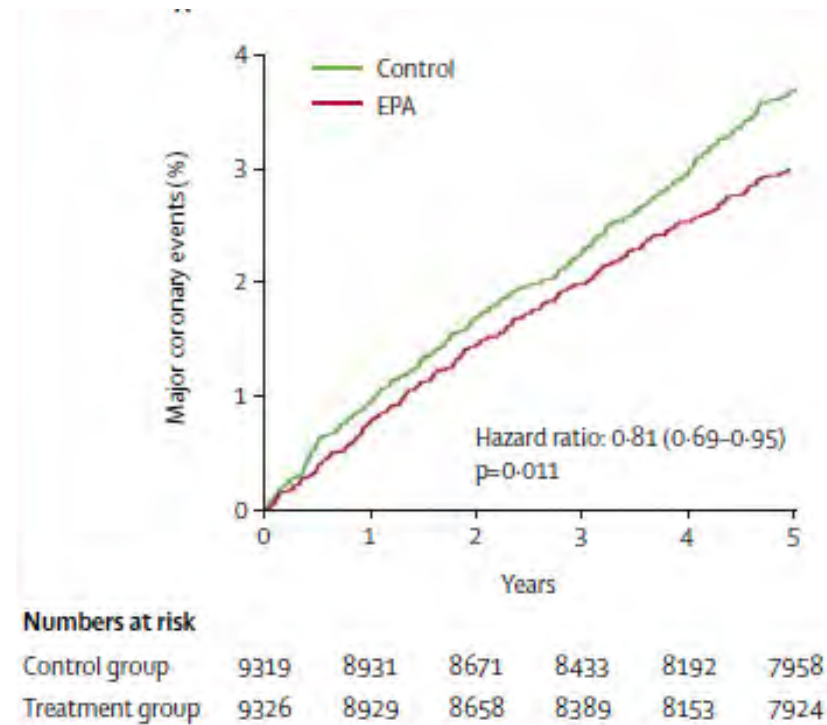
** Ridker PM, et al; JUPITER Study Group. *N Engl J Med* 2008; 359: 2195-207. より作図

**Clinical profile of subjects with 2 or 1 feature-positive plaques
who developed and did not develop ACS**

	ACS n=11 (15%)	No ACS n=61 (85%)	<i>p value</i>
Age	66.3±8.2	65.8±9.5	0.84
Male Gender	11 (100%)	51 (83.6%)	0.34
Hypertension	8 (62.5%)	31 (50.8%)	0.21
Hyperlipidemia	9 (75.0%)	36 (59.0%)	0.19
Diabetes Mellitus	2 (25.0%)	18 (29.5%)	0.72
Smoking*	4 (25.0%)	19 (31.1%)	0.74
Obesity (>25)	1 (12.5%)	8 (13.1%)	0.99
Previous MI	8 (72.7%)	32 (52.5%)	0.33
Previous PCI	8 (72.7%)	32 (52.5%)	0.33
Statin Use After CTA	6 (62.5%)	41 (67.2%)	0.50

Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis

Mitsuhiro Yokoyama, Hideki Origasa, Masunori Matsuzaki, Yuji Matsuzawa, Yasushi Saito, Yuichi Ishikawa, Shinichi Oikawa, Jun Sasaki, Hitoshi Hishida, Hiroshige Itakura, Toru Kita, Akira Kitabatake, Noriaki Nakaya, Toshiie Sakata, Kazuyuki Shimada, Kunio Shirato, for the Japan EPA lipid intervention study (JELIS) Investigators



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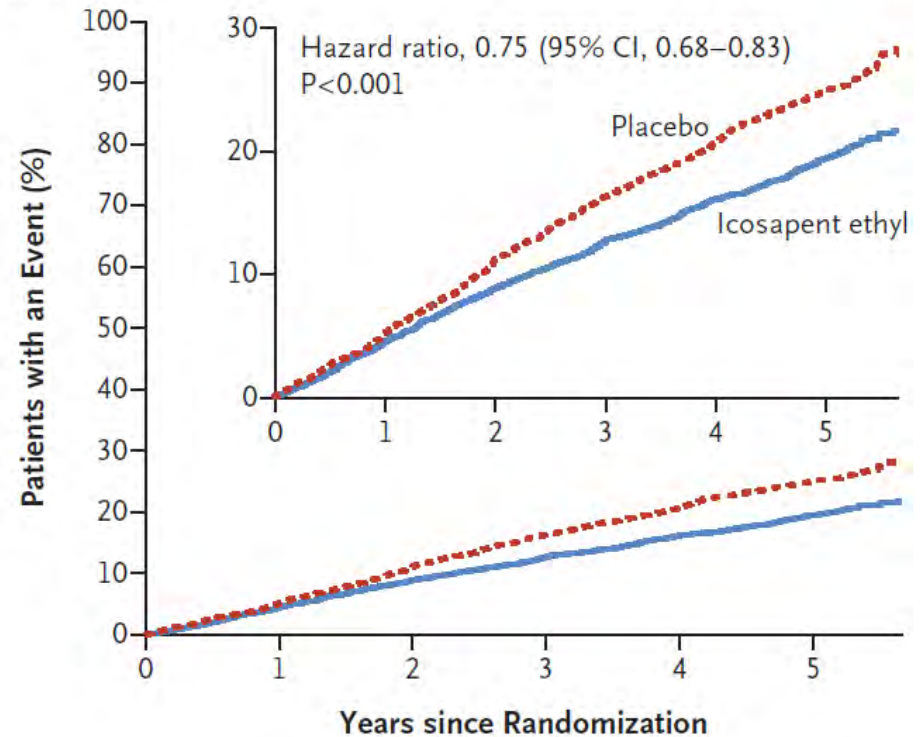
VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Pt with CAD or DM
 On statin
 TG 135 to 499 mg/dl
 LDL-C 41 to 100 mg/dl
 EPA 4g or placebo

A Primary End Point



No. at Risk

Placebo	4090	3743	3327	2807	2347	1358
Icosapent ethyl	4089	3787	3431	2951	2503	1430

Endpoint:
 cardiovascular death, nonfatal myocardial infarction,
 nonfatal stroke, coronary revascularization, or unstable

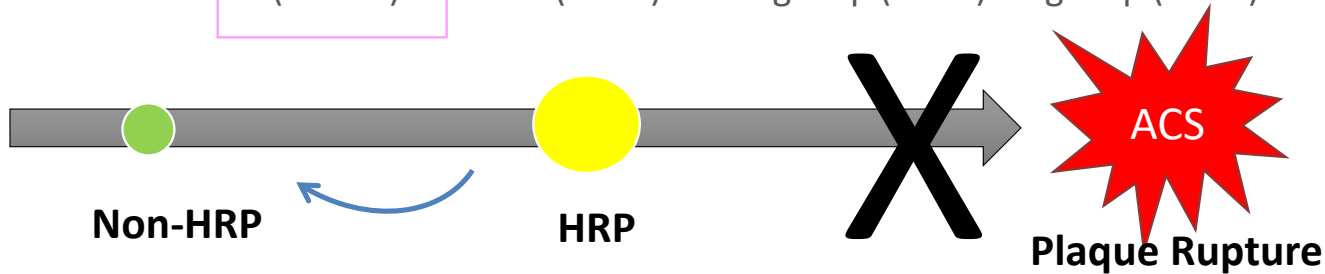
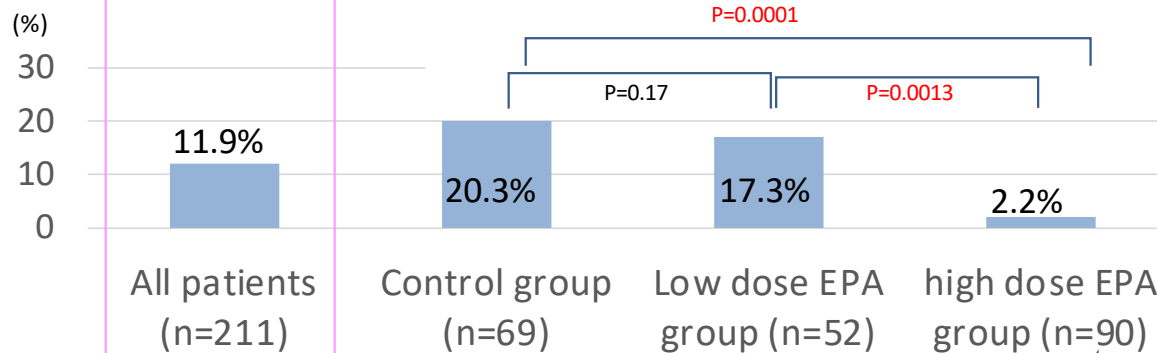
Plaque progression and EPA treatment in ACS pts

Cardiac event: 31/317 (10%) at 12 month (median)

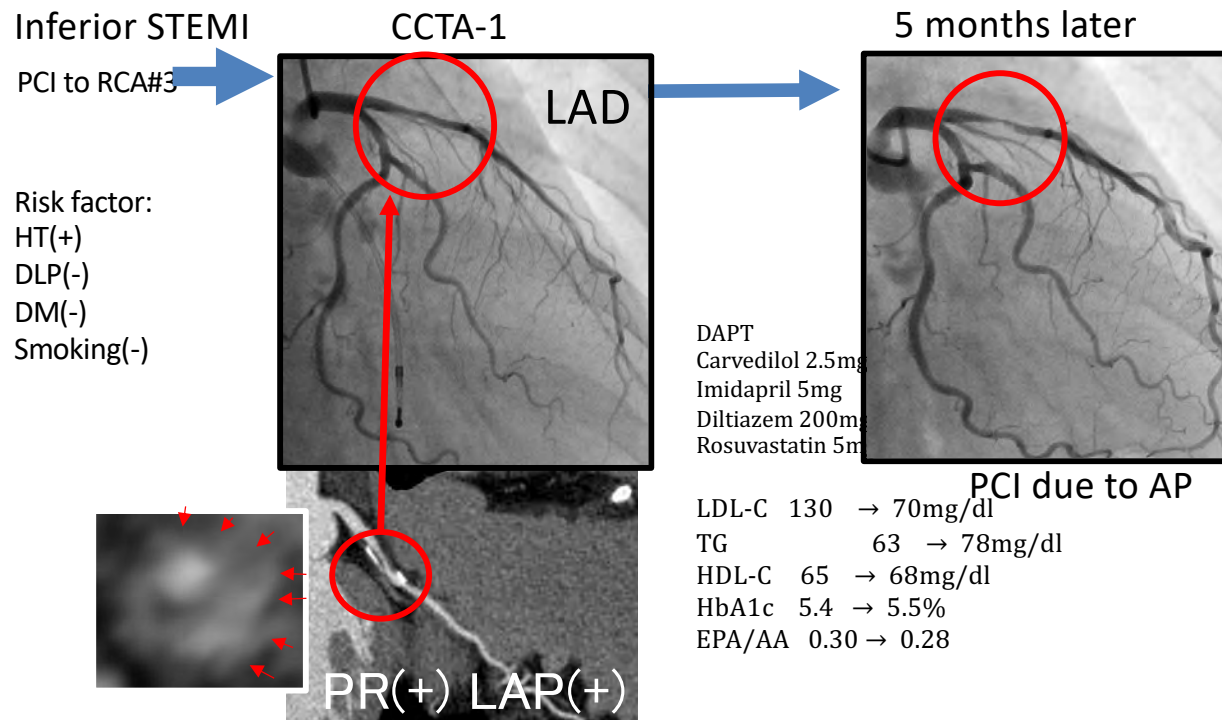
CT findings

	All patients (n=211)	Control group (n=69)	Low dose EPA group (n=52)	high dose EPA group (n=90)	P
CCTA-1					
Presence of HRP n(%)	75 (35.6)	24 (34.8)	21 (40.3)	30 (33.3)	0.69

Plaque progression



症例 3: 67 year-old female



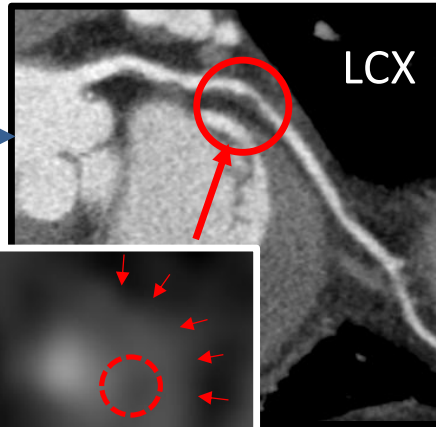
症例 4: 83 year-old male

Inferior STEMI

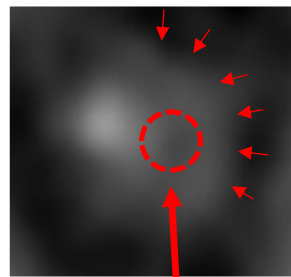
PCI to RCA#2

CCTA-1

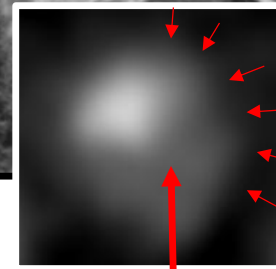
CCTA-2



Risk factor:
HT(+)
DLP(-)
DM(-)
Smoking(-)



17HU:LAP(+)



79HU:LAP(-)

Pitavastatin 2mg
EPA 1800mg

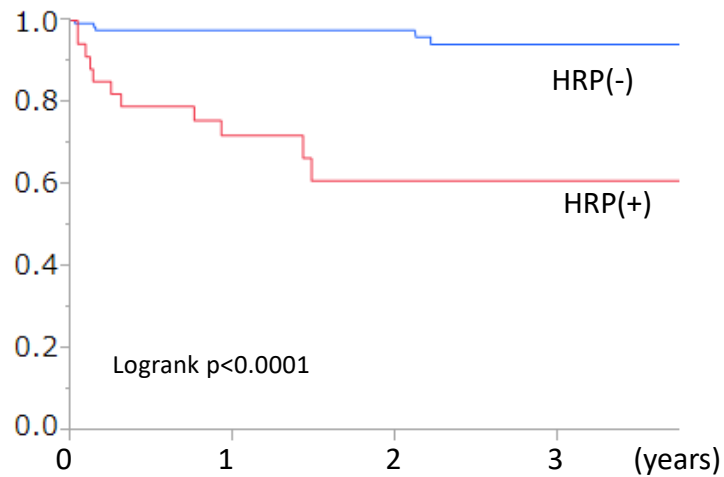
LDL-C	142	→	78mg/dl
TG	60	→	118mg/dl
HDL-C	44	→	46mg/dl
HbA1c	5.4	→	5.6%
EPA/AA	0.18	→	1.32



CADの一次予防におけるHRP

Eicosapentaenoic acid to arachidonic acid (EPA/AA) ratio as an associated factor of high risk plaque on coronary computed tomography in patients without coronary artery disease

Yasuomi Nagahara^a, Sadako Motoyama^{a,*}, Masayoshi Sarai^a, Hajime Ito^a, Hideki Kawai^a, Yoko Takakuwa^a, Meiko Miyagi^a, Daisuke Shibata^b, Hiroshi Takahashi^a, Hiroyuki Naruse^a, Junichi Ishii^a, Yukio Ozaki^a



	0	1	2	3
HRP(-)	156	99	66	23
HRP(+)	37	19	6	3

	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Age	1.04	1.00-1.08	0.026	1.03	0.99-1.08	0.089
Male	1.92	0.92-4.23	0.082			
BMI	0.99	0.89-1.06	0.66			
Hypertension	1.46	0.70-3.15	0.31			
Dyslipidemia	1.44	0.70-2.99	0.31			
Uncontrolled Dyslipidemia	1.92	0.92-4.23	0.082			
Diabetes mellitus	2.57	1.09-5.87	0.032	2.08	0.75-5.59	0.15
Current smoking	2.58	1.15-5.67	0.022	2.58	1.02-6.44	0.046
EPA	0.99	0.97-0.99	0.027			
AA	1.00	0.99-1.01	0.47			
DHA	0.99	0.98-1.00	0.28			
EPA/AA ratio	0.79*	0.63-0.95*	0.012	0.65*	0.48-0.85*	0.0006
DHA/AA ratio	0.88*	0.75-1.02*	0.08			
HbA1c	1.23	0.80-1.81	0.32			
TC	1.00	0.98-1.00	0.35			
TG	1.00	0.99-1.00	0.97			
HDL-C	0.98	0.96-1.01	0.22			
LDL-C	1.00	0.99-1.01	0.61			
Hs-CRP	1.08	0.68-1.53	0.65			
CACS	1.00	1.0000-1.0012	0.049	1.00	0.9881-1.0004	0.23
Number of vessel disease	2.26	1.54-3.37	<0.0001	1.87	1.06-3.31	0.031
Plaque burden	1.08	1.03-1.15	0.0018	1.08	0.99-1.17	0.087

冠動脈CT検査の進歩と不安定プラーク

- 不安定プラークの検出
ハイリスクプラーク: PR、LAP
プラーク進展 (plaque progression)
- 不安定プラークの治療
治療の効果判定
一次予防: HRPに関するマーカー