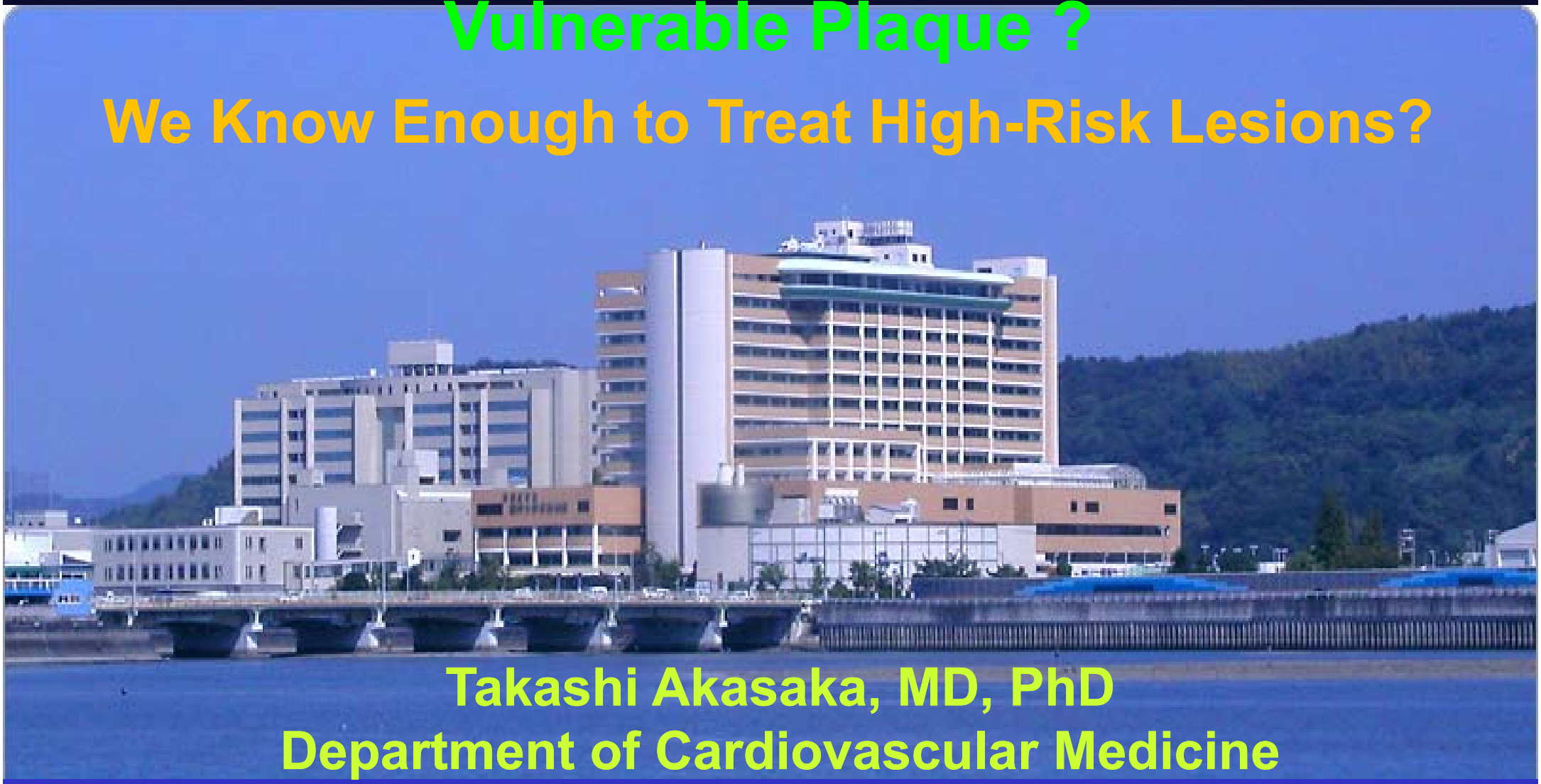
Can We Identify Vulnerable Patients & Vulnerable Plaque ?

We Know Enough to Treat High-Risk Lesions?



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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.

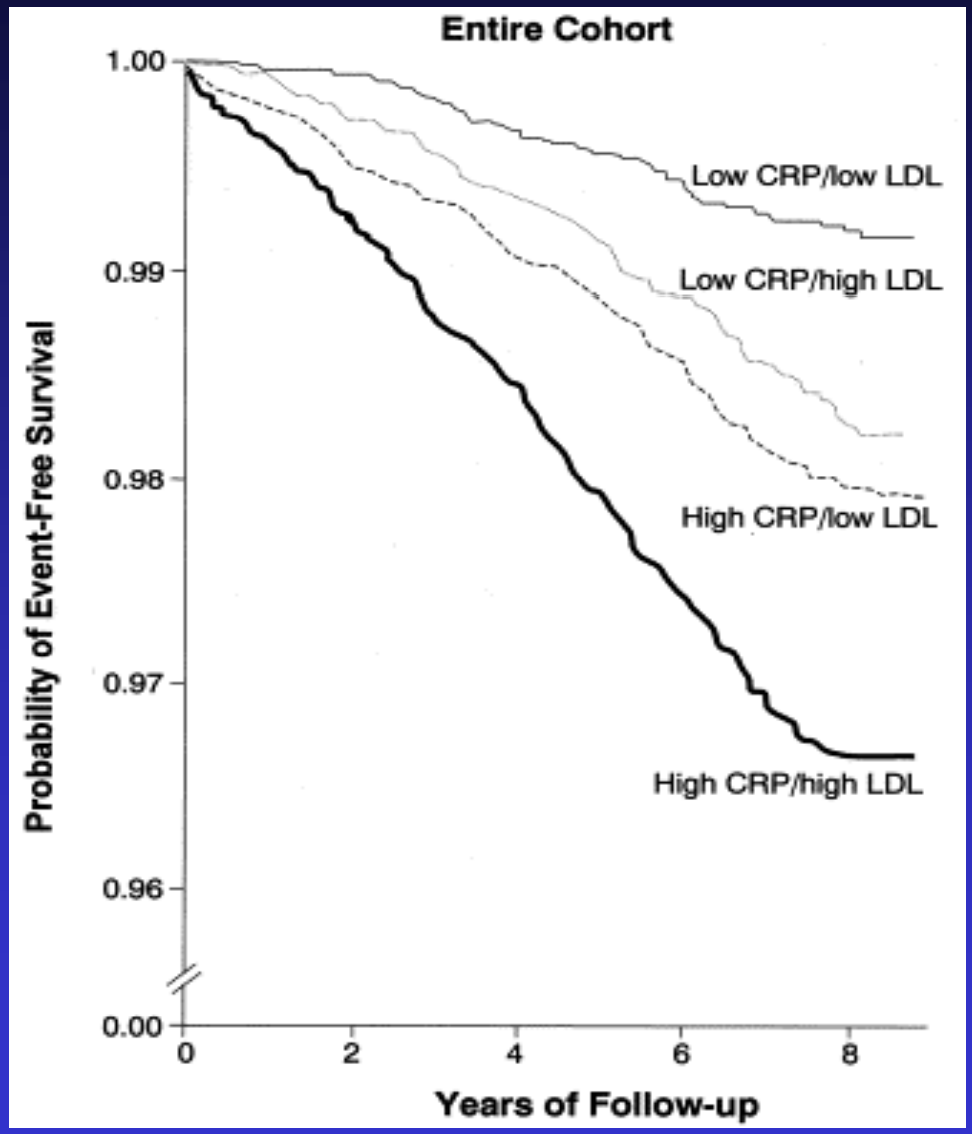
Affiliation/Financial Relationship

- **Grant/Research Support** : Abbott Vascular Japan
  Boston Scientific Japan
  Goodman Inc.
  Sent Jude Medical Japan
  Terumo Inc.

- **Consulting Fees/Honoraria** : Goodman Inc.
  GE Medical Healthcare
  Sent Jude Medical Japan
  Terumo Inc.

Cardiovascular event-free survival probability according to high or low hs-CRP & LDL cholesterol

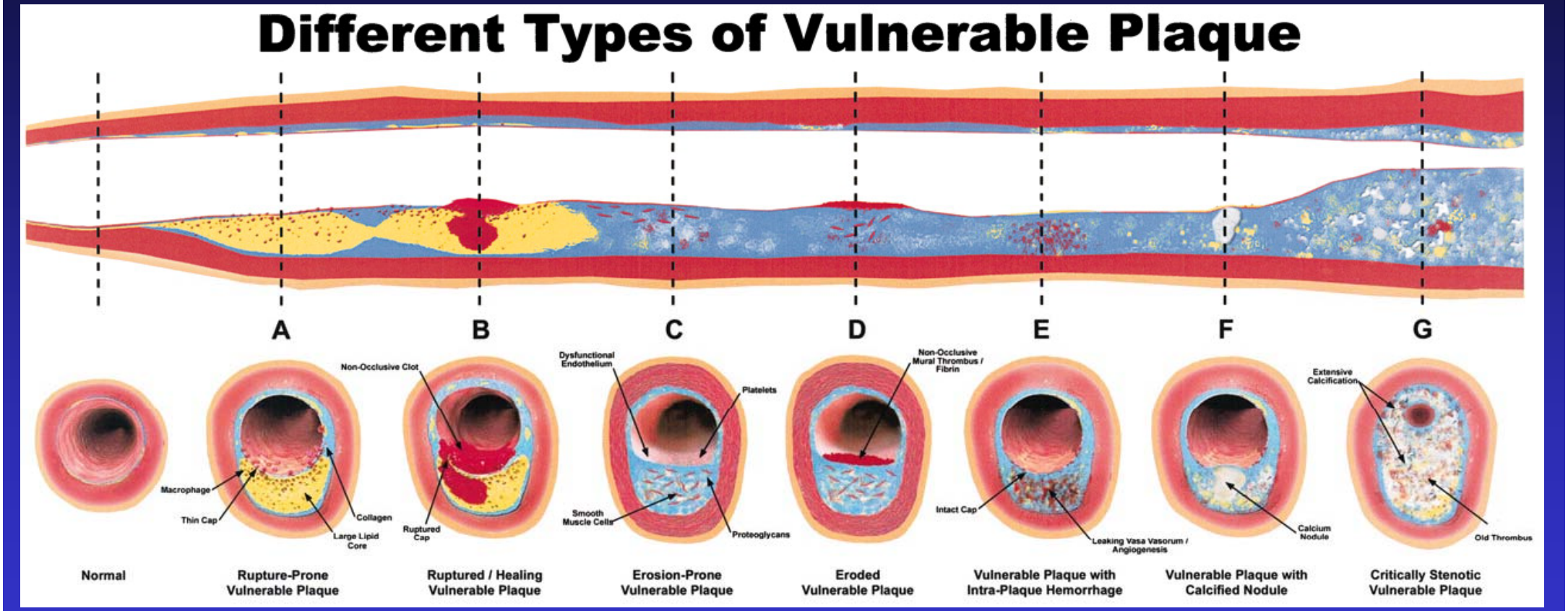
Ridker PM et al. N Engl J Med 2002;347:1557-65



動脈硬化プラークの進展P. Circulation 2001;104:365-372

Progression of atherosclerotic plaque

(Naghavi M, et al. Circulation 2003;108:1664-1672)

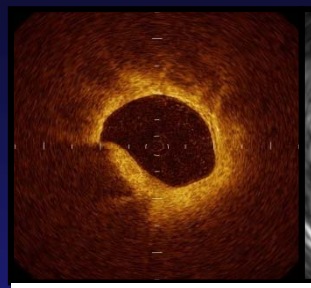
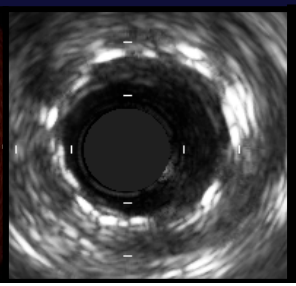
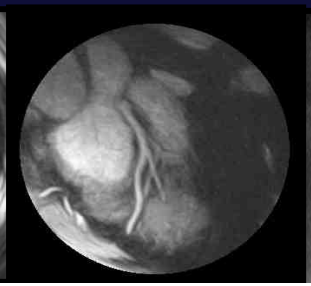
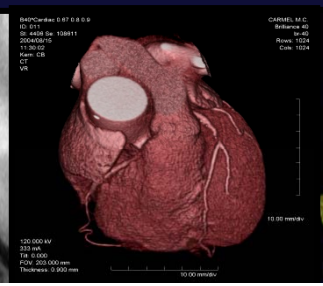


Positive remodering is an adaption for atherosclerotic change.
ACS may occur even in insignificant stenosis.

Coronary lesion assessment

- Anatomical assessment
  - CAG
  - IVUS
  - MSCT
  - MRI
  - Echo
  - OCT
  - Molecular Imaging
- Physiological assessment
  - Stress ECG
  - Stress scintigraphy
  - Stress Echo
  - PET
  - MRI (Perfusion image)
  - Contrast Echo
  - Doppler Echo
    - TTE
    - TEE
    - Transcatheter（Doppler GW）
  - Coronary pressure
    - Transcatheter（Pressure GW）

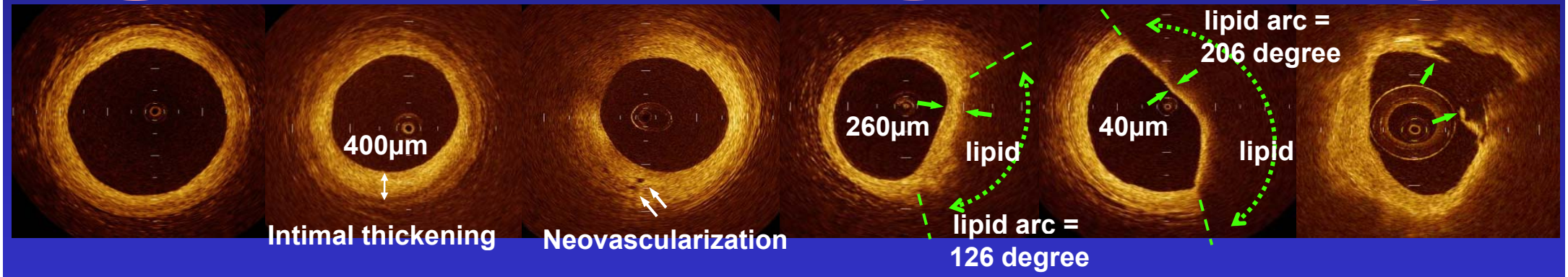
Comparison among coronary imaging techniques

	OCT	IVUS	MRI	CAG	MDCT	Angioscopy
						
Resolution	10 – 15	80 – 120	80 – 300	100-200	300	<200
Probe Size	140	700	1000	N/A	N/A	800
Contact	No	Yes	No	No	No	No
Ionizing Radiation	No	No	No	Yes	Yes	No
Imaging Target	Layer	Layer	Density	Blood Flow	Density	Surface
Other	**Tissue Characterization**	N/A	N/A	Flow Only	CT number	Surface Only

Each modality may have advantages and disadvantages.

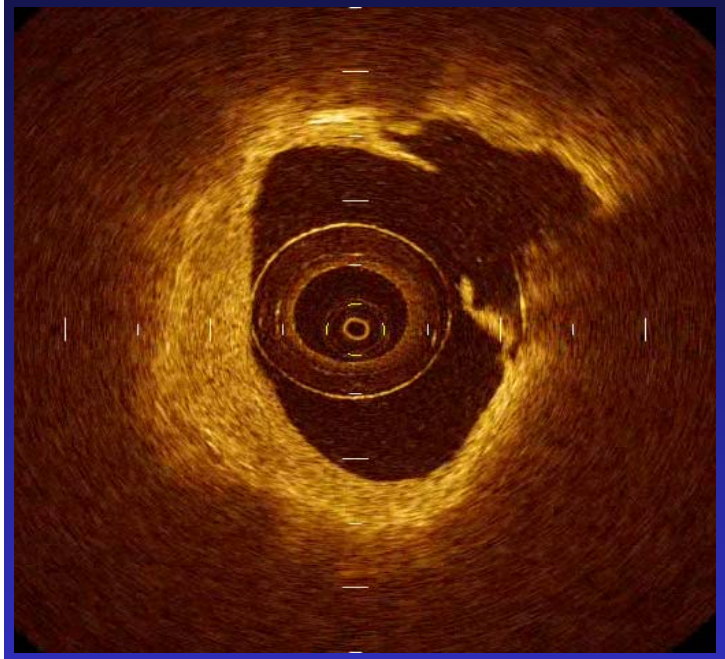
Progression of atherosclerosis & corresponding OCT Images

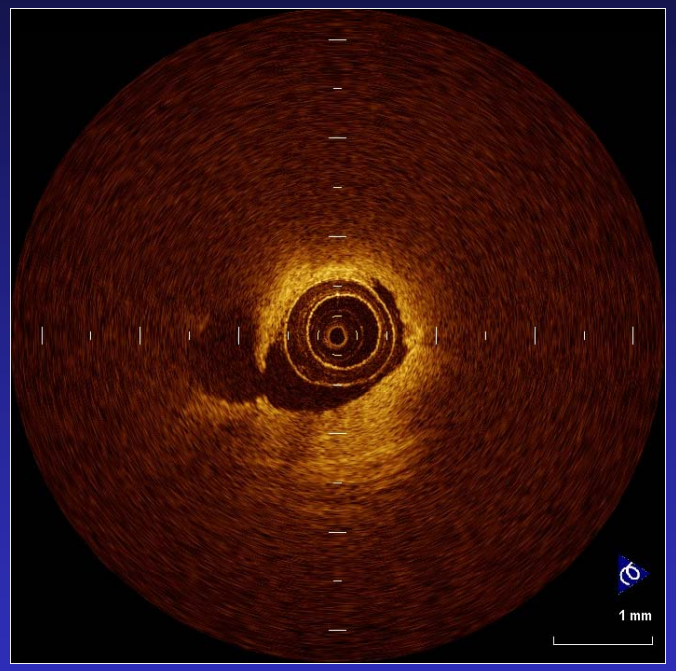
A	B	C	D	E	F
Normal	Intimal thickening	Early plaque formation with neovascularization	Fibrous cap atheroma	Thin-cap fiboratheroma	Plaque rupture

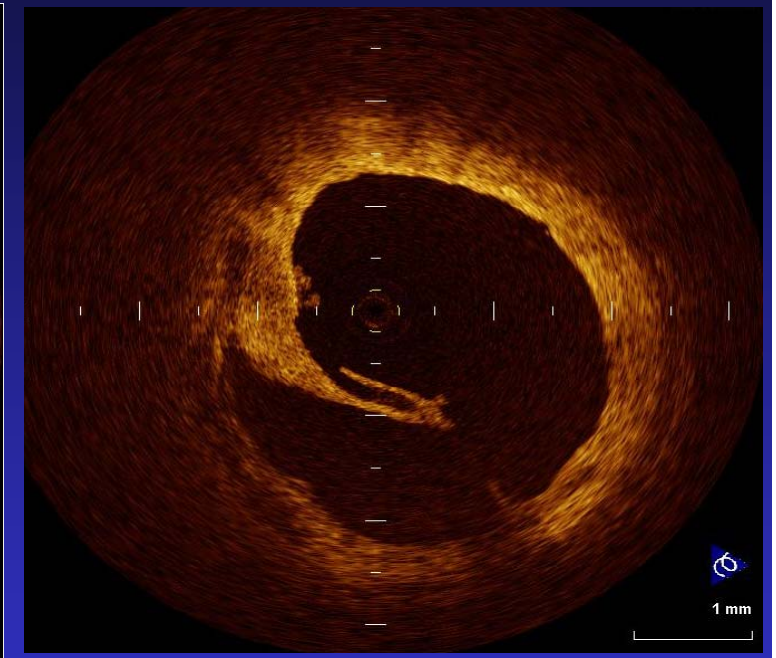


- Extracelluler lipid
- Machrophage form cells
- Smooth muscle cells
- Neovascular vessel
- Necrotic core
- Calcified plaque
- Thrombus
- Collagen

Plaque rupture (Plaque disruption)

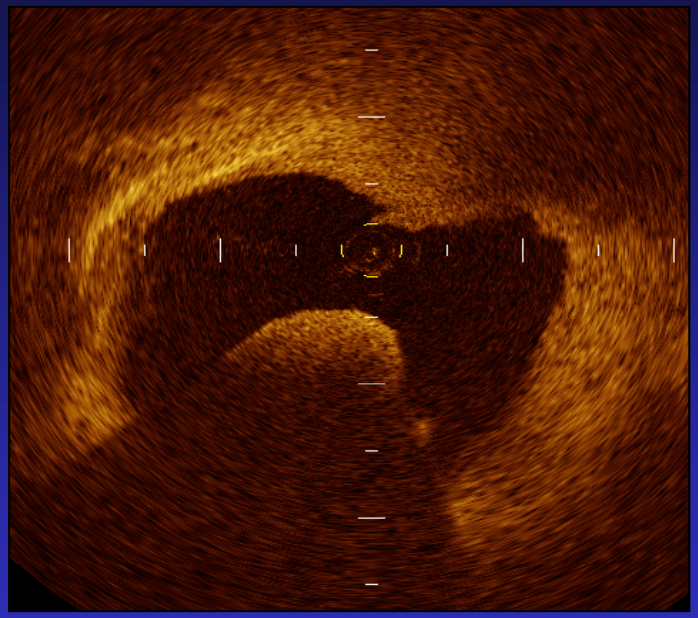
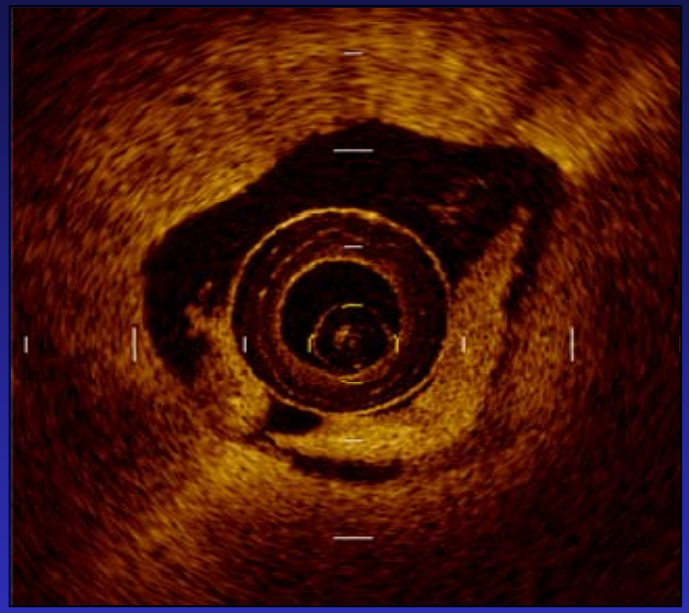
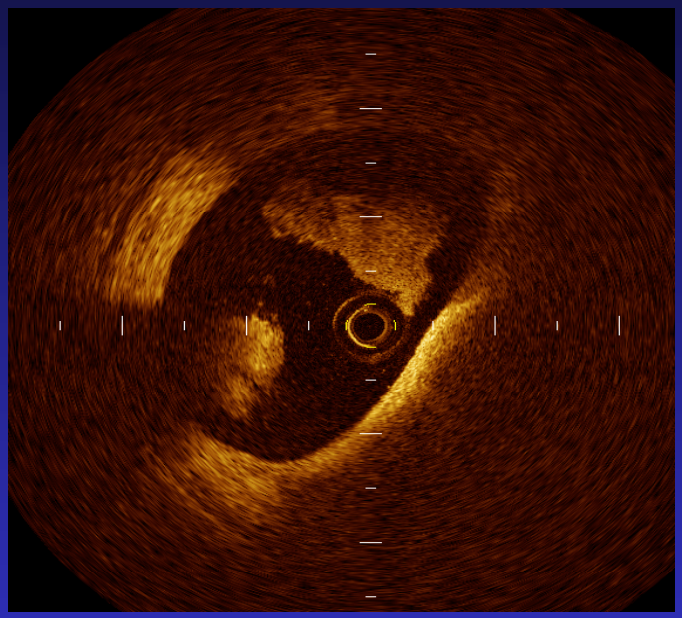






Plaque rupture could be identified by the findings of discontinuity of the fibrous cap and ulcer (cavity) formation at the site of the discontinuing fibrous cap.

Red & white thrombus

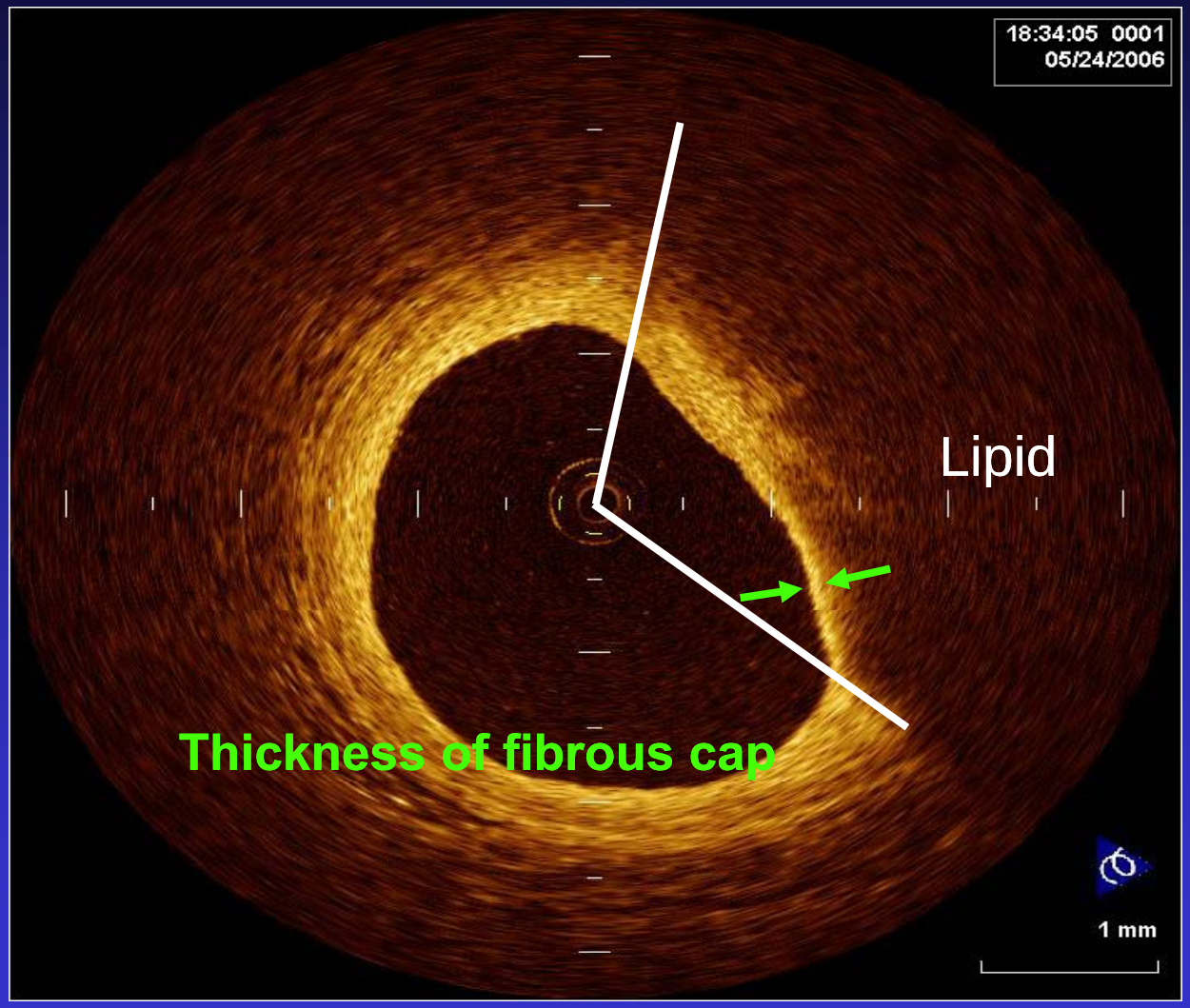
Red thrombus	White thrombus	Mixed thrombus
		
Protrusion mass with shadow	Protrusion mass without shadow	Protrusion mass with & without shadow

Kume T, Akasaka T, et al (Am J Cardiol 97:1713-1717 , 2006)
Kubo T, Akasaka T, et al. (J Am Coll Cardiol 50:933-939,2007)

Thin-capped Fibroatheroma (TCFA)

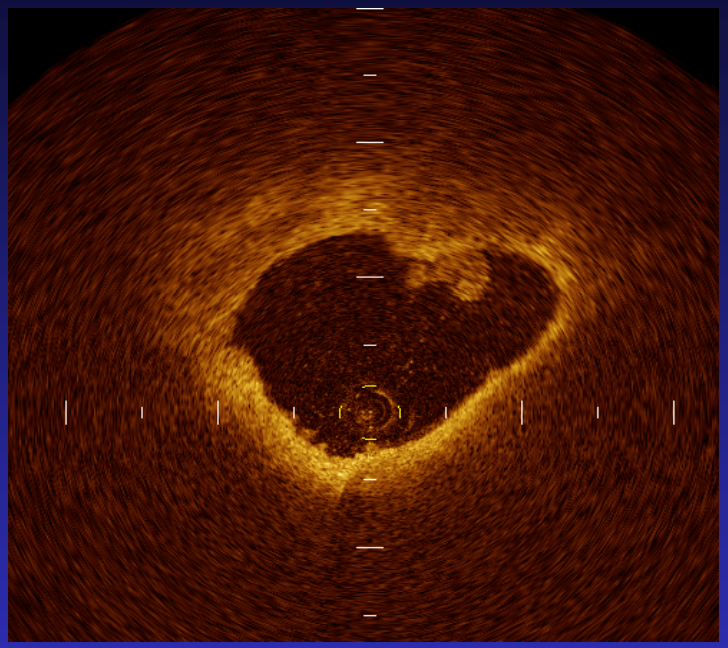
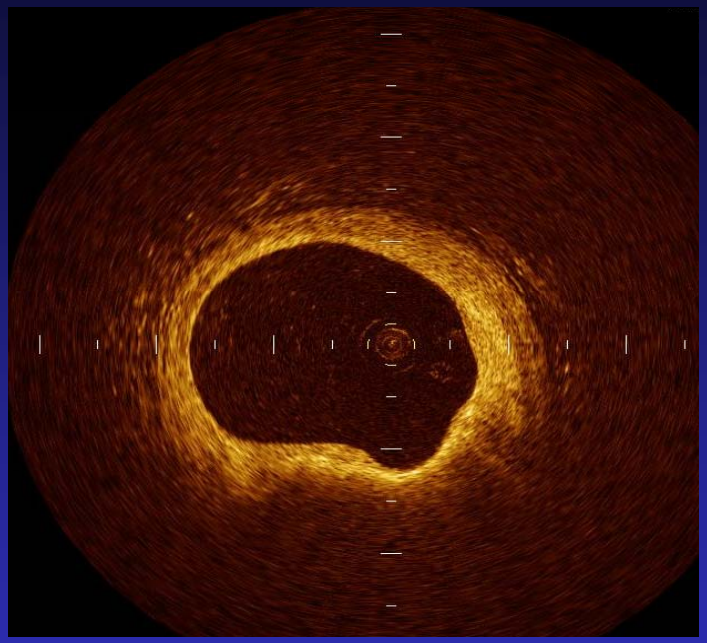
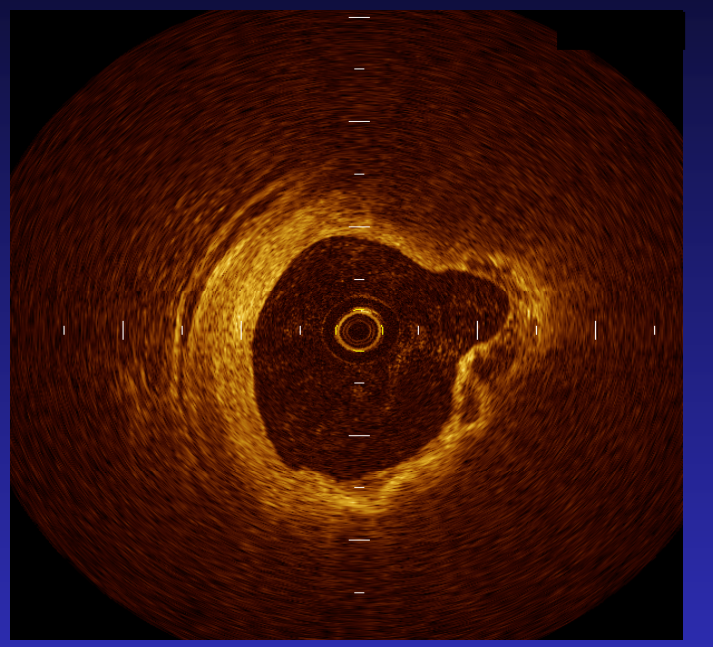
The TCFA was defined as a plaque with lipid content in more than 2 quadrants and the thinnest part of a fibrous cap measuring less than 65 μm by histology.

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



Plaque ulceration

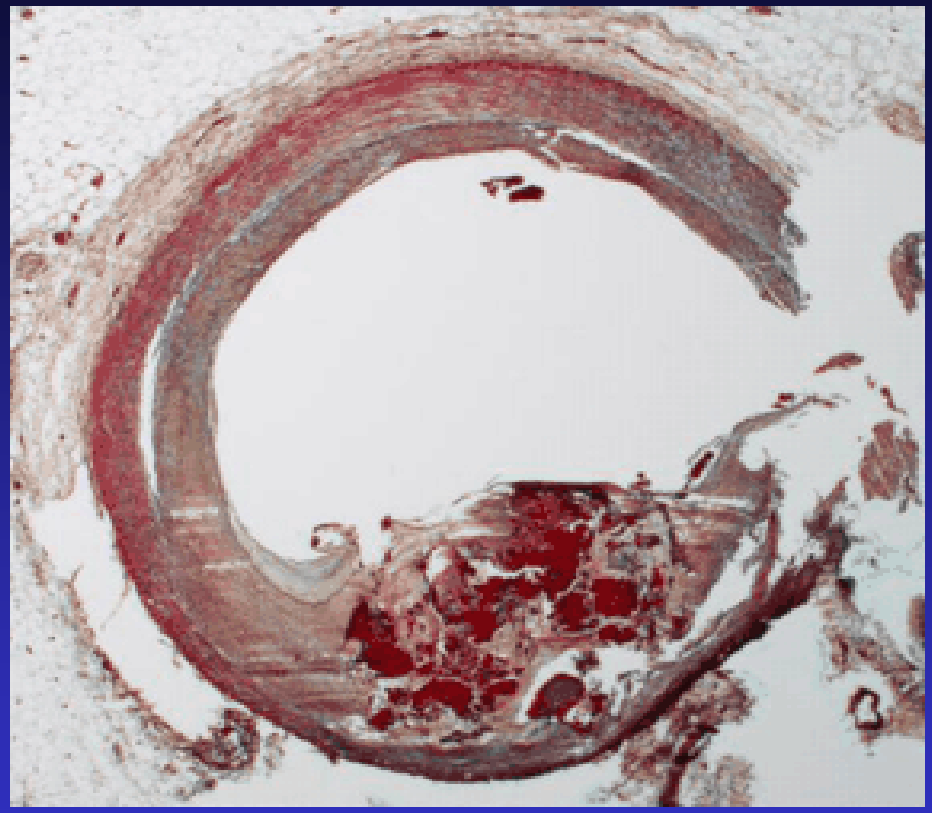
Erosion

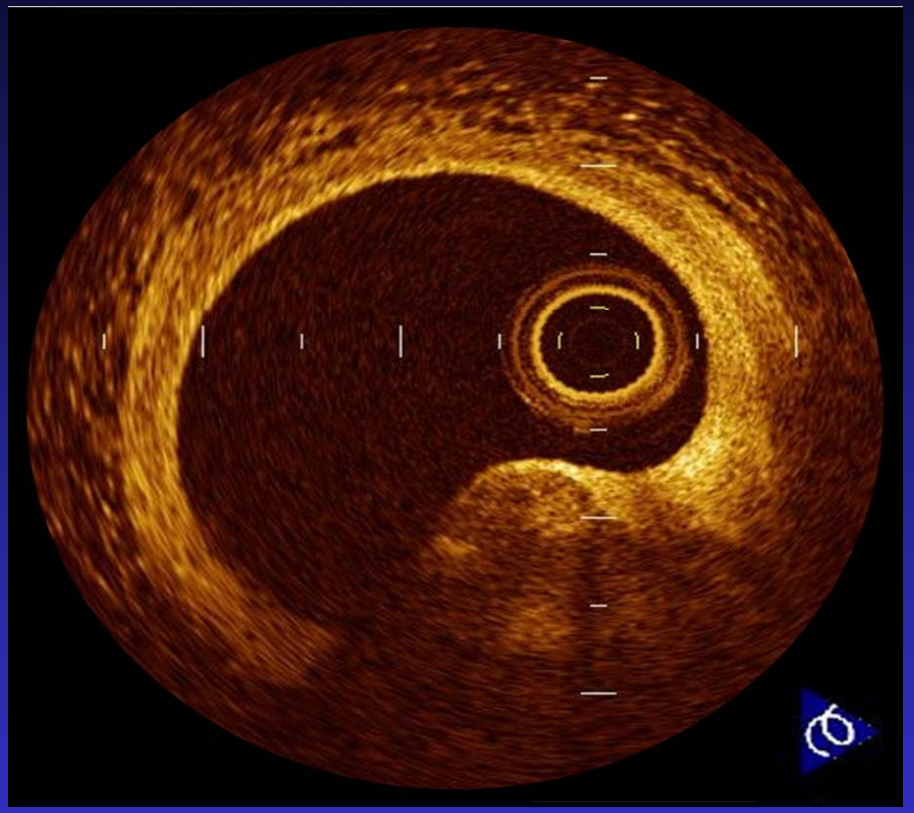
Plaque ulceration could be identified a hollow at the culprit site, especially if there is no rupture.

Plaque erosion could be identified in a broad band spectrum from denudation of several endothelium to ulcer formation without rupture in the culprit site.

Calcified nodule



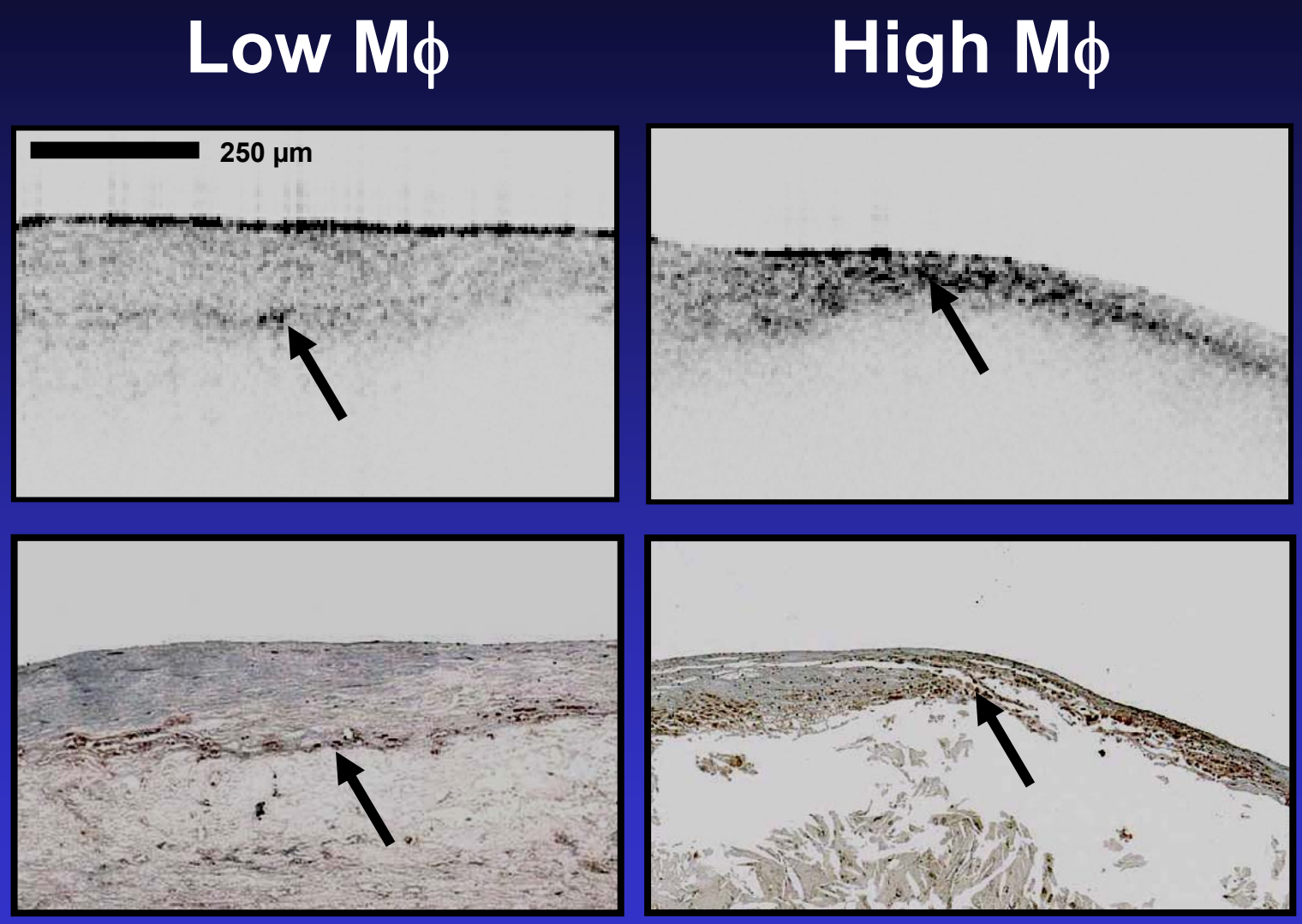
Virmani R et al. Am J Cardiol. 2011



Calcified nodule is identified as a protrusion of well-delineated, heterogeneous region with attenuation of OCT signal.

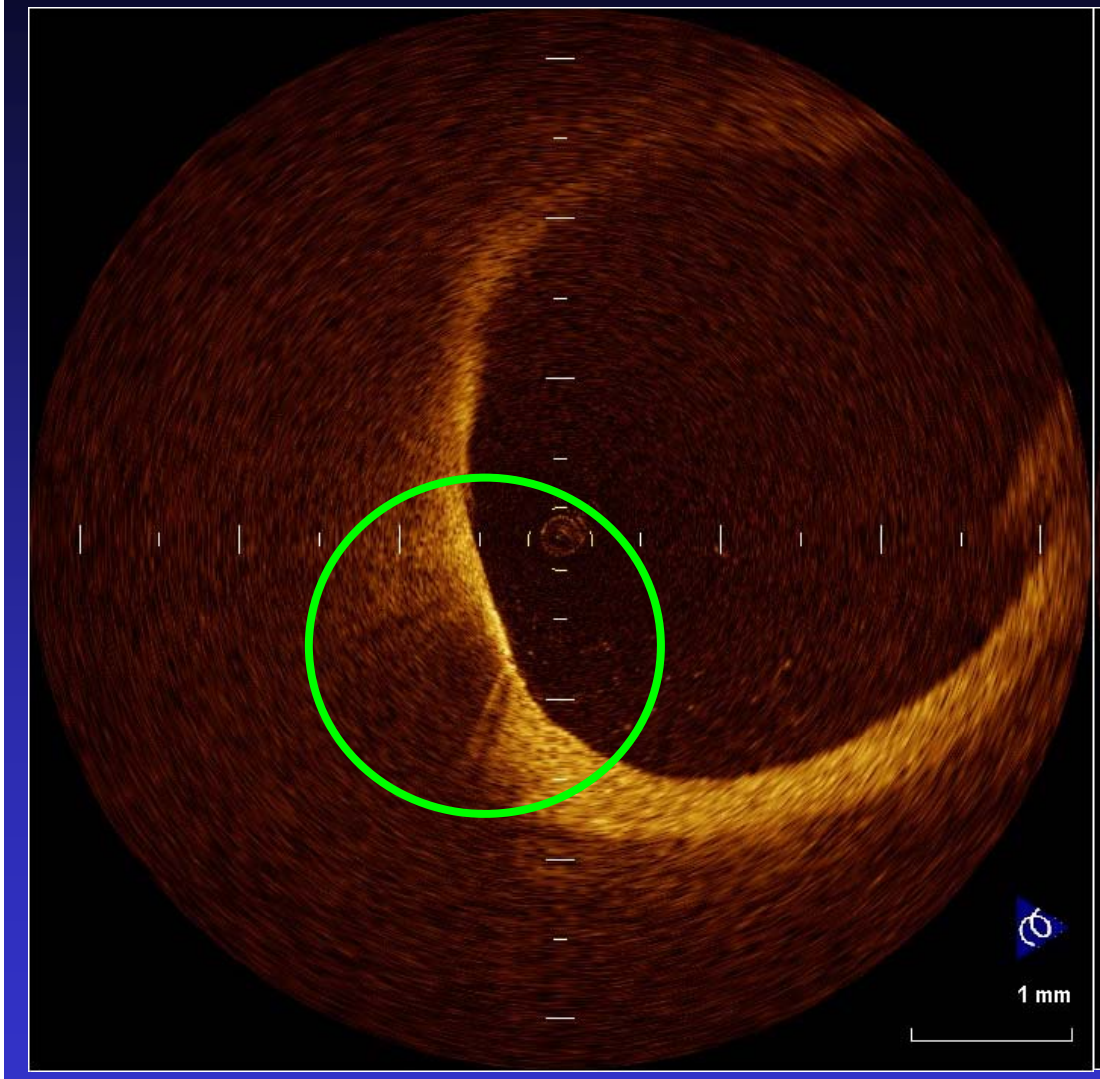
Kubo T, Akasaka T, et al. Cardiol Res Pract 2011.

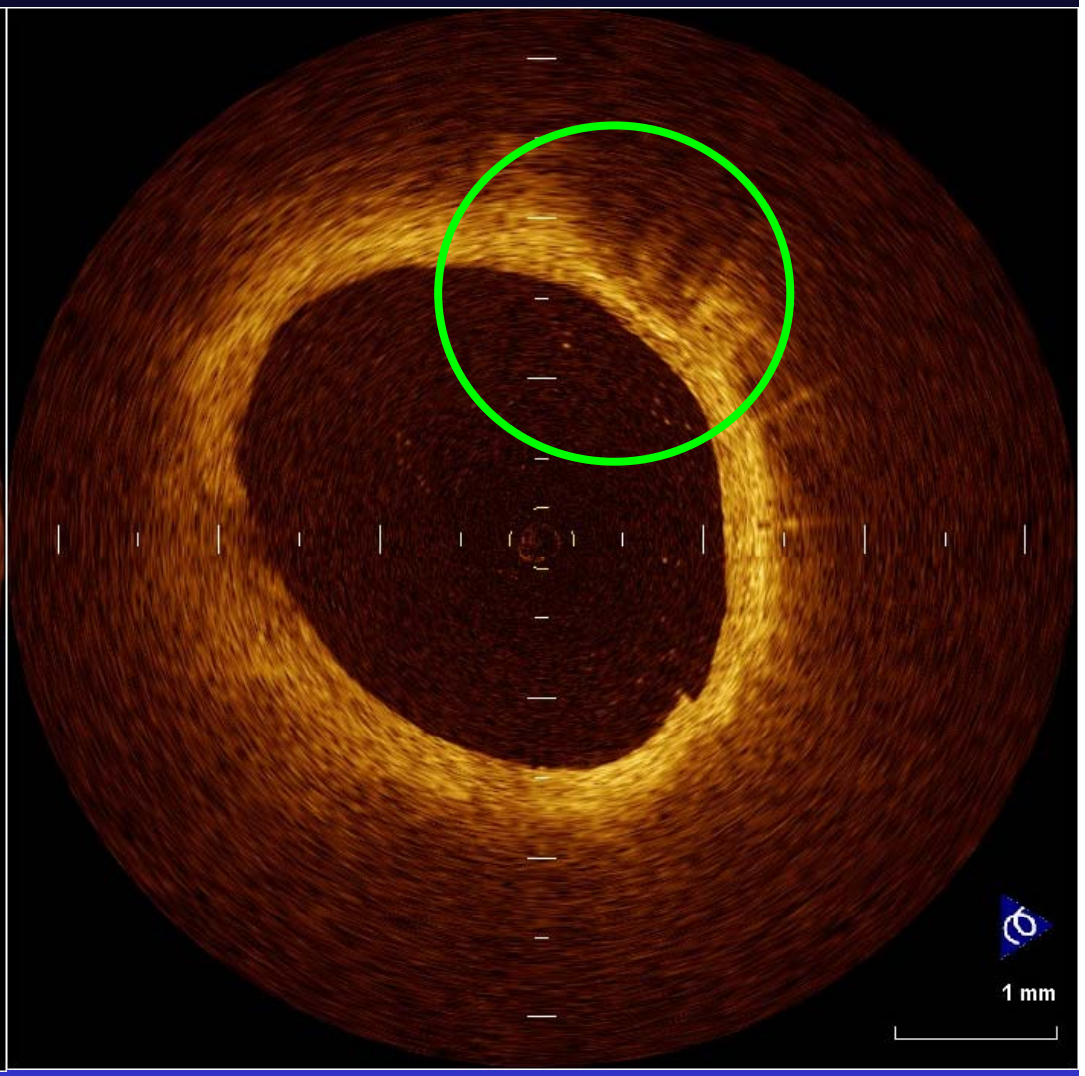
OCT findings of macrophages



Tearney GJ et al. Circulation, 107:113-119, 2003

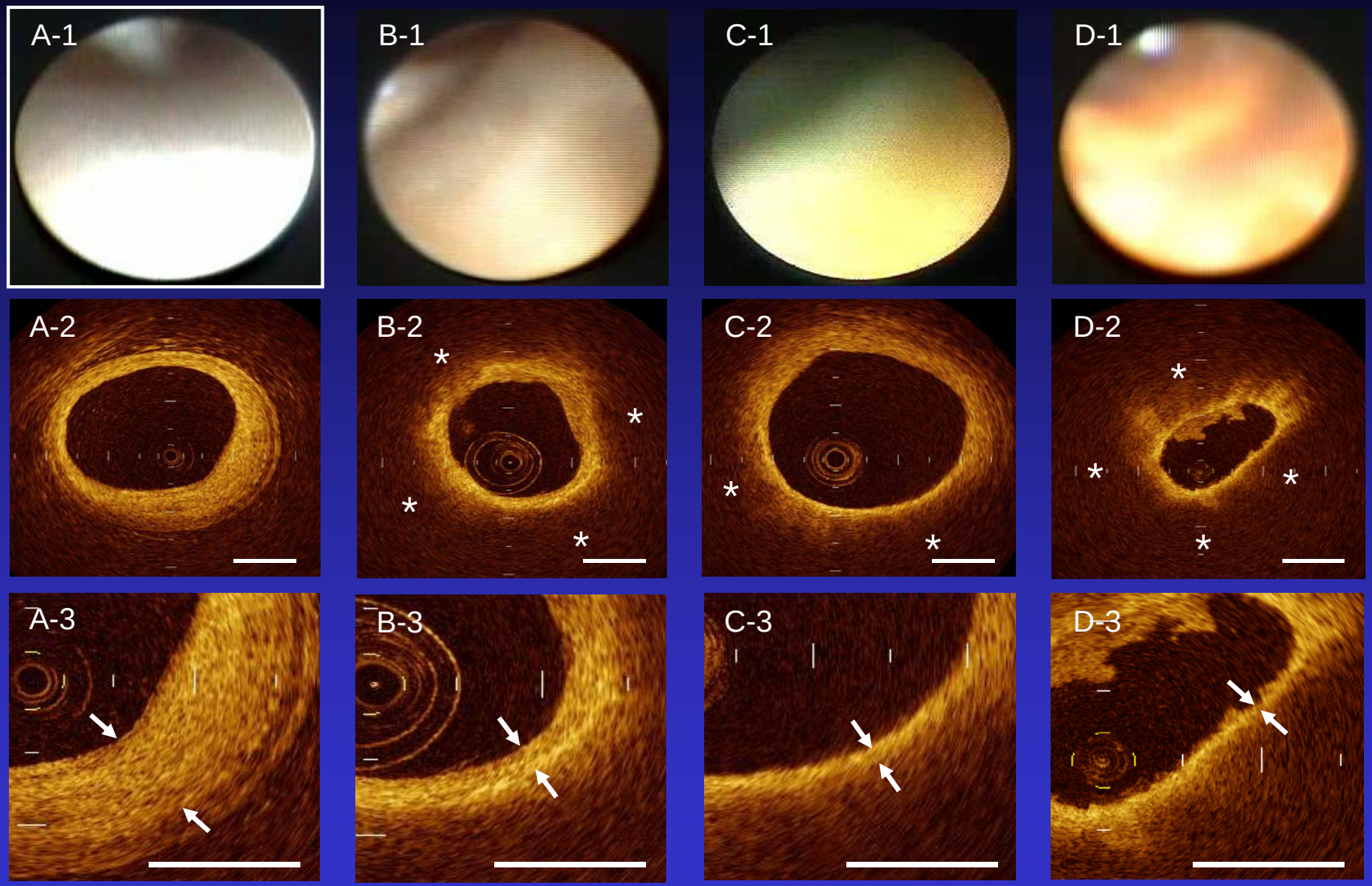
Identification of macrophage





Extremely high signal with rapid attenuation on the surface of the vessel wall or within fibrous tissue might demonstrate macrophage accumuration.

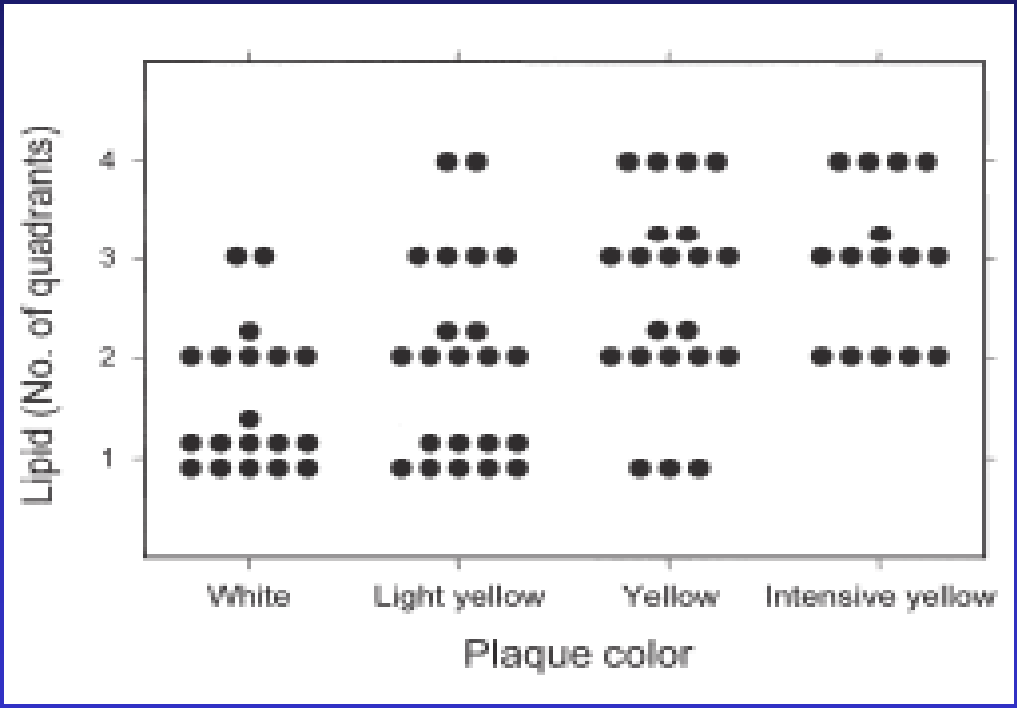
Corresponding Images of OCT and Angioscopy



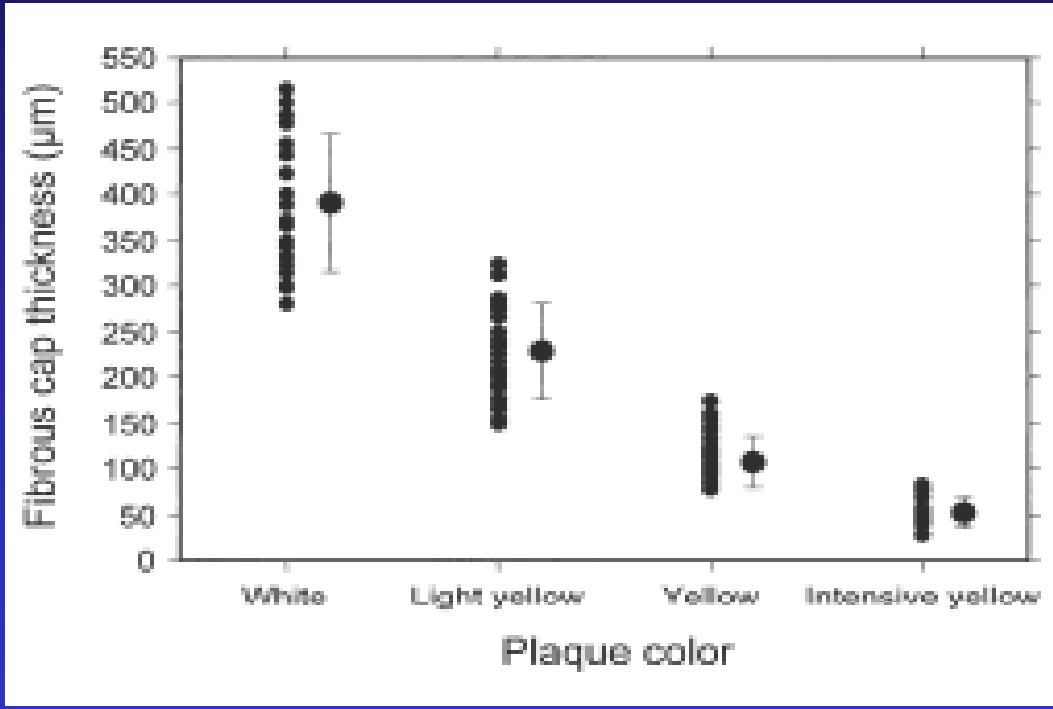
（Kubo T, et al. J Am Coll Cardiol Intv 1:74-80,2008）

Angioscopy vs OCT

Plaque color vs lipid size



Plaque color vs fibrous cap thickness



（Kubo T, et al. J Am Coll Cardiol Intv 1:74-80,2008）

Criteria for defining vulnerable plaque

(Naghavi M, et al. Circulation 2003;108:1664-1672)

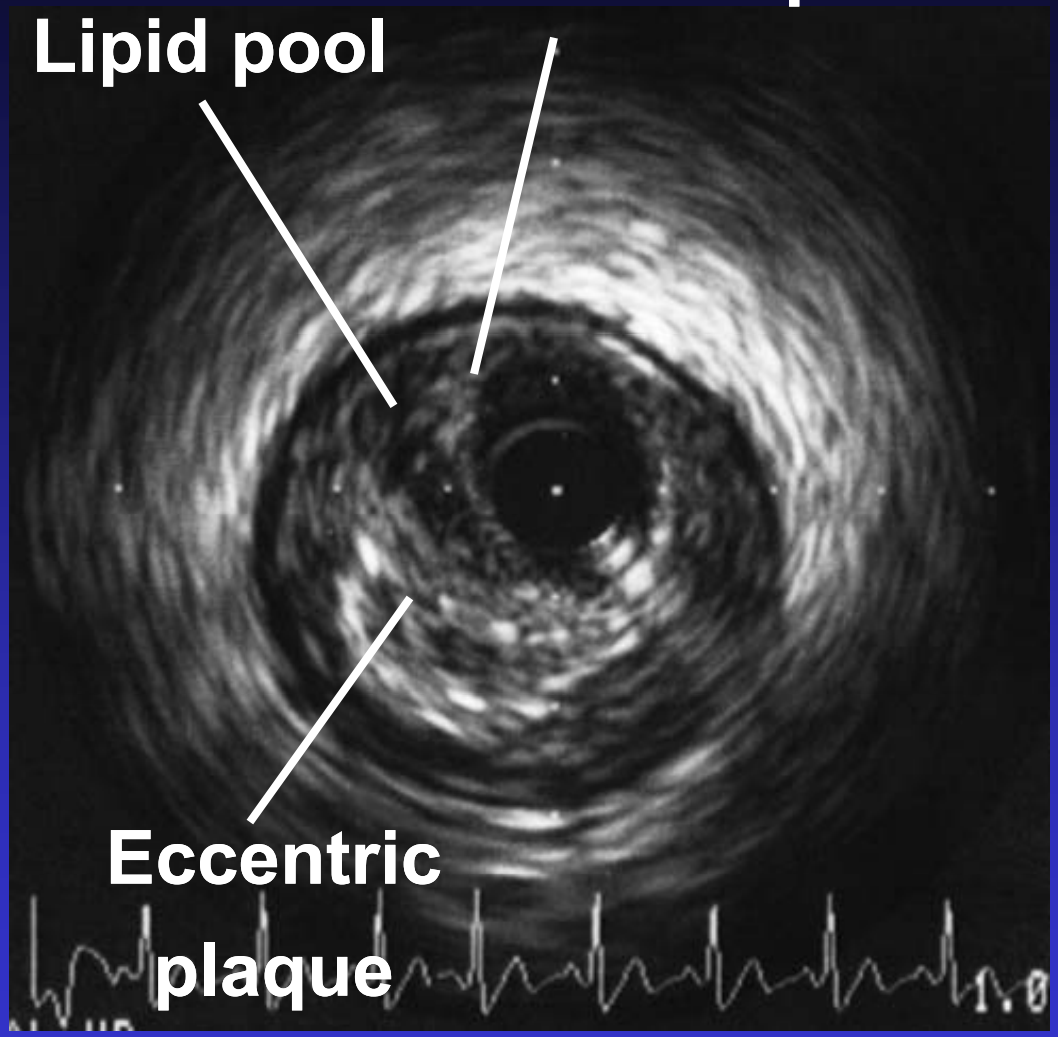
Major criteria

- **Active inflammation (monocyte/macrophage and sometimes T-cell infiltration)**
- **Thin cap (< 65 μm) with large lipid core**
- **Endotherial denudation with superficial platelet aggregation**
- **Fissued plaque**
- **Stenosis > 90%**

Minor criteria

- **Superficial calcified nodule**
- **Glistening yellow**
- **Intraplaque hemorrhage**
- **Endotherial dysfunction**
- **Outward (positive) remodering**

Vulnerable plaque



① Positive remodering

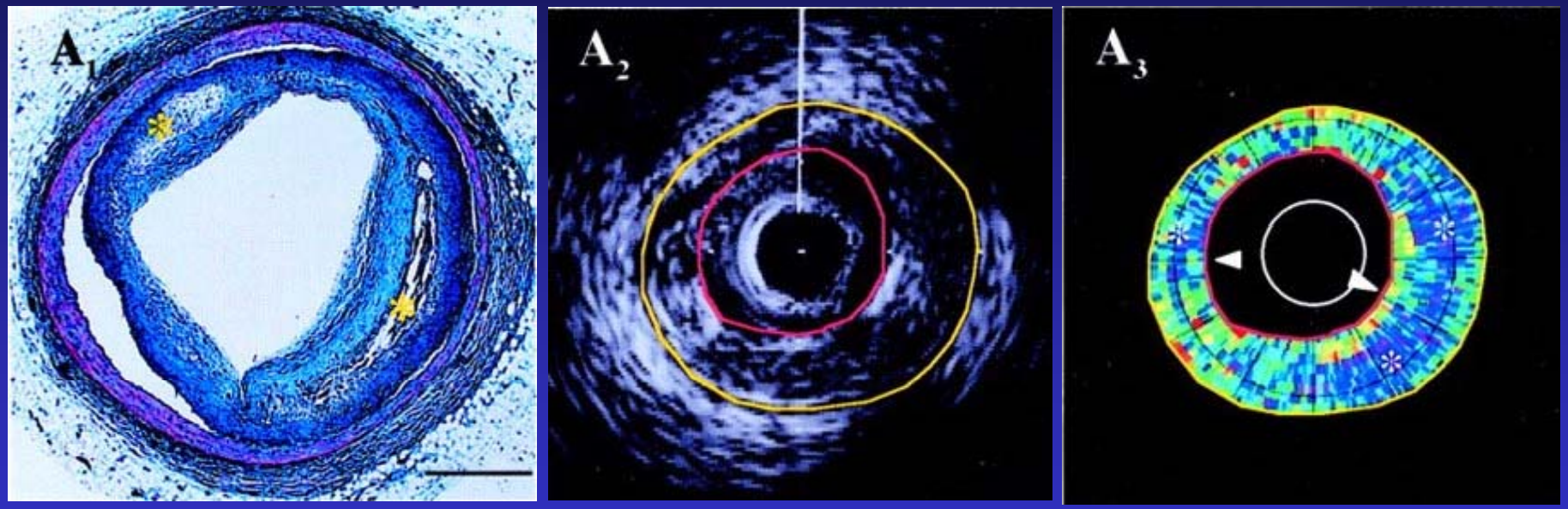
② Eccentric plaque

③ Low echoic area (lipid pool)

④ Thin fibrous cap

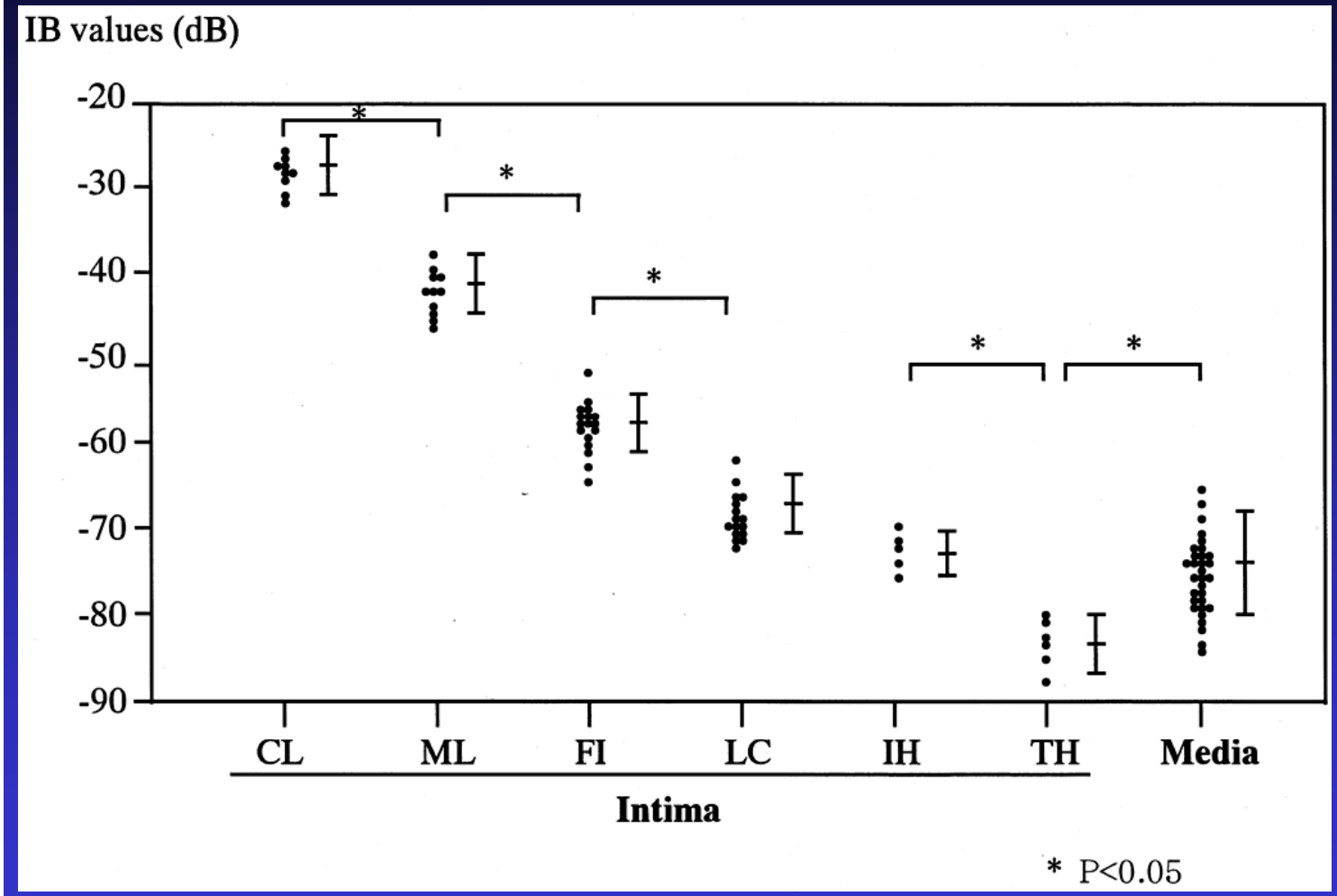
IVUS allow us to identify plaque characteristics, but it is not sufficient enough in resolution & tissue characterization.

Tissue characterization by IB



(Kawasaki M, et al. Circulation 105:2487–2492, 2002)

Tissue characterization by IB



CL; calcification

ML; mixed lesion

FI ; fibrosis

LC; lipid core

IH ; intimal hyperplasia

TH; thrombus

(Kawasaki M, et al. Circulation 105:2487–2492, 2002)

Prediction of ACS by IB

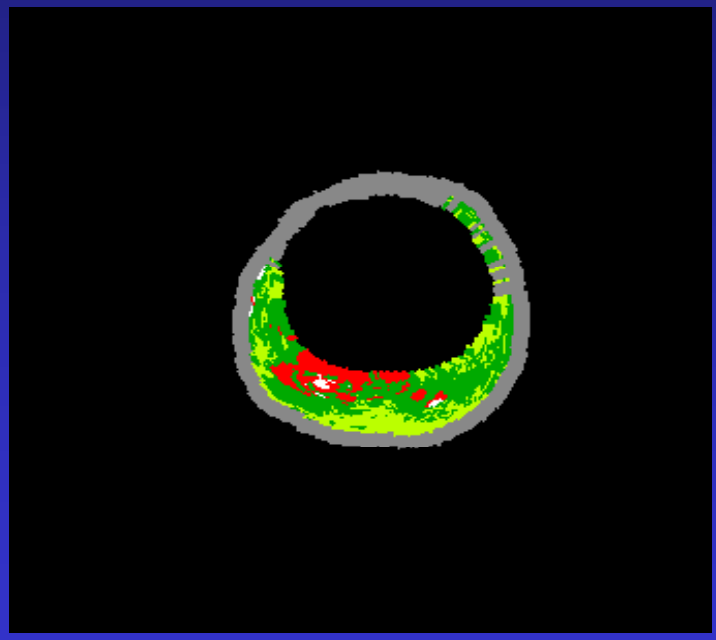
Baseline IVUS Characteristics

	Vulnerable Plaques (n = 10)	Stable Plaques (n = 143)	p
Vessel area, mm^2	13.9 ± 2.0	14.2 ± 3.5	0.72
Lumen area, mm^2	6.1 ± 1.2	6.7 ± 2.0	0.31
Plaque area, mm^2	8.0 ± 2.0	7.5 ± 2.4	0.41
Plaque burden, %	60 ± 9	52 ± 9	0.014
Diameter stenosis, %	35 ± 7	31 ± 7	0.10
Area stenosis, %	57 ± 8	52 ± 9	0.09
Eccentricity rate	0.70 ± 0.10	0.55 ± 0.17	0.013
Remodeling index	1.30 ± 0.08	1.16 ± 0.16	0.006
Fibrous area, %	23 ± 6	47 ± 14	<0.0001
Lipid area, %	72 ± 10	50 ± 16	<0.0001

(Kawasaki M, et al. J Am Coll Cardiol 47:734–741, 2006)

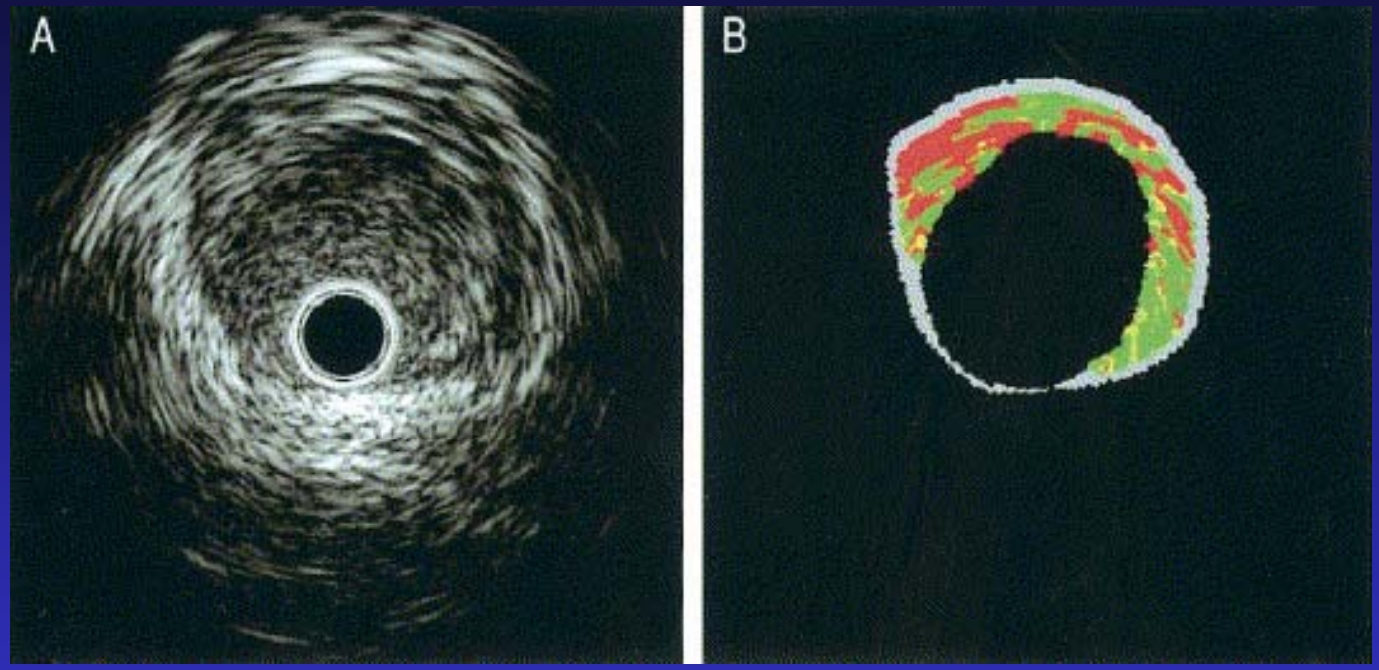
VH™ IVUS

- Tissue characterization is performed by several indexes obtained from RF signal including frequency, IB, power, spectral gradient, etc.
-
  - Fibrous Tissue
  - Fibro-fatty
  - Necrotic Core
  - Dense Calcium



IVUS-derived TCFA

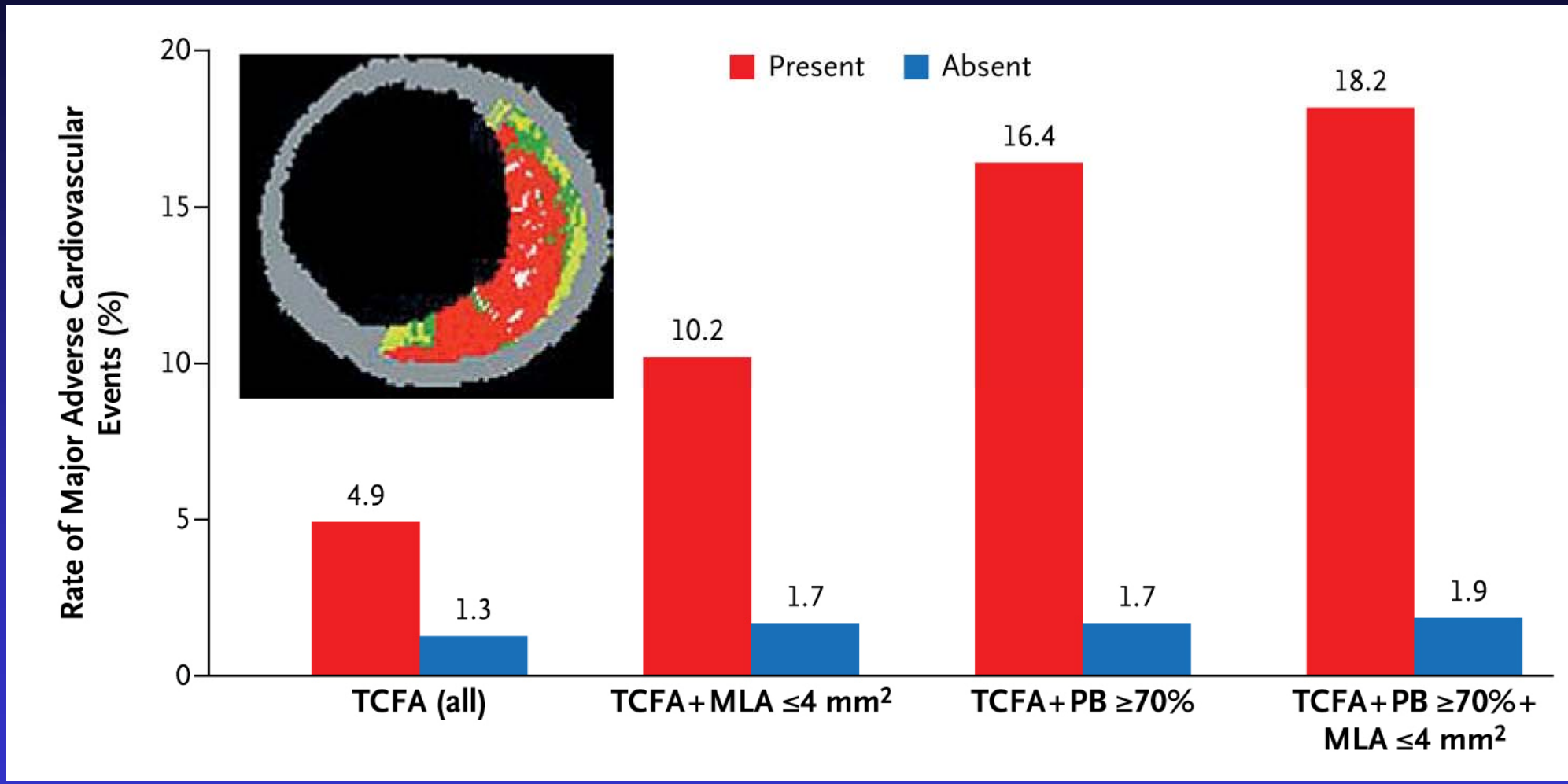
(Rodriguez-Granillo GA, et al. J Am Coll Cardiol 46:2038-2042, 2005)



- Percent atheroma volume = (EEM area – Lumen area)/EEM area x100≧40%
- Nectrotic core≧10%
- Without evident overlying fibrous tissue

PROSPECT trial

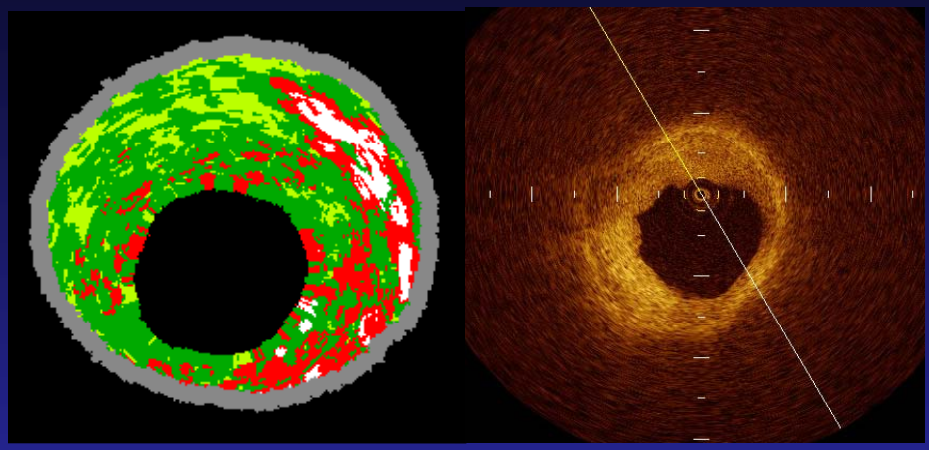
(Stone GW, et al. N Engl J Med 364:226-235, 2011)



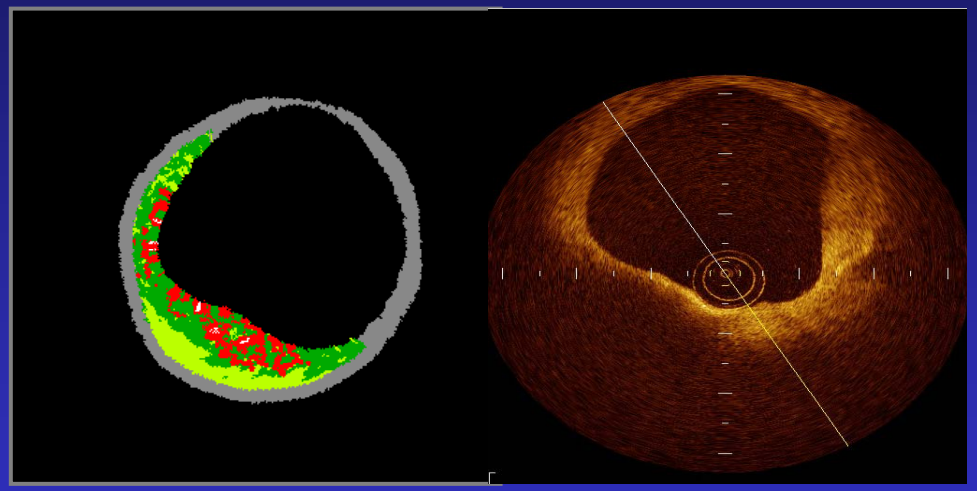
Predictive value of IVUS tissue characterization is not so high compared with gray-scale IVUS information such as MLA & PB.

VH-IVUS vs OCT

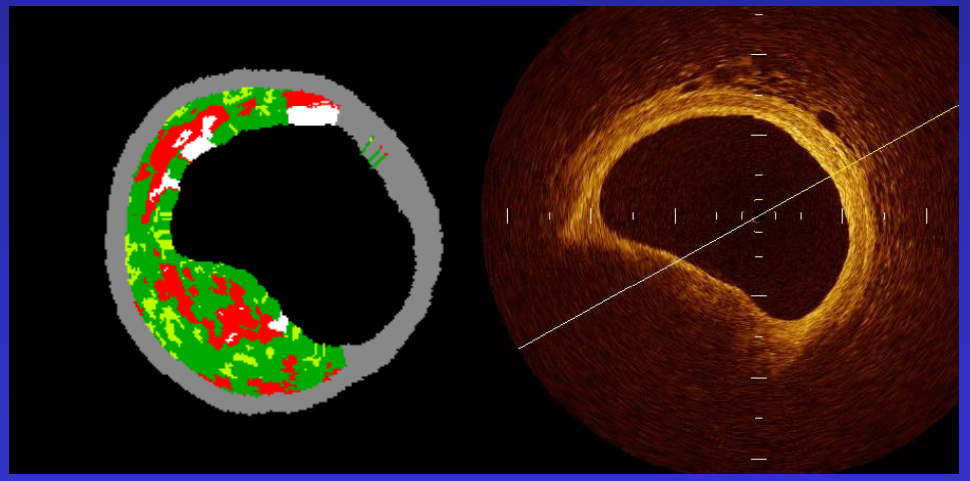
(Sawada T, et al Eur Heart J 29:1136-1146, 2008)



Without evident overlying fibrous tissue



Without evident overlying fibrous tissue



With evident overlying fibrous tissue

Concordance & discordance between VH-IVUS and OCT in the assessment of TCFA

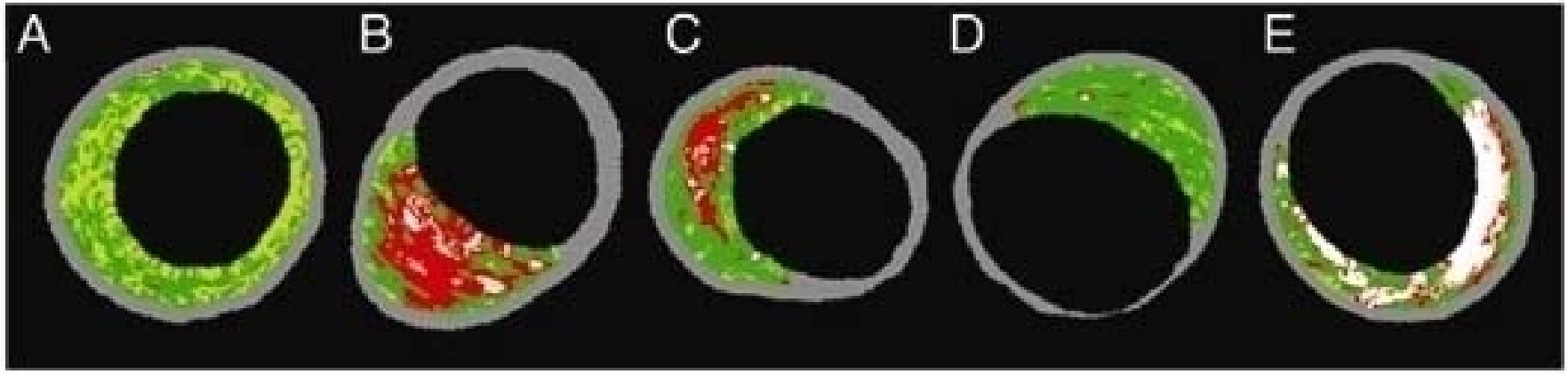
Table 4

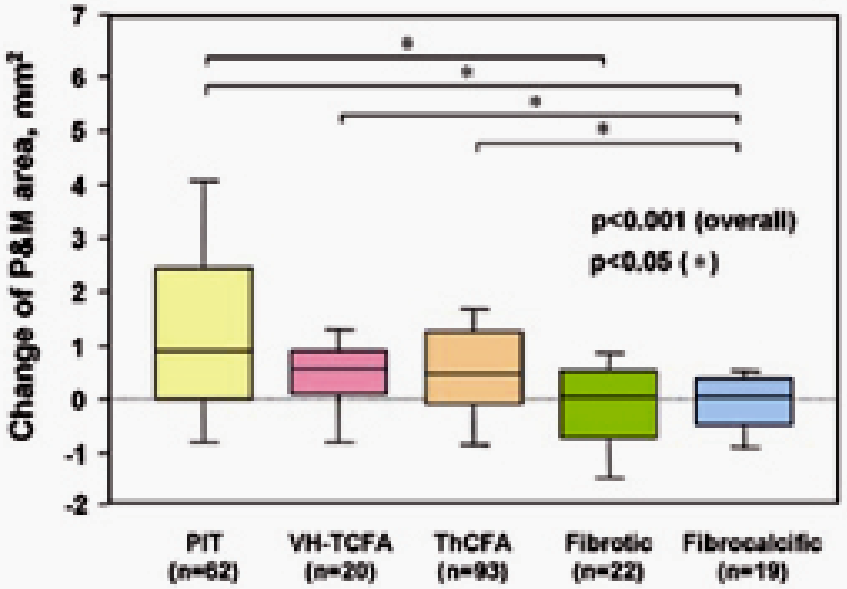
IVUS-VH Diagnosis \ OCT Diagnosis	TCFA (n=11)	Not TCFA (n=36)
VH-TCFA (n=31)	9	22
Not VH-TCFA (n=16)	2	14

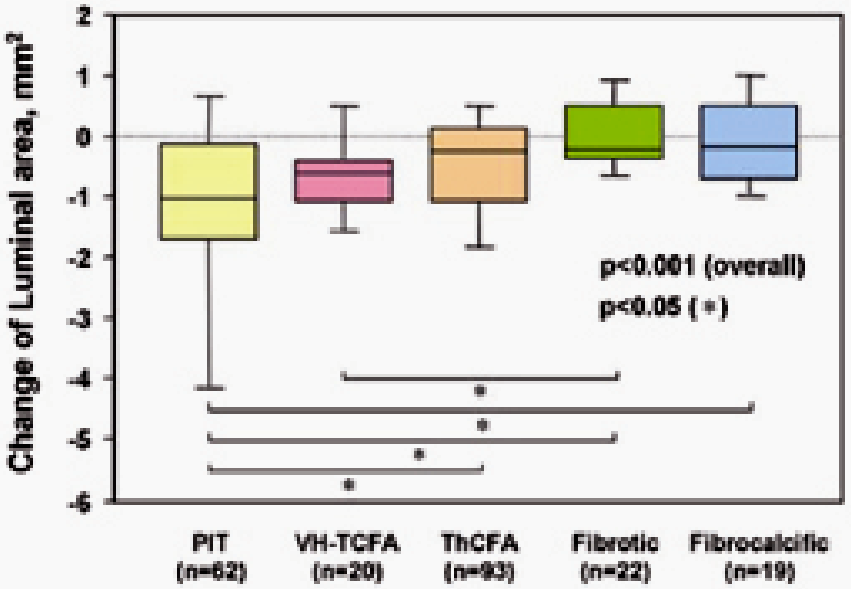
Discordance between VH-IVUS & OCT has been described by Sawada T, et al. (Eur Heart J 29:1136-1146, 2008)

Changes of plaque, media & lumen area

PIT VH-TCFA ThCFA Fibrotic Fibrocalcific





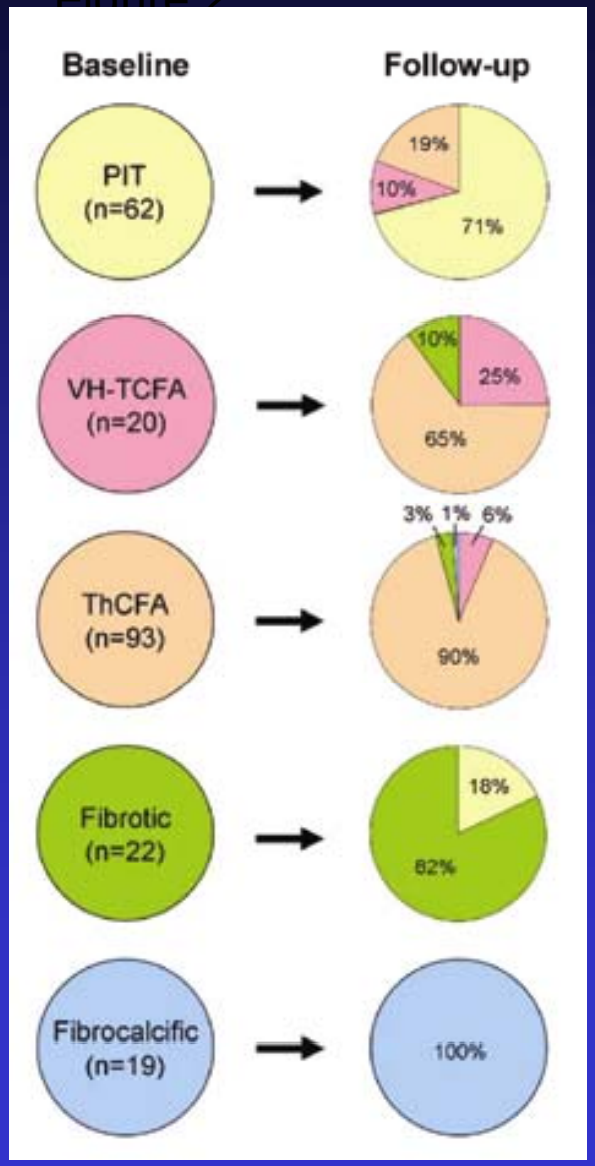


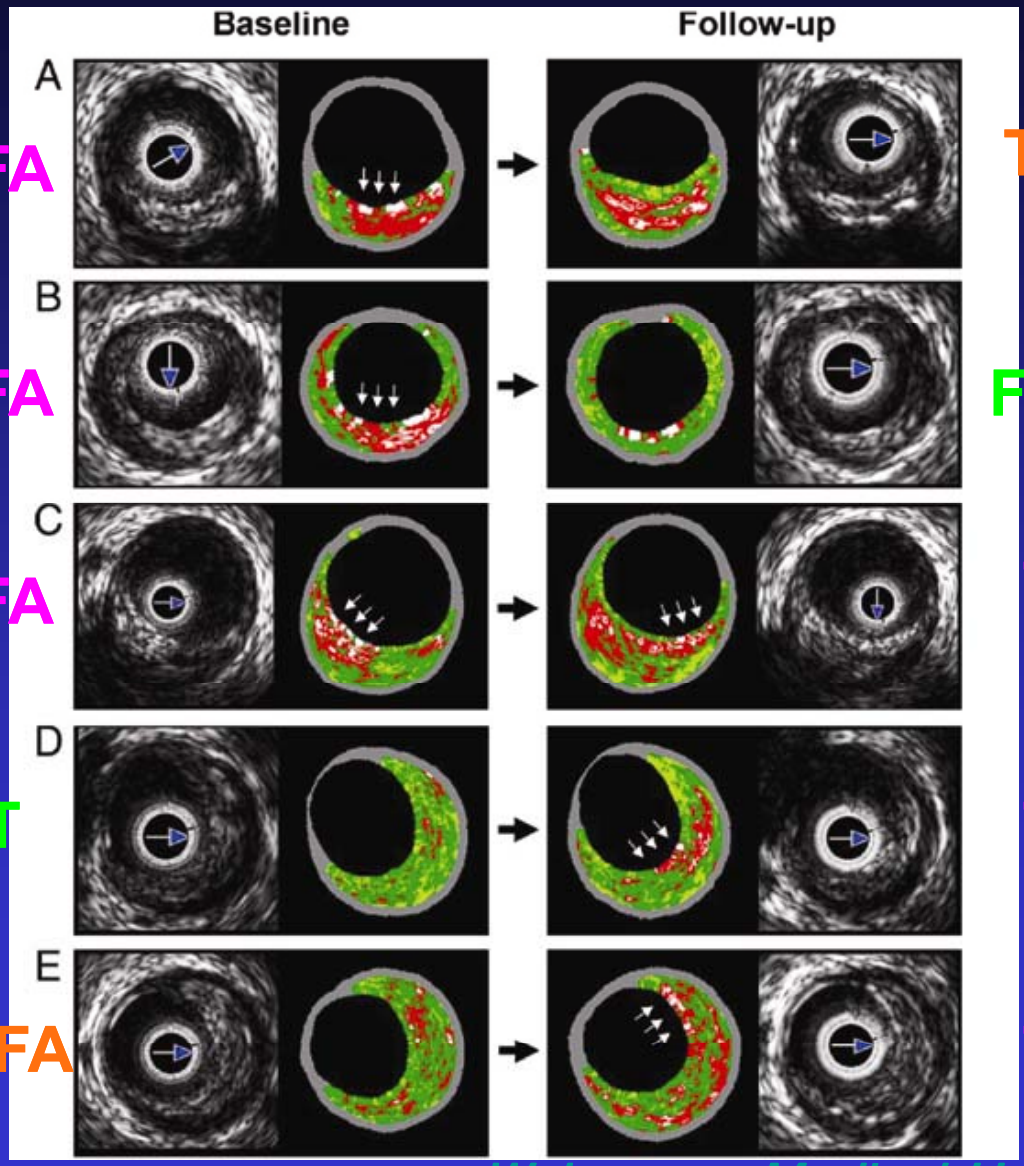
(Kubo T, et al. J Am Coll Cardiol 55;1590-1597, 2010)

Coronary lesion morphology by VH-IVUS

(Kubo T, et al. J Am Coll Cardiol 55;1590-1597, 2010)

Figure 2





Controversy in plaque characterization by VH-IVUS

(Thim T, et al. Cir Cardiovasc Imaging. 2010;3:384-391)

Figure 2

Unreliable Assessment of Necrotic Core by Virtual Histology Intravascular Ultrasound in Porcine Coronary Artery Disease

Troels Thim, MD; Mette Kallestrup Hagensen, MSc; David Wallace-Bradley, MSc; Juan F. Granada, MD; Greg L. Kaluza, MD, PhD; Ludovic Drouet, MD, PhD; William P. Paaske, MD, DMSc; Hans Erik Bøtker, MD, PhD, DMSc; Erling Falk, MD, DMSc

Background—Intravascular ultrasound–derived virtual histology (VH IVUS) is used increasingly in clinical research to assess composition and vulnerability of coronary atherosclerotic lesions. However, the ability of VH IVUS to quantify individual plaque components, in particular the size of the destabilizing necrotic core, has never been validated. We tested for correlation between VH IVUS necrotic core size and necrotic core size by histology in porcine coronary arteries with human-like coronary disease.

Methods and Results—In adult atherosclerosis-prone minipigs, 18 advanced coronary lesions were assessed by VH IVUS in vivo followed by postmortem microscopic examination (histology). We found no correlation between the size of the necrotic core determined by VH IVUS and histology. VH IVUS displayed necrotic cores in lesions lacking cores by histology.

Conclusions—We found no correlation between necrotic core size determined by VH IVUS and real histology, questioning the ability of VH IVUS to detect rupture-prone plaques, so-called thin-cap fibroatheromas. **(*Circ Cardiovasc Imaging*. 2010;3:384-391.)**

Intravascular imaging modalities

- IVUS
  - Gray scale
  - IB
  - Virtual histology

  } available

  - Elastography
  - Palpography

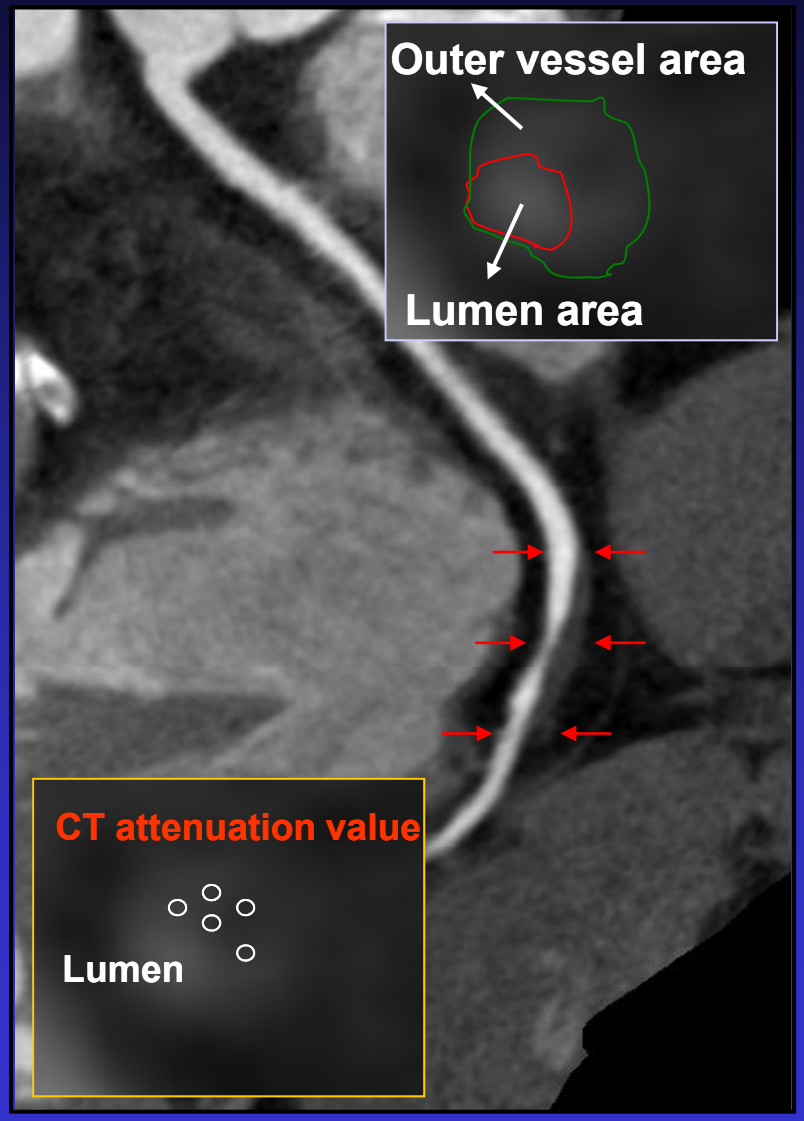
  } not available

- Angioscopy
- OCT
- NIR system

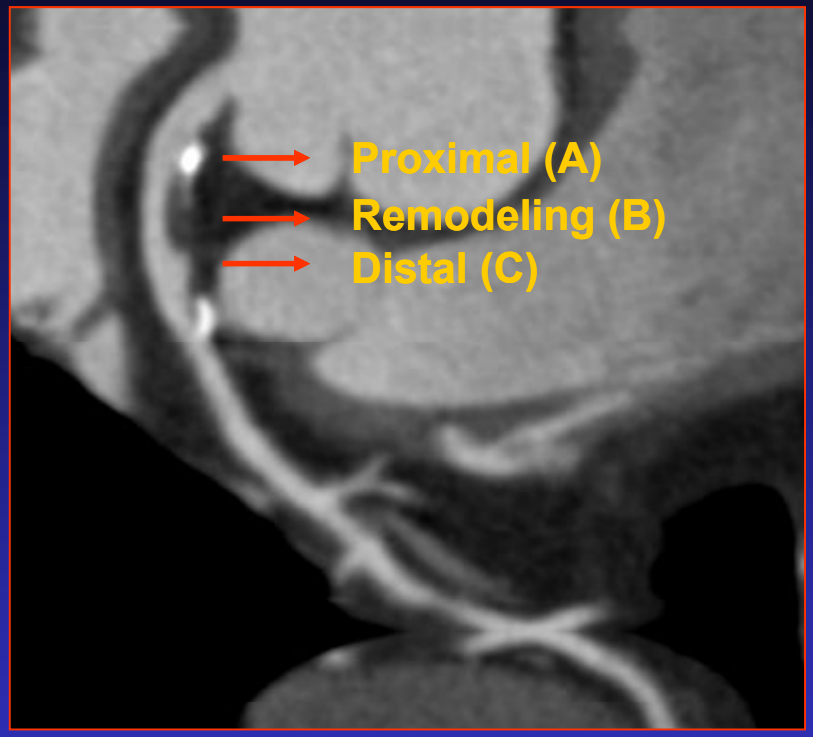
} available

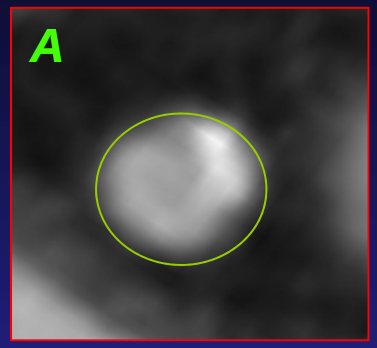
Assessment by MDCT

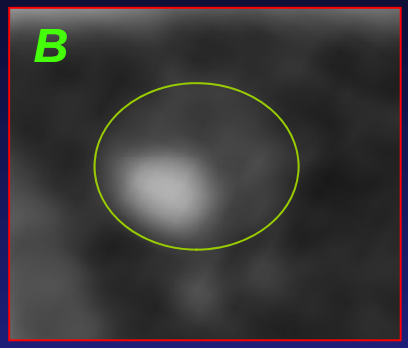
- Outer vessel area
- Lumen area
- % Plaque area
  = vessel area – lumen area
- Positive remodeling
  (Remodeling Index ≧ 1.05)
- CT attenuation value
- Ring-like sign

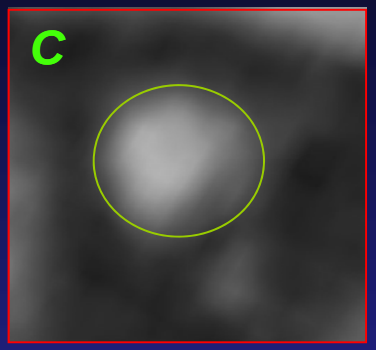


Remodeling Index Assessed by MDCT







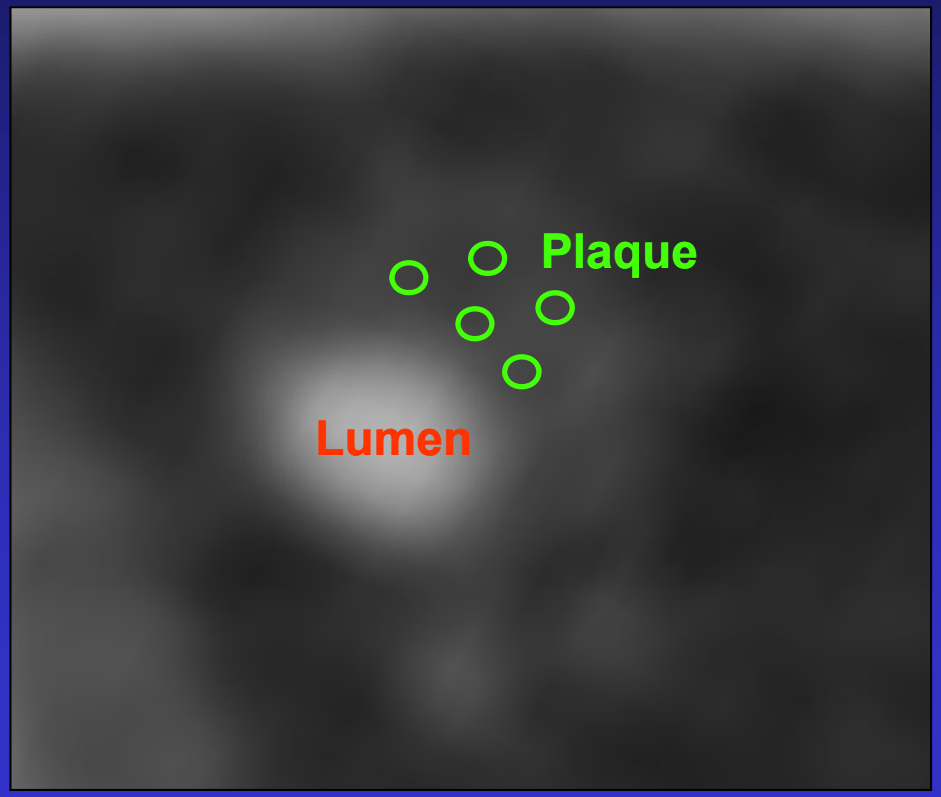


$$\text{Remodeling Index} = \frac{2 \times \text{Culprit area}}{\text{Prox. + Distal reference area}}$$

Positive remodeling: Remodeling Index ≧ 1.05

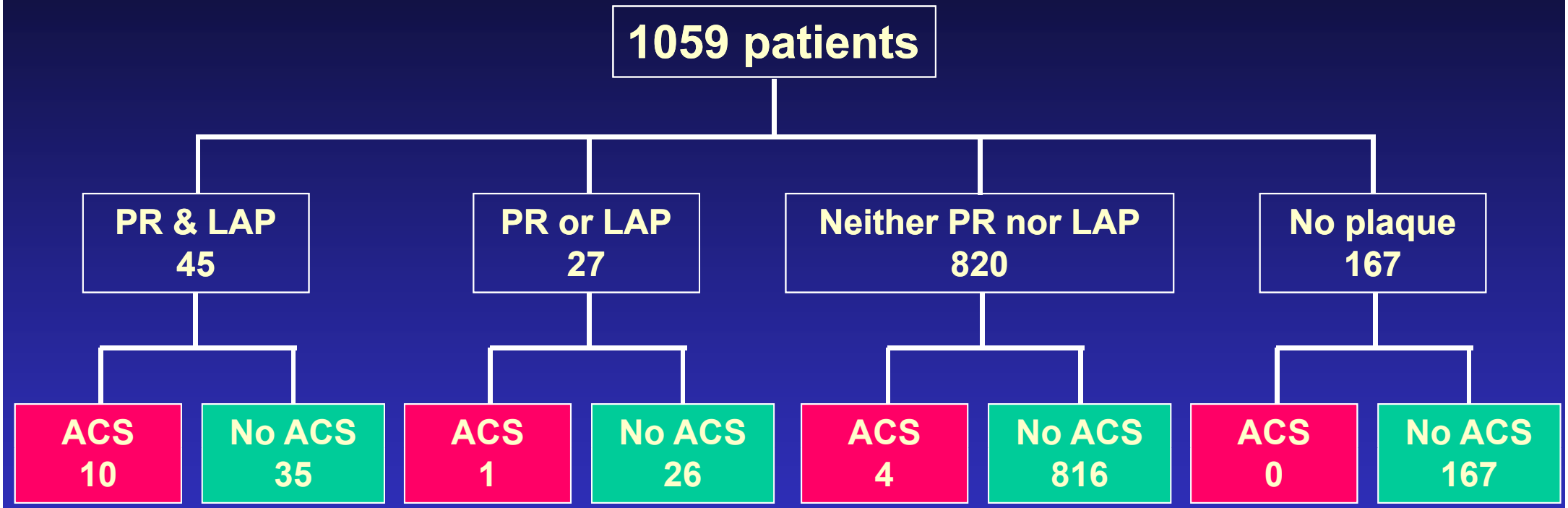
- The arterial remodeling index was defined as the ratio between the outer vessel area at the site of maximal luminal narrowing and the mean of the proximal and distal reference sites.
- Positive Remodeling was defined as remodeling index ≧ 1.05.

The Assessment of CT Attenuation Value



The CT values of plaques were measured in multiple (at least 3 sections) cross-sectional images along the plaque and averaged.

Patient population & event



PR: positive remodeling
LAP: low-attenuation plaque

Motoyama S, et al. J Am Coll Cardiol 54: 49-57, 2009

Treatment of vulnerable plaque

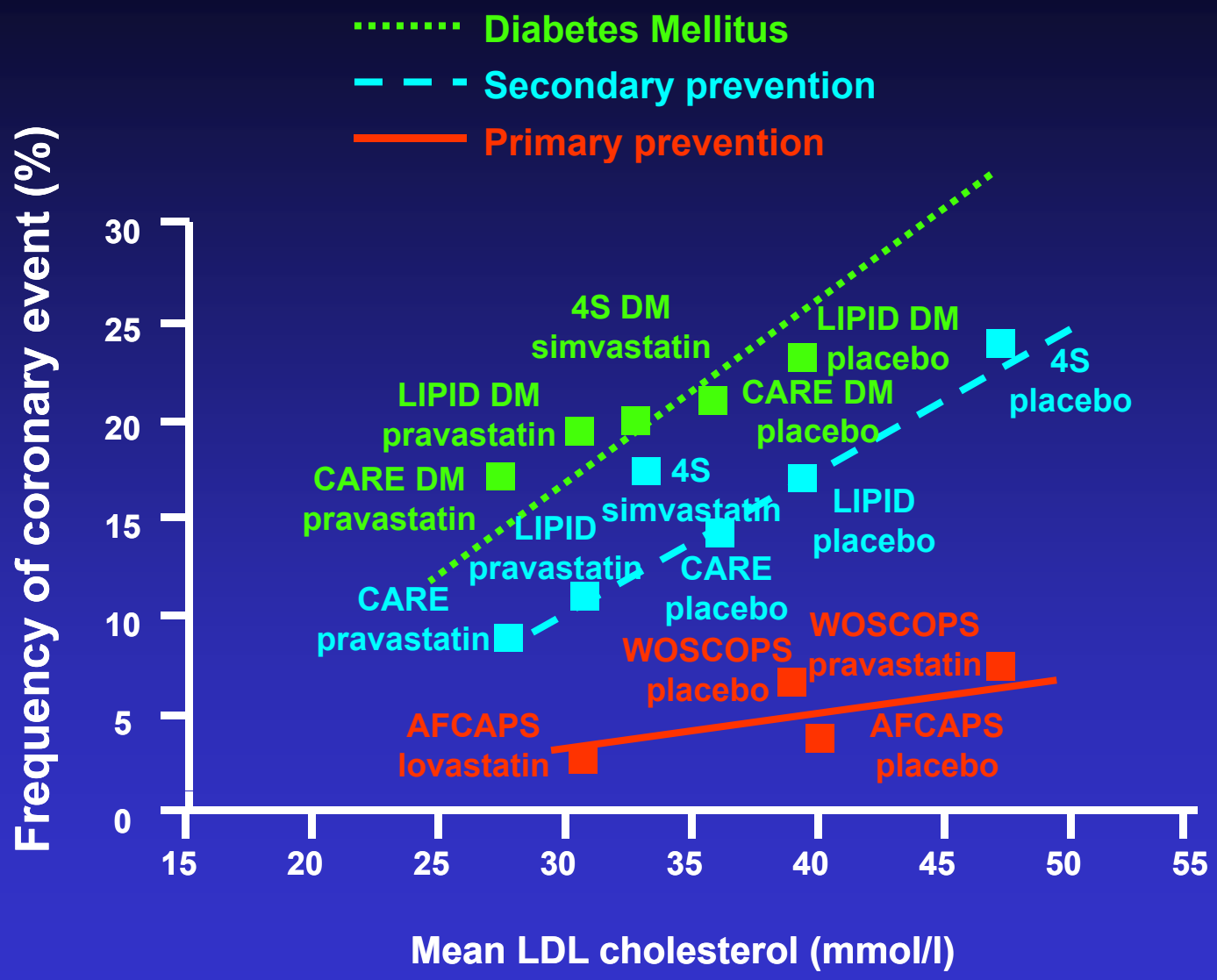
Local approach

- **Plaque sealing by stent**
- **Plaque stabilization by local drug delivery**

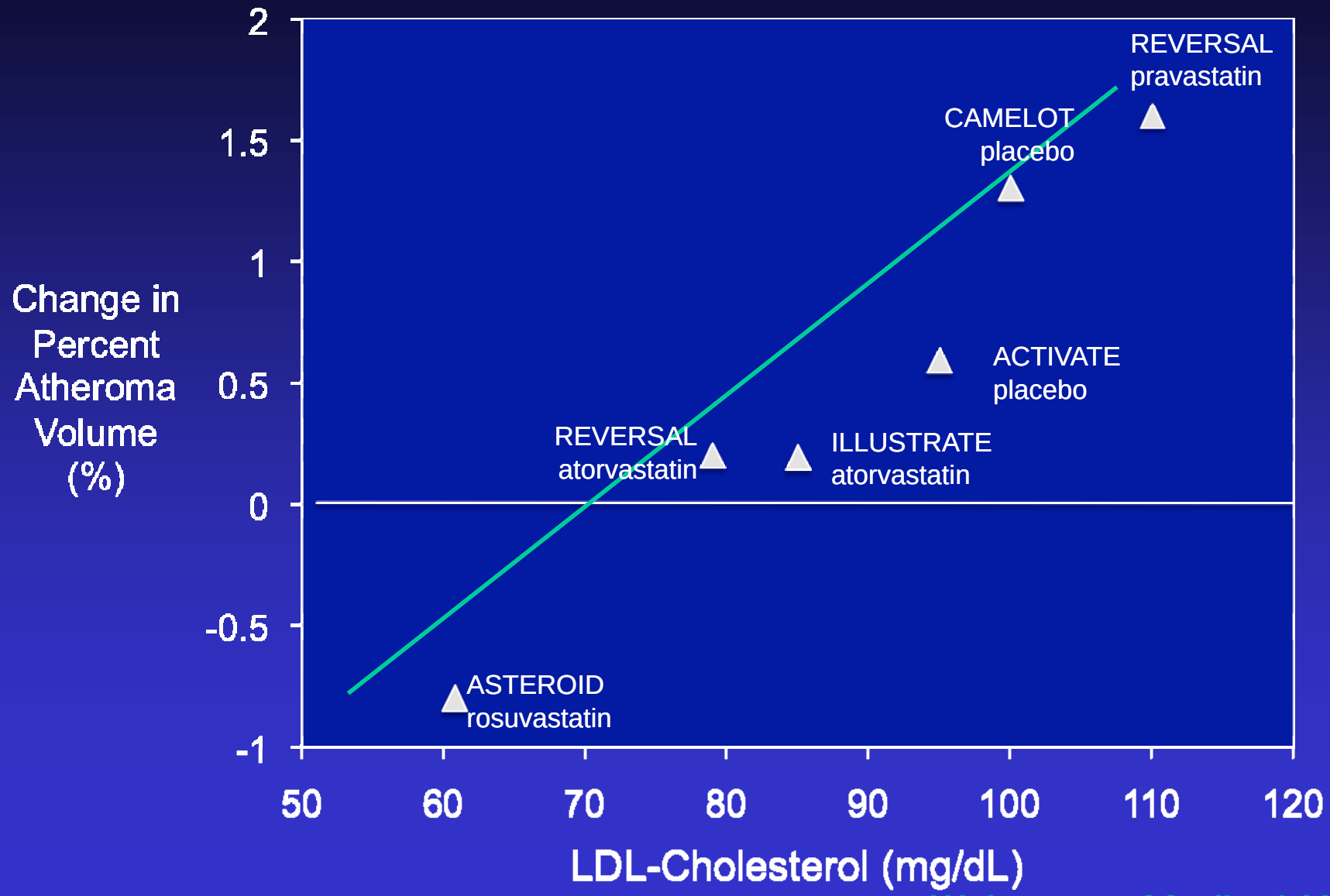
Systemic approach

- **Change lifestyle**
- **Reduction of risk factor**
- **Medication**

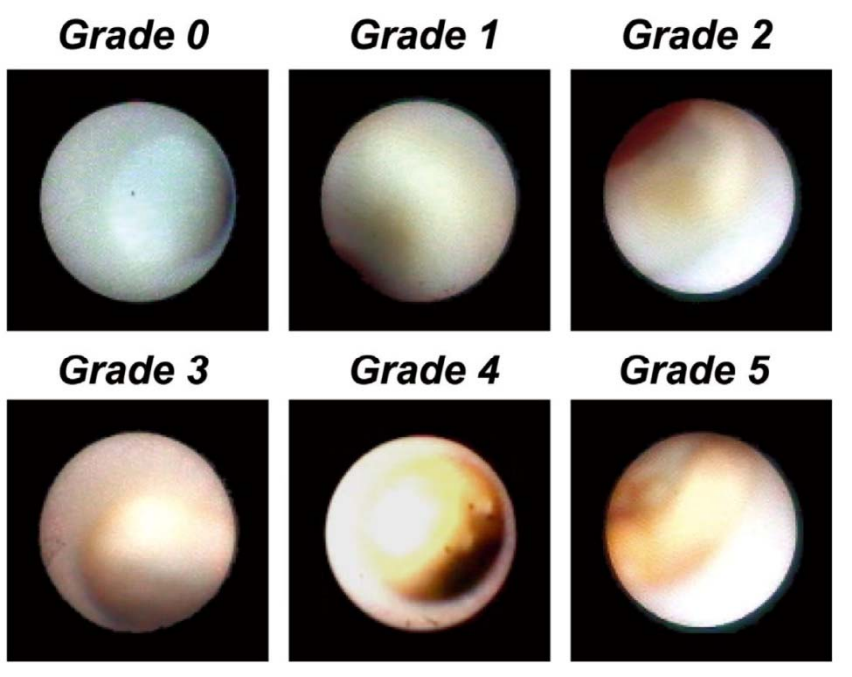
LDL cholesterol & coronary event

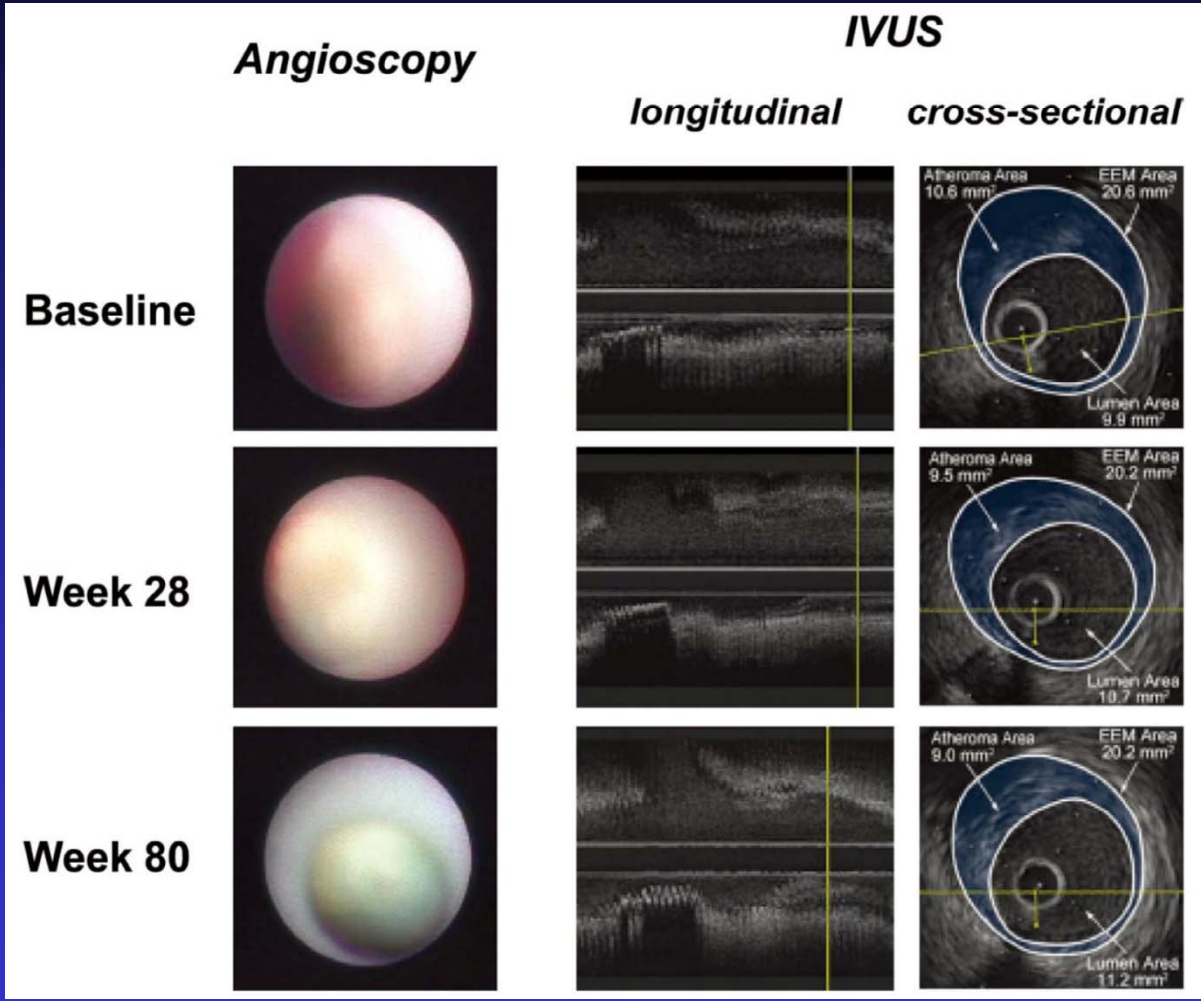


LDL vs Atheroma volume



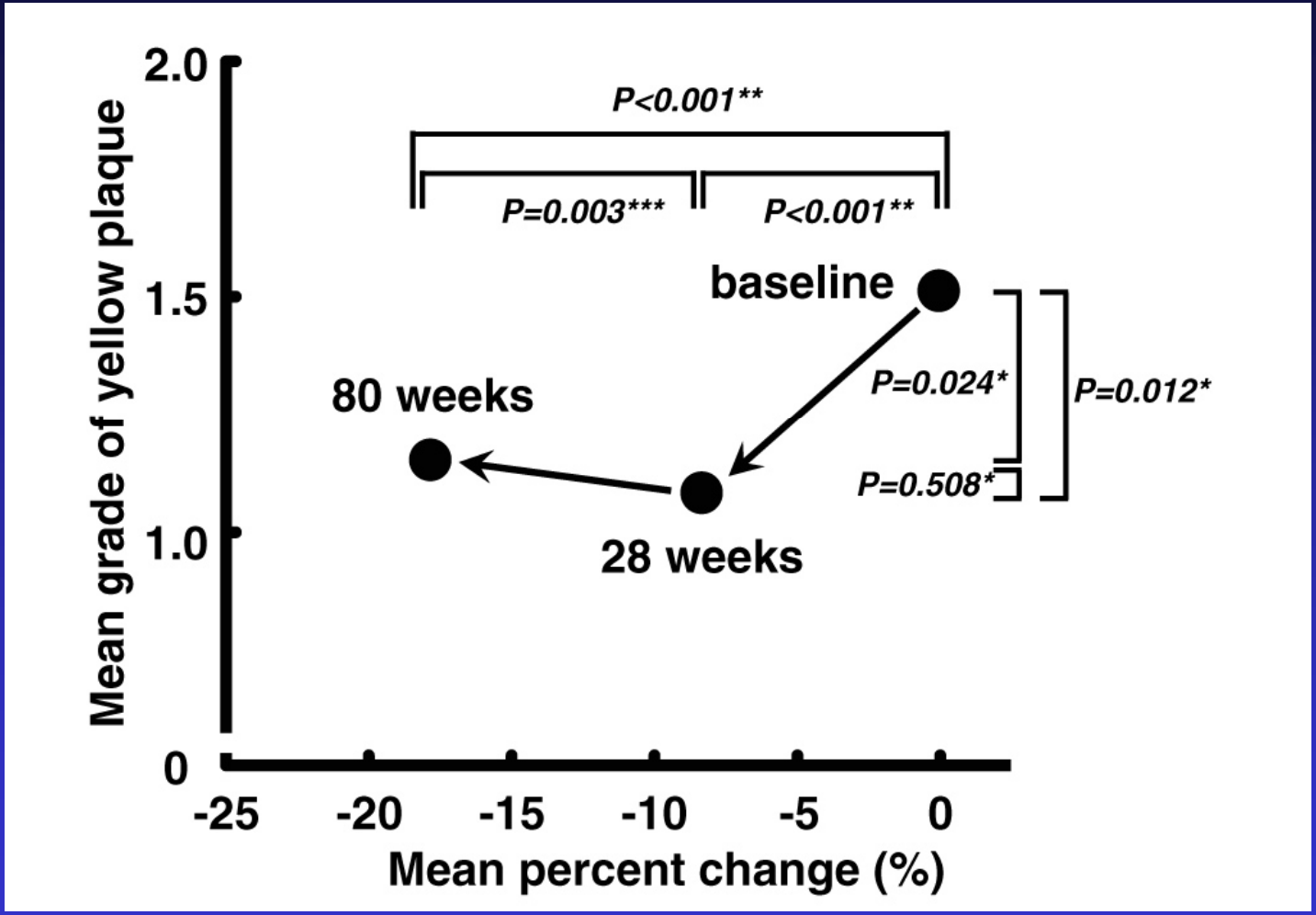
Changes in plaque color & volume by statin





(Hirayama A, *et al*: *Circ J* 73; 718-725, 2009)

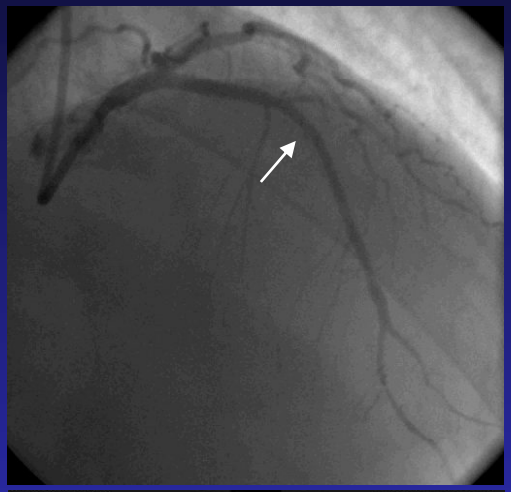
Changes in plaque color & volume by statin



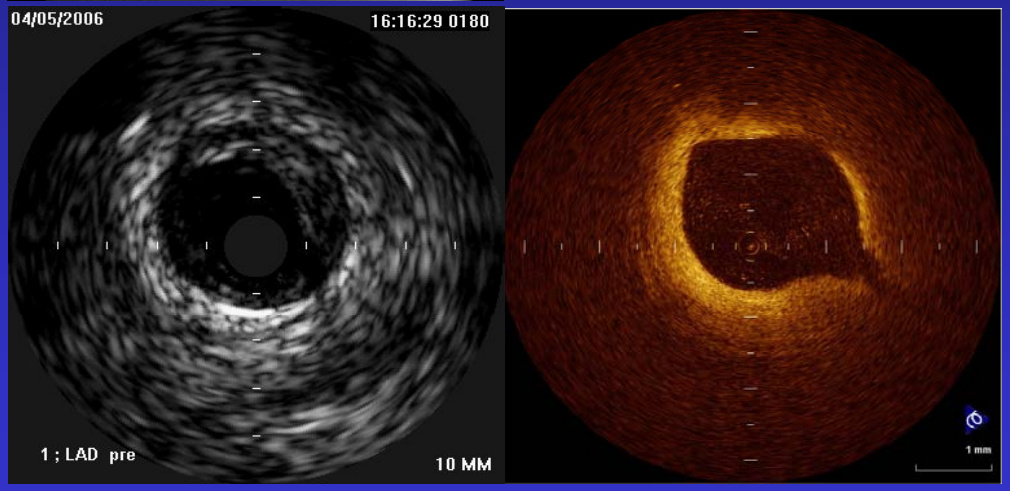
(Hirayama A, *et al*: *Circ J* 73; 718-725, 2009)

OCT assessment of non-culprit lesion (47y.o. male)

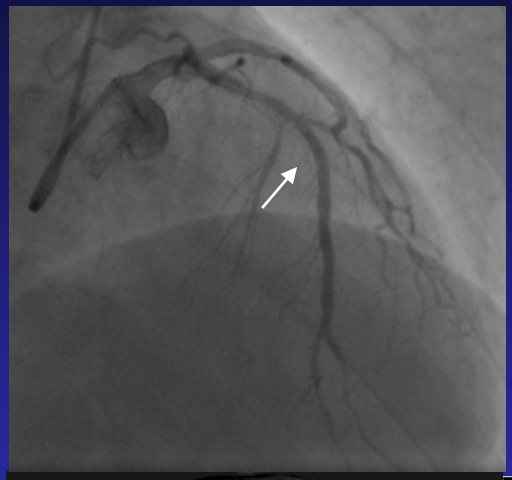
Baseline



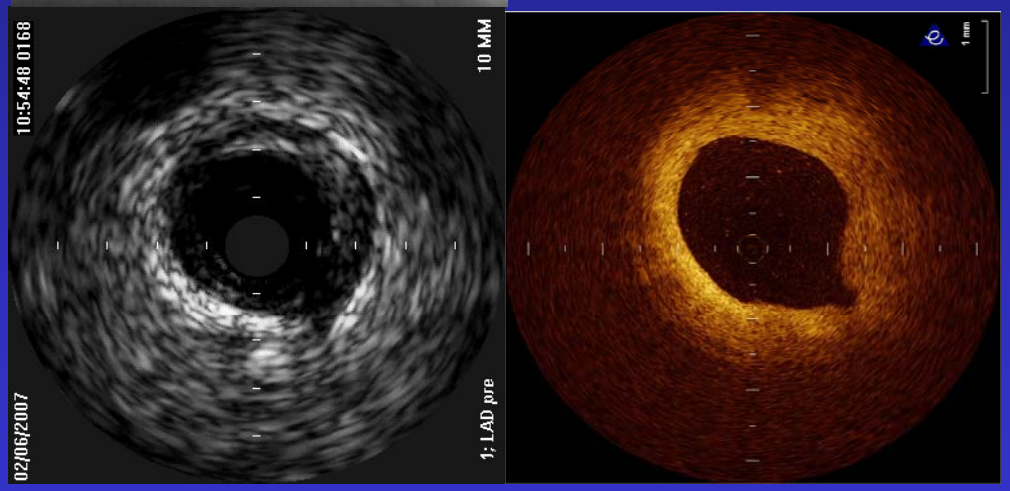
T.Chol. 200 mg/dl
TG 79 mg/dl
HDL-C 47 mg/dl
LDL-C 128 mg/dl



9 month later

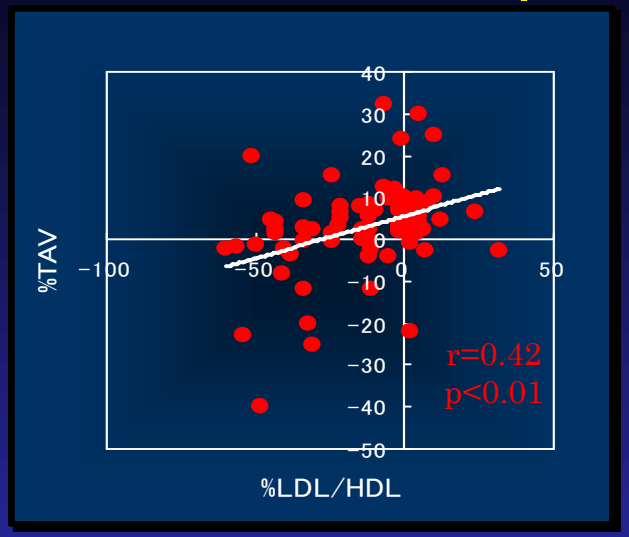


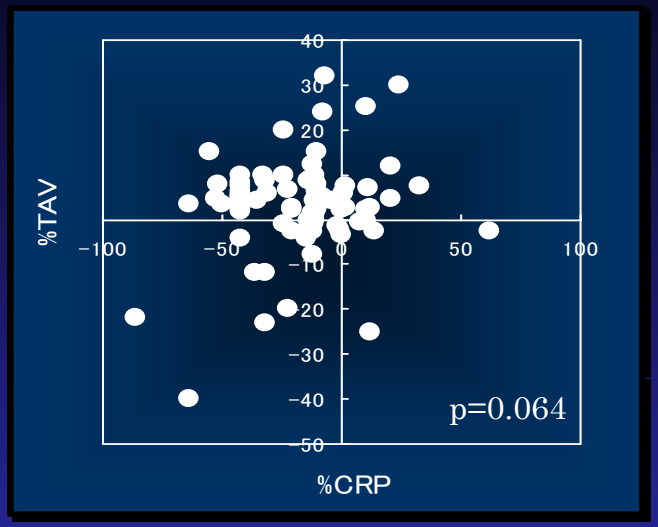
T.Chol. 187 mg/dl
TG 133 mg/dl
HDL-C 49 mg/dl
LDL-C 98 mg/dl

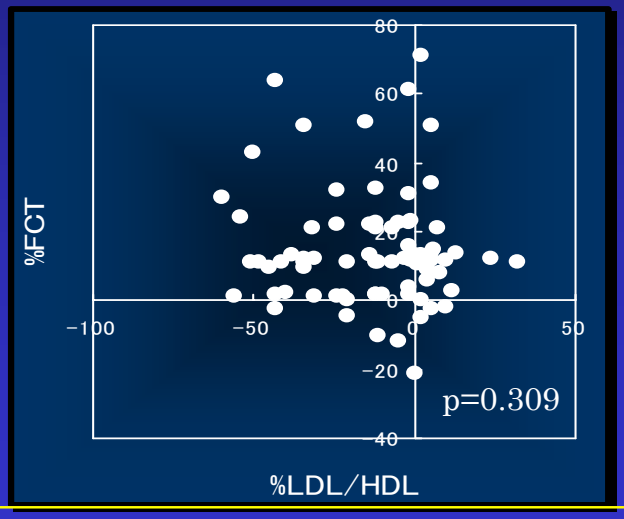


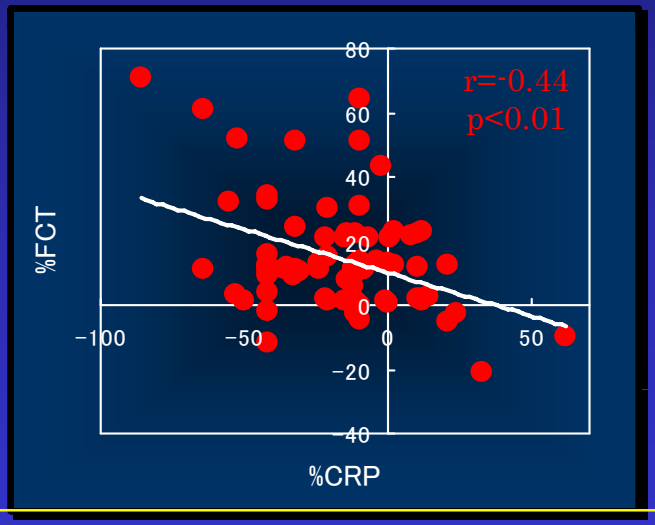
（Takarada S, et al. Atherosclerosis 202: 491- 497, 2009 ）

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）

Univariable and multivariable logistic regression analyses as predictors of plaque stabilization

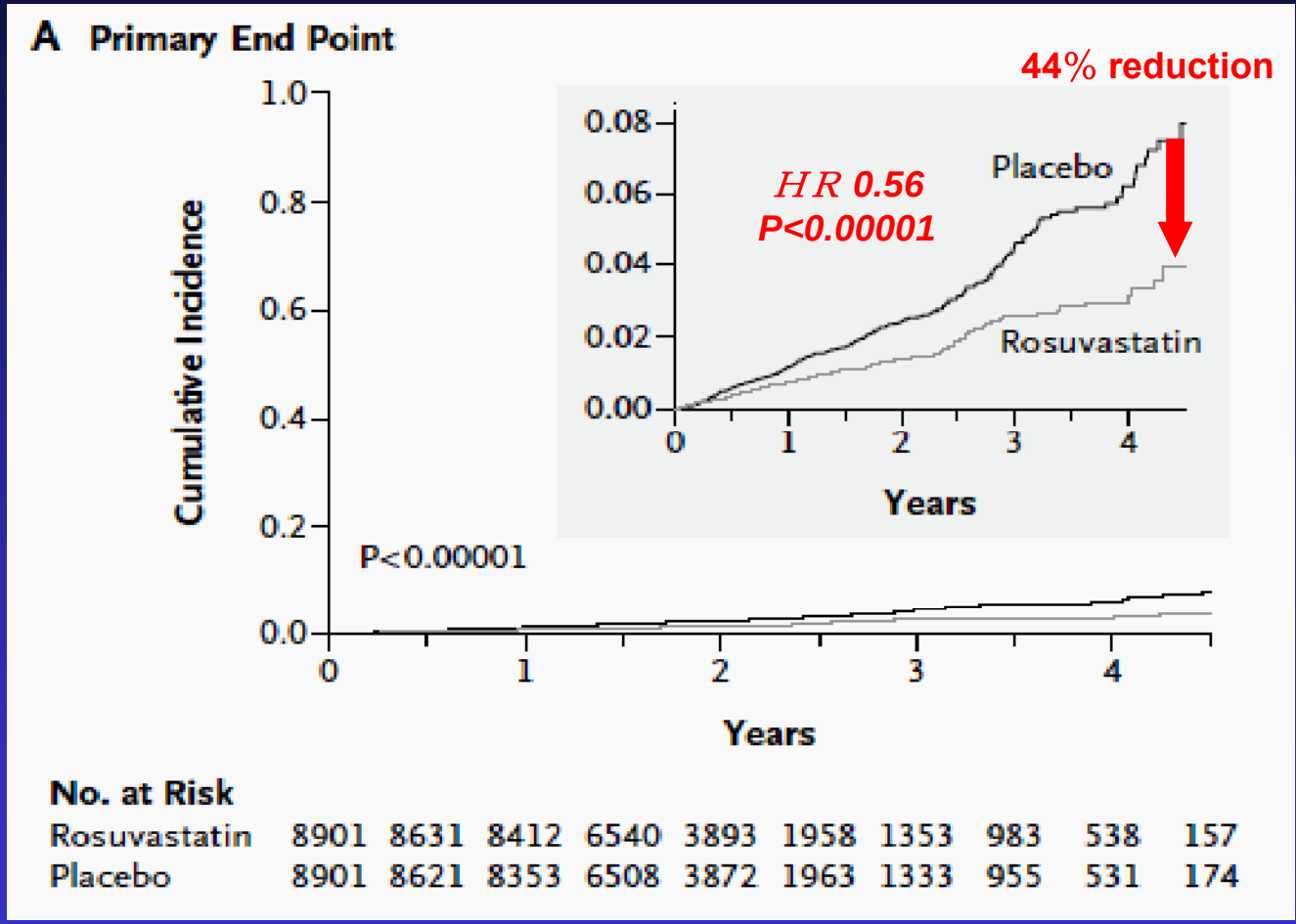
	univariable analysis : OR(95% CI)	p-value		multivariable analysis :OR(95%CI)	p-value
age,y	0.52 (0.93-1.04)	p=0.60			
gender	1.38 (0.46-5.4)	p=0.86			
HLP	0.91(0.33-2.51)	p=0.86			
HT	0.53 (0.17-1.09)	p=0.08		0.72 (0.22-1.7)	p=0.73
DM	0.56 (0.14-0.97)	p=0.04		0.74 (0.23-2.4)	p=0.84
statin	3.57 (1.66-12.6)	p=0.002		1.45 (1.15-15.9)	p=0.02

"Plaques stabilization" was defined by decreasing TAV and increasing FCT.
In the present study, 31 plaques (39%) stabilized.

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

JUPITER trial

N Engl J Med 2008;359:2195-207.



Conclusions

- Newly developed invasive and non-invasive imaging modalities may improve the assessment of tissue characterization and coronary pathophysiology for the identification of vulnerable plaques (VPs).

- OCT may have a potential to demonstrate the pathophysiology of the coronary artery disease in vivo in detail compared with other imaging modalities.

- Future development of molecular imaging and chemical mediators may allow us to identify VPs more precisely.

- VPs are the manifestation of systemic atherosclerosis, and not local but systemic approach should be ideal for their treatment .