Vulnerable plaque

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Introduction

- Coronary events continue to be the leading cause of death in the developed countries.
- Sudden cardiac death is the first sign of coronary atherosclerosis in a large proportion of patients.
- And even those who survive an acute coronary syndrome remain at high risk
- For primary and secondary prevention, the efforts has focused on vulnerable patients and vulnerable plaques.

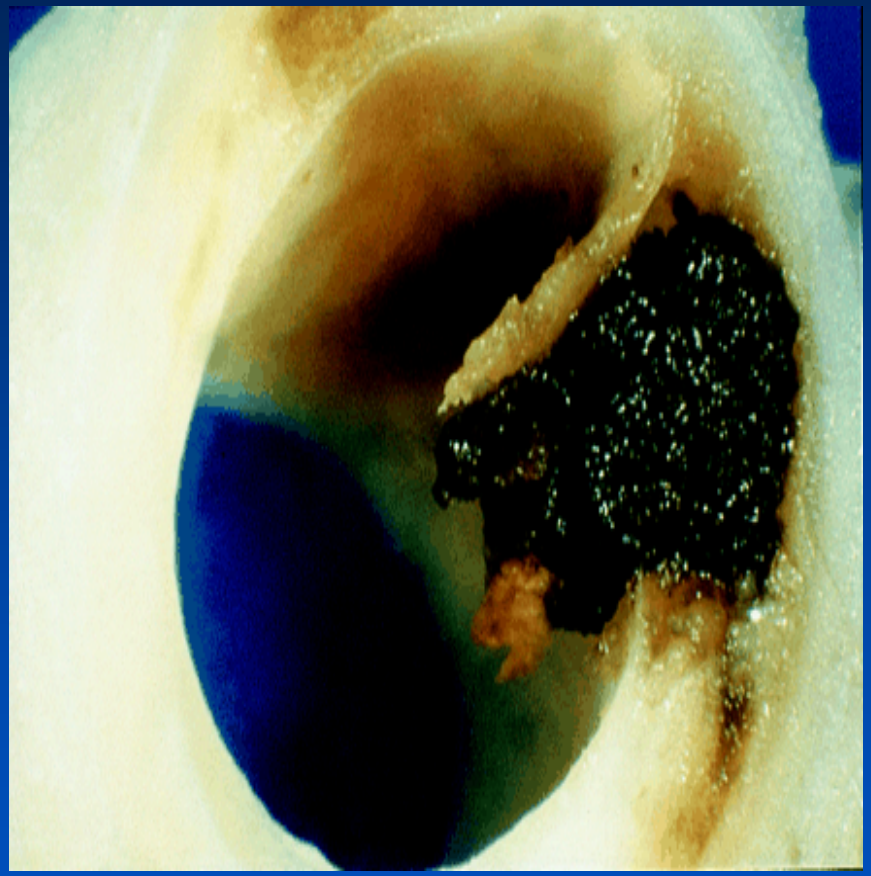
Hazard Rates Per Year for Target-Lesion and Non-Target Lesion Events

1,228 post- 2nd generation stent patients
(3 Trials & 1 Registry)

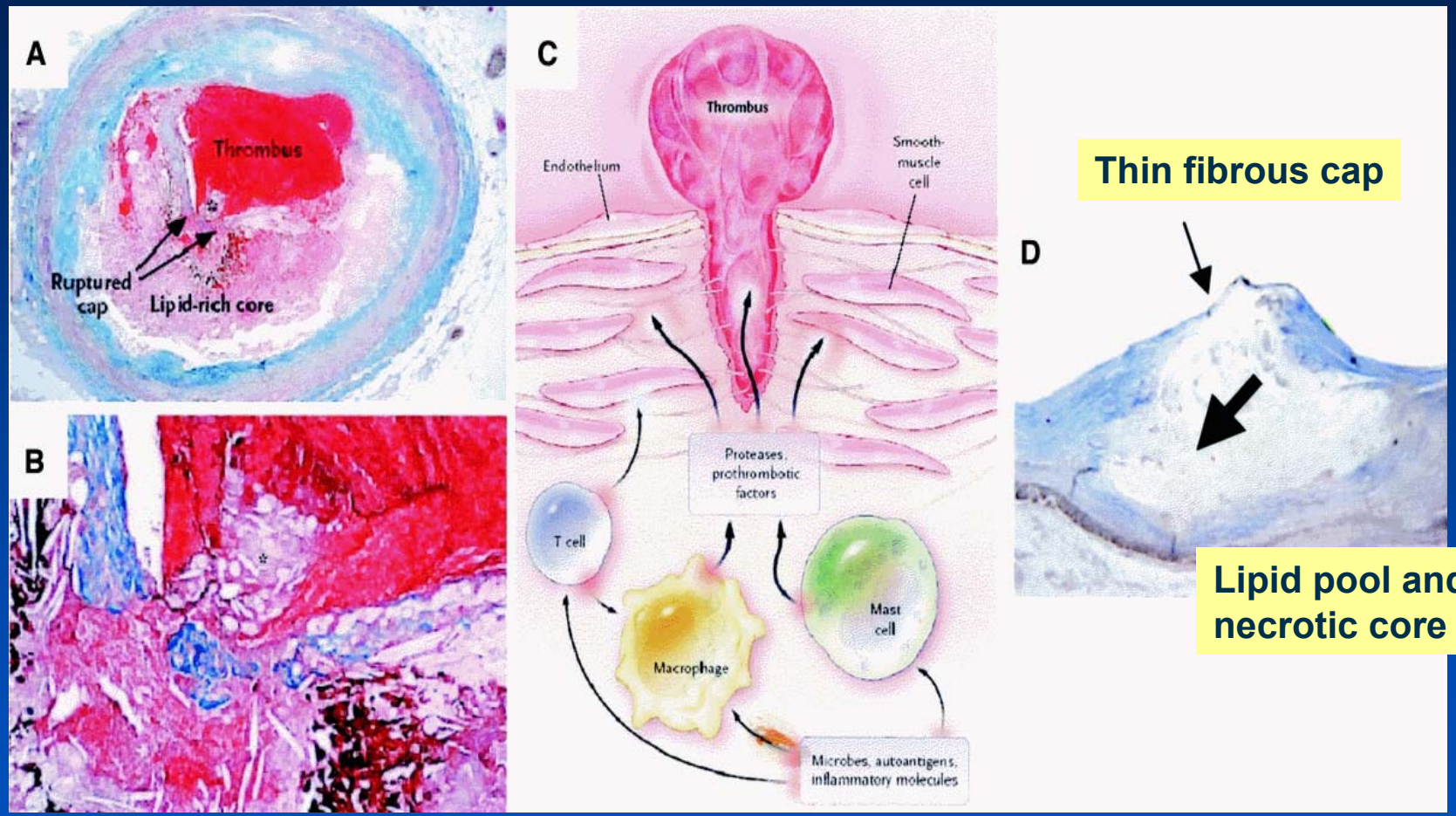
Cutlip, DE et al *Circulation* 2004:110:1226-30

Pathologic study

Pathologic and autopsy studies have reported that rupture of a vulnerable plaque and subsequent thrombus formation is the most important mechanism leading to an acute coronary syndrome (ACS)



Culprit and Vulnerable Plaques



Waxman, Circulation 2006;114:2390-2411

Underlying Pathologies of "Culprit" Coronary Lesions

- Ruptured plaques (70%)
  - Stenotic (20%)
  - Non-stenotic (50%)
- Non-ruptured plaques (30%)
  - Erosion
  - Calcified nodule
  - Others/Unknown

Plaque vulnerability does not equate to percent stenosis

Naghavi M. Circulation 2003; 108: 1664-72

Pathologic Definition of VP
It can not be detectable in clinical practice.

Major criteria

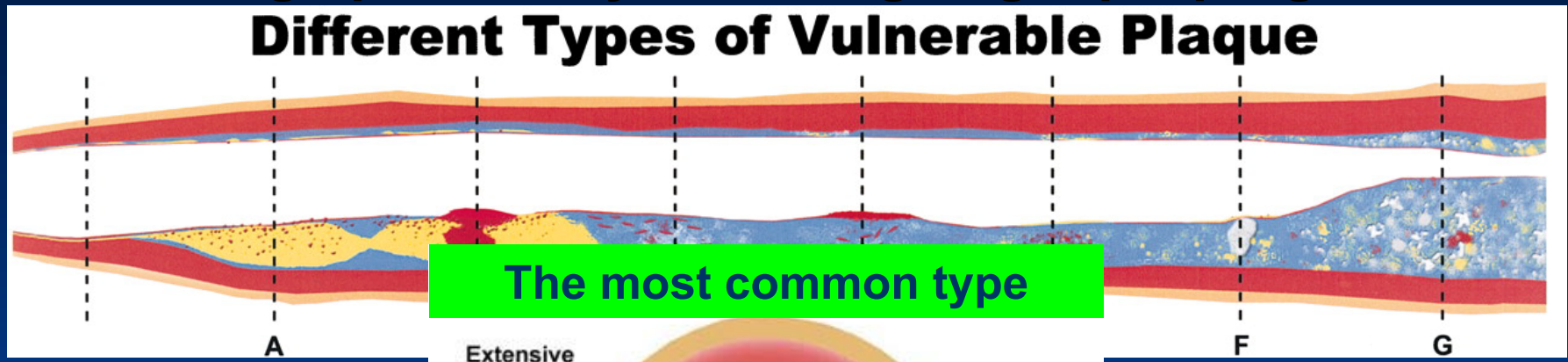
- Active inflammation (monocyte/macrophage and sometimes T-cell infiltration)
- Thin cap with large lipid core
- Endothelial denudation with superficial platelet aggregation
- Fissured plaque
- Stenosis > 90%

Minor criteria

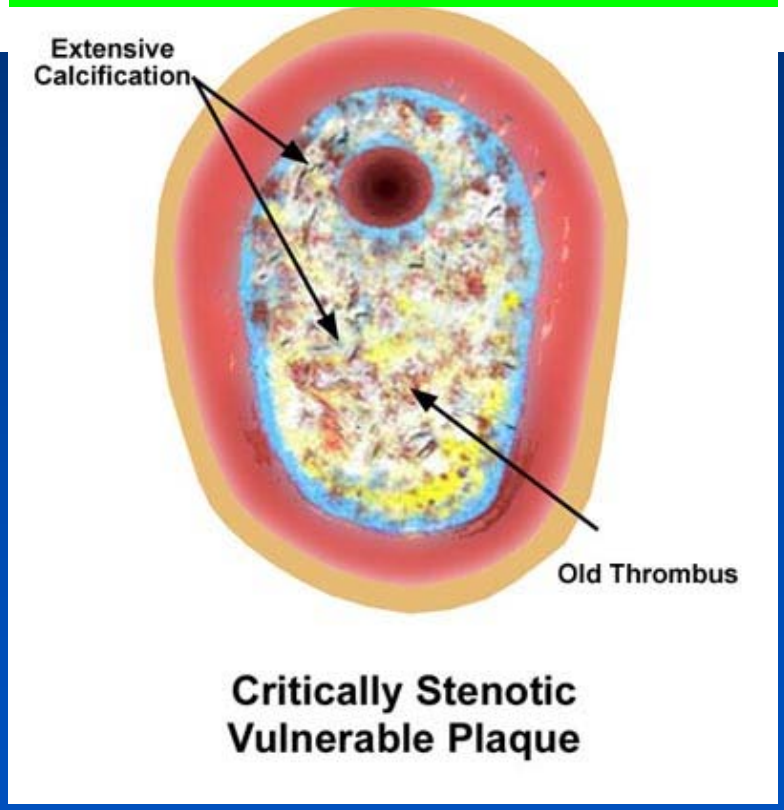
- Superficial calcified nodule
- Glistening yellow
- Intraplaque hemorrhage
- Endothelial dysfunction
- Outward (positive) remodeling

Naghavi et al. Circulation 2003;108:1664-72

"Vulnerable Plaque" = thrombosis-prone plaque and plaque with a high probability of undergoing rapid progression



The most common type



Naghavi et al. Circulation 2003;108:1664-72

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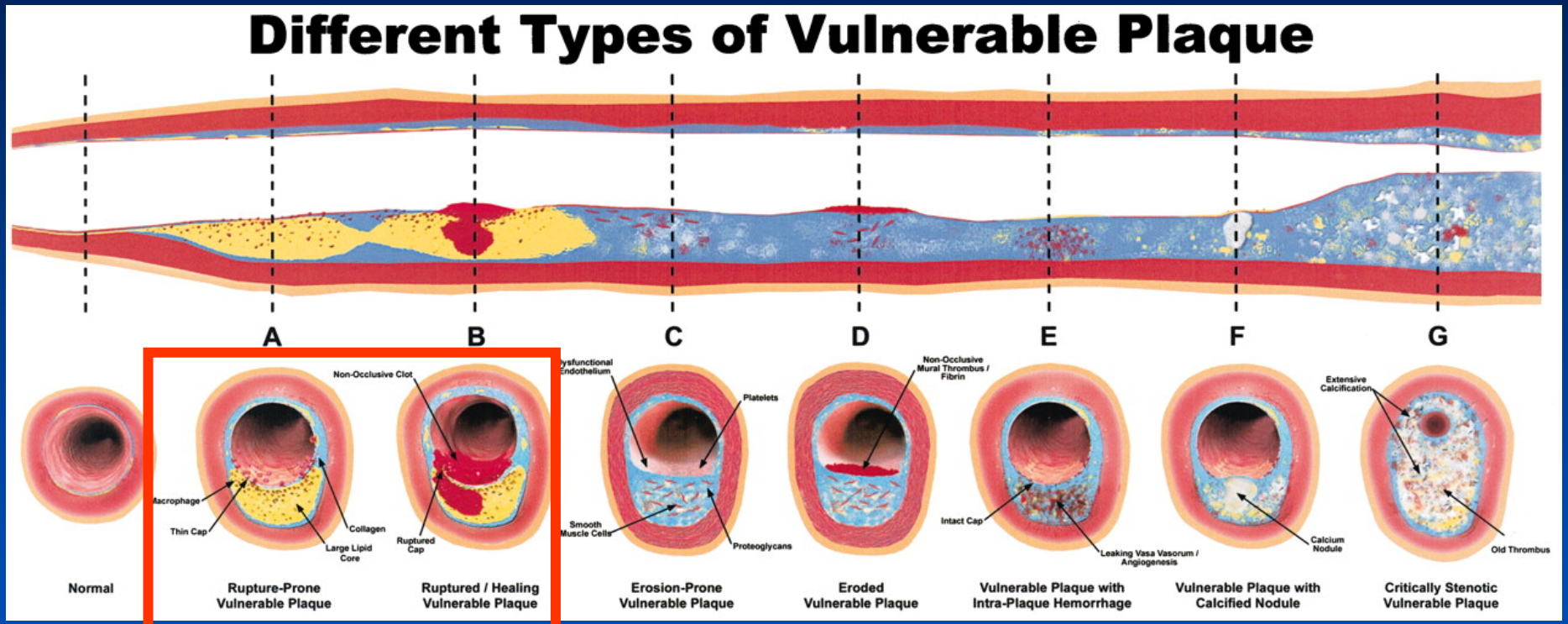


70% of ACS culprit lesions

30% of ACS culprit lesions

Naghavi et al. Circulation 2003;108:1664-72

Methods to Image Vulnerable plaques

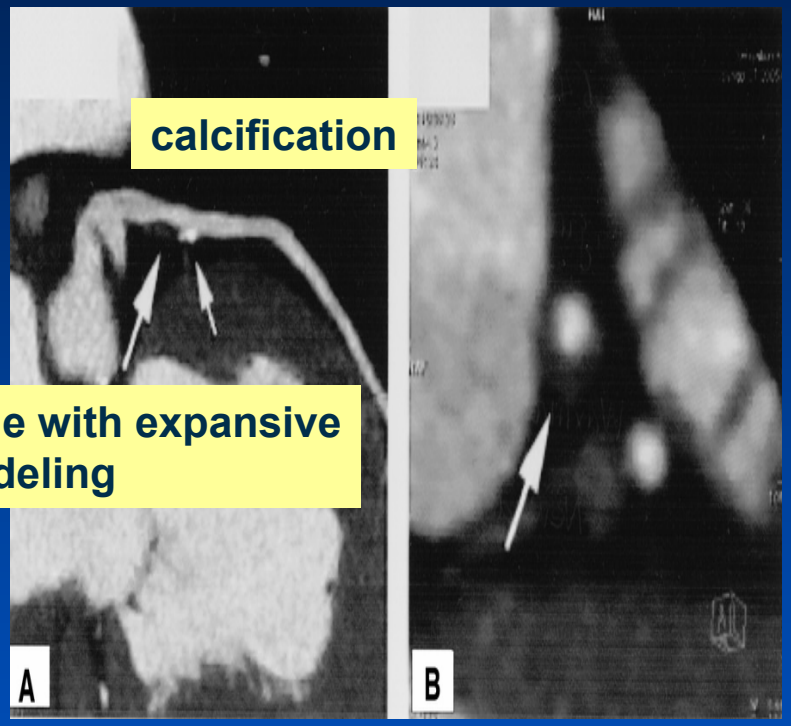
Noninvasive Methods

- MDCT
- MRI
- Near-infrared molecular imaging

Invasive Methods

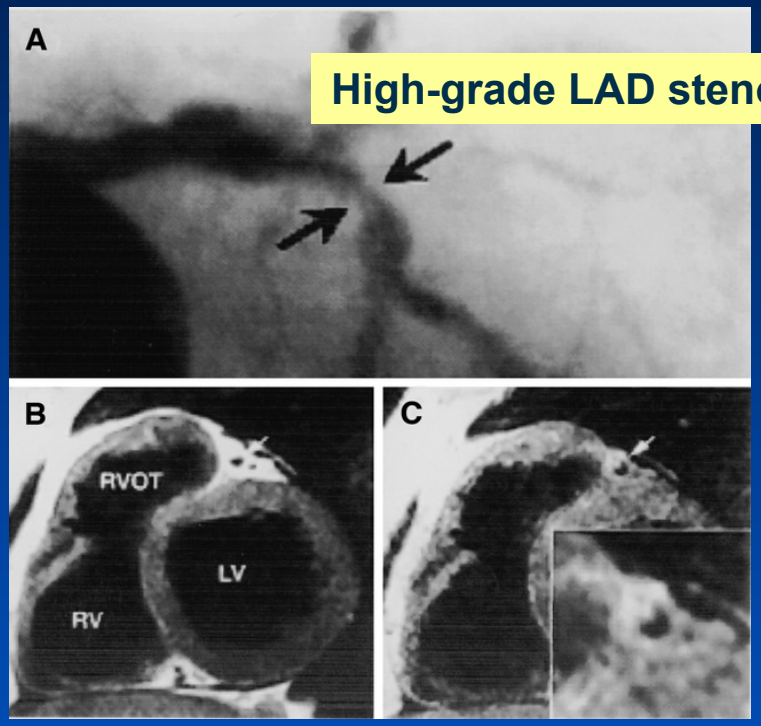
- Coronary angiography
- Intravascular ultrasound: Standard IVUS, Elastography, Virtual Histology
- Angioscopy
- Optical coherence tomography (OCT)
- Thermography
- Intracoronary MRI

Coronary MDCT and MRI



Plaque with expansive remodeling

Cross-sectional image

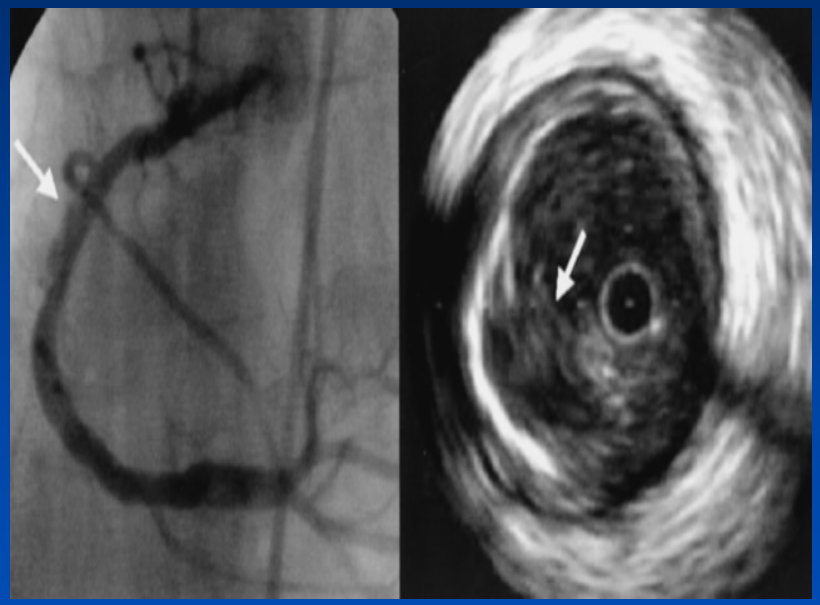


High-grade LAD stenosis

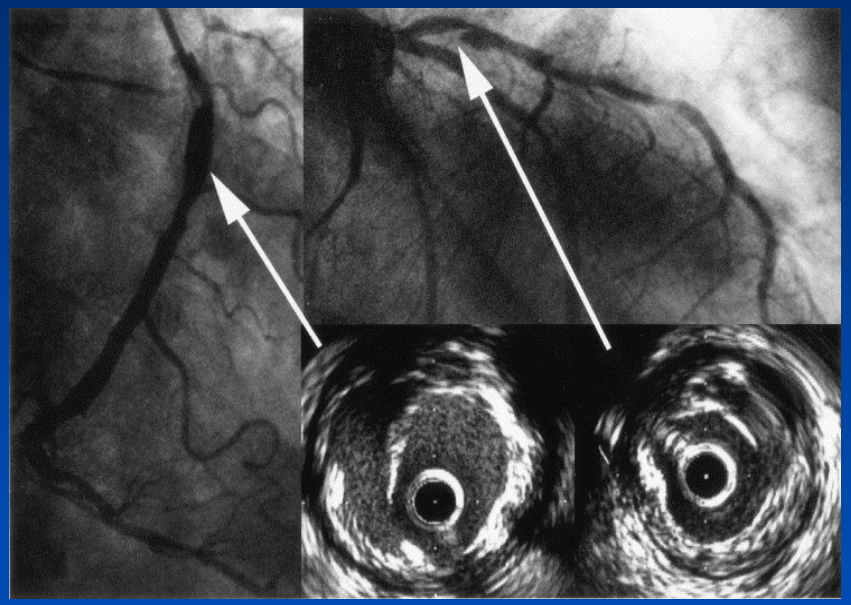
Large eccentric plaque with heterogeneous intensity

Waxman, Circulation 2006;114:2390-2411

Ruptured Plaque: Angiographic and IVUS Images



Hong MK, Circulation 2004;110:928



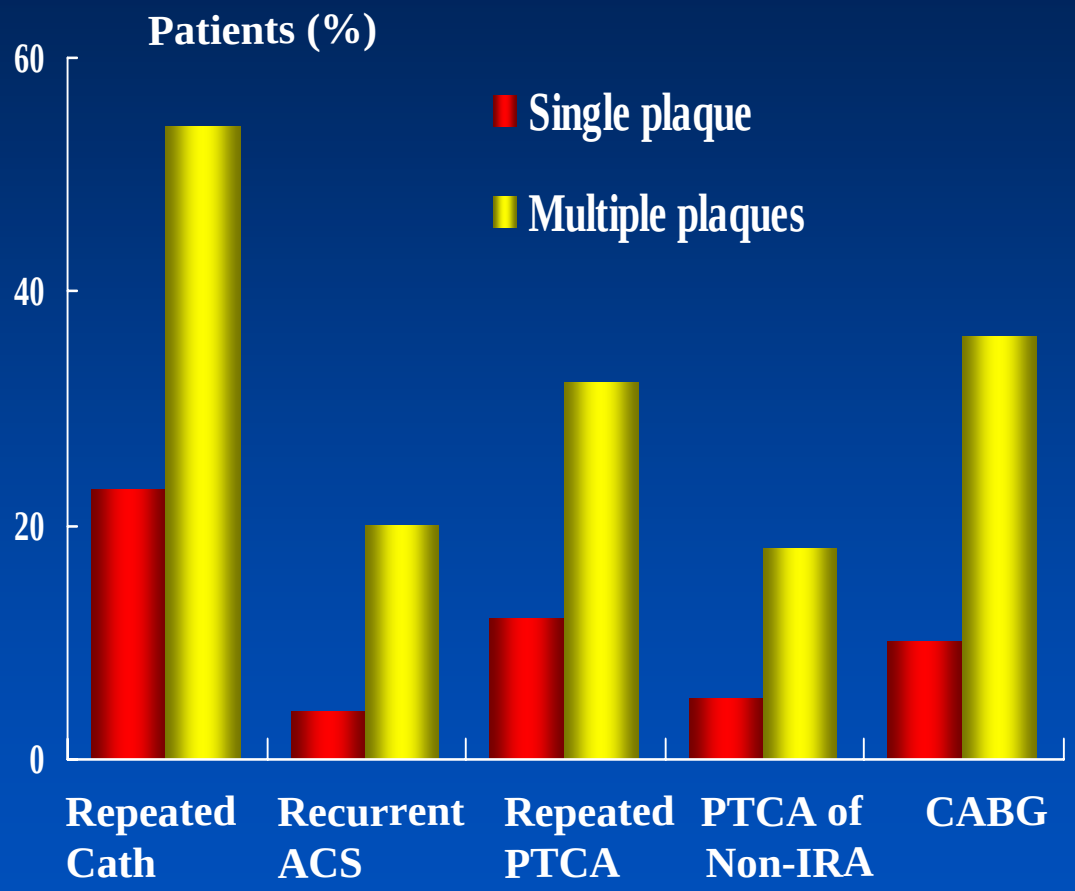
Tanaka A, JACC 2005;45:1594-9

Angiographic Study

One previous study using coronary angiography:

1. 40% of patients with an AMI had multiple complex plaques,

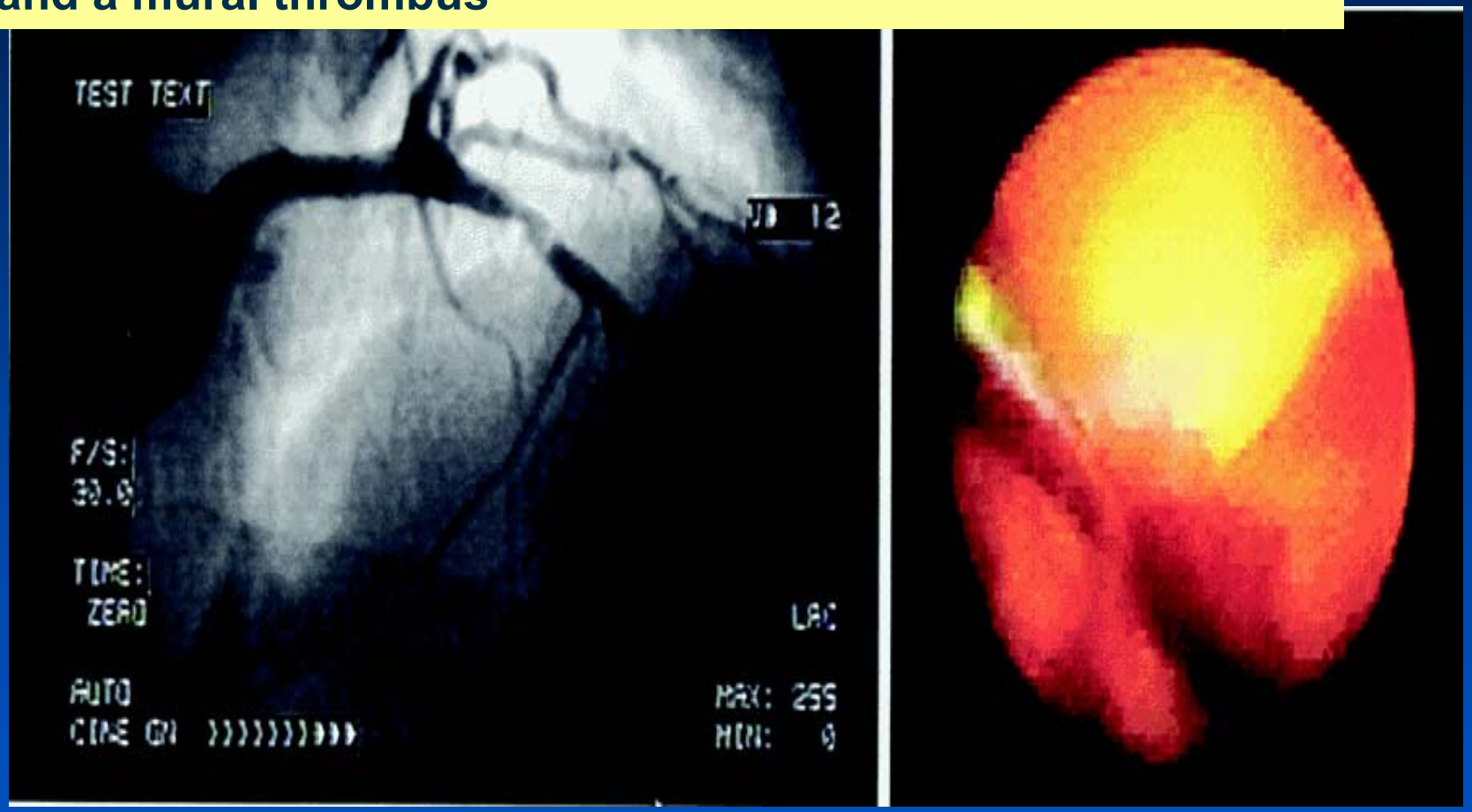
2. These patients had an increased incidence of recurrent ACS, repeat intervention (particularly of non–infarct-related lesions), and CABG in the subsequent year.



Goldstein JA, et al. N Engl J Med. 2000; 343:915–922.

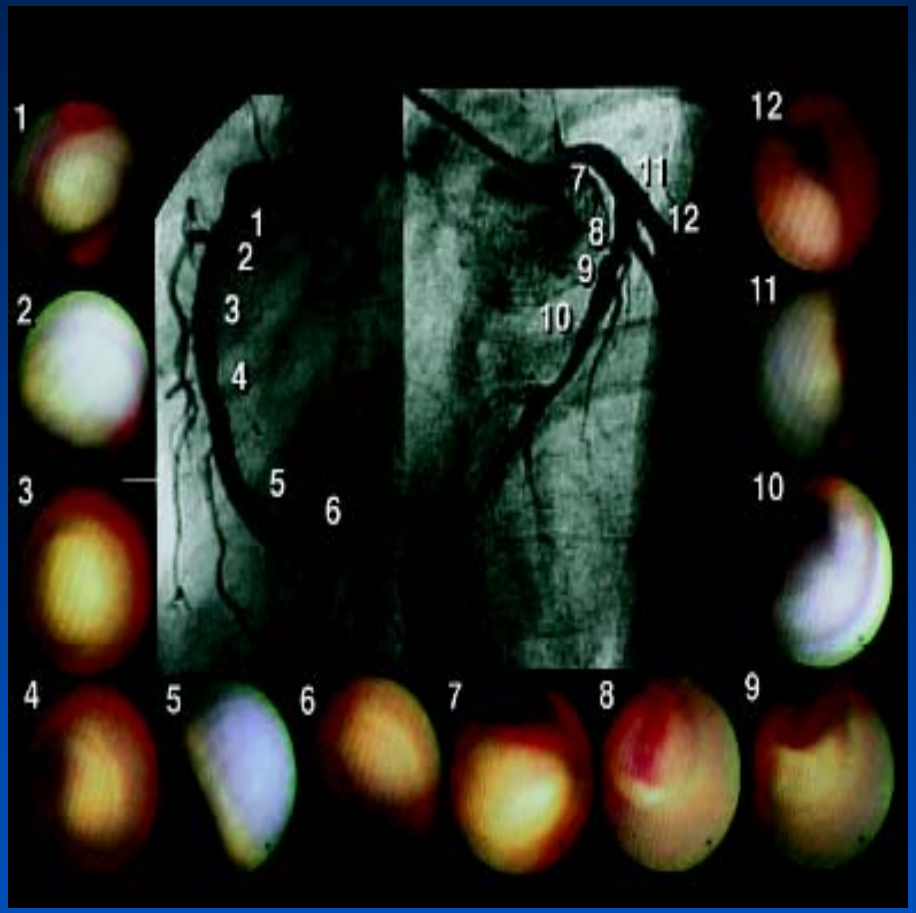
Angioscope image

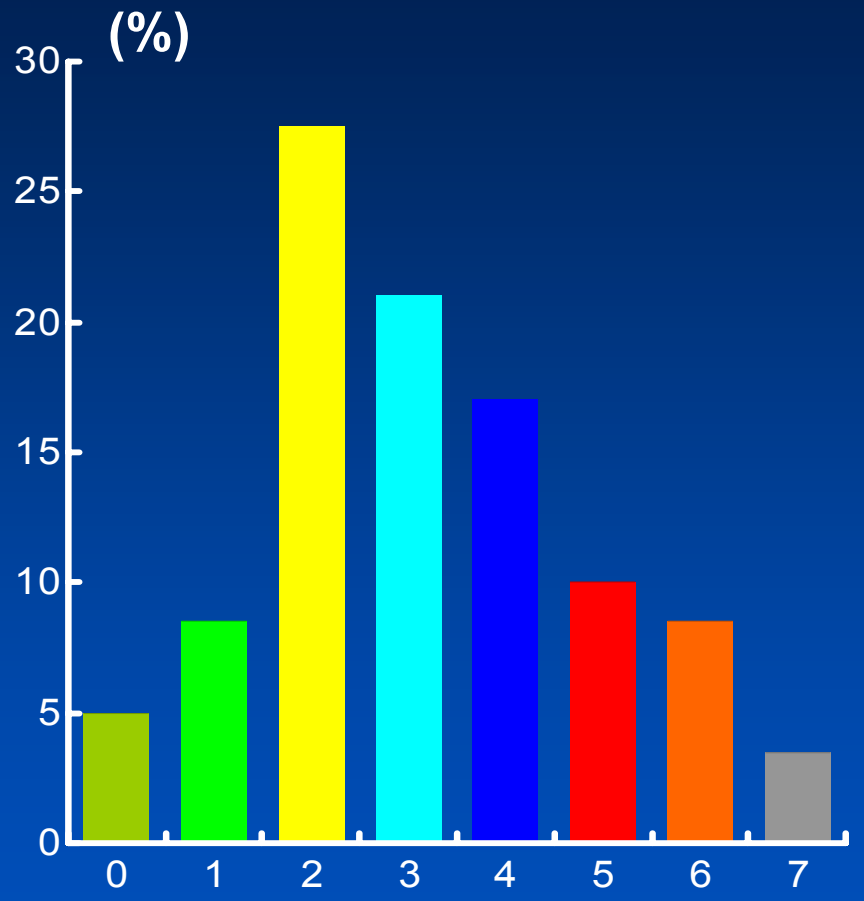
A high-yellow color intensity plaque with intimal disruption and a mural thrombus



Waxman, Circulation 2006;114:2390-2411

Angioscopic study

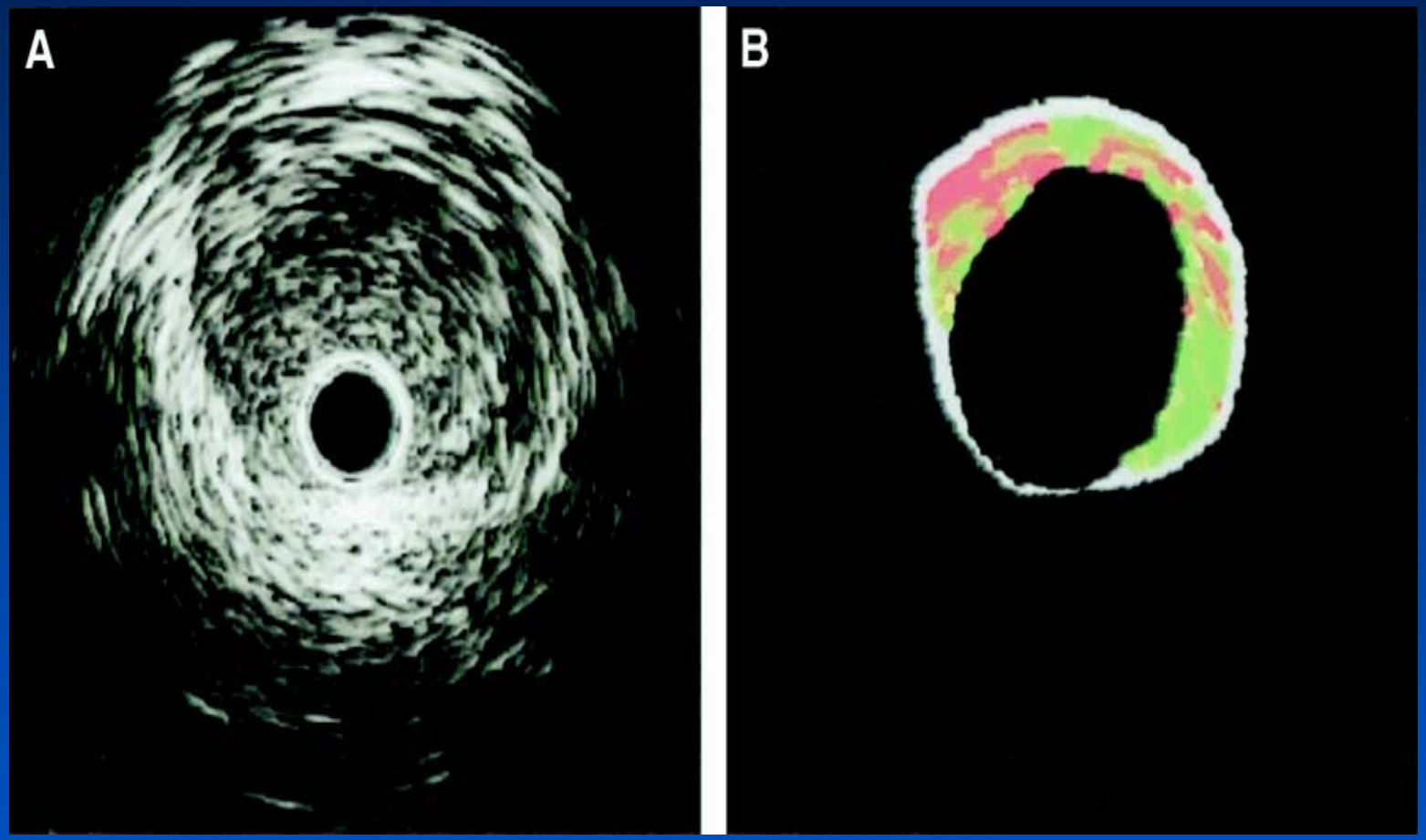




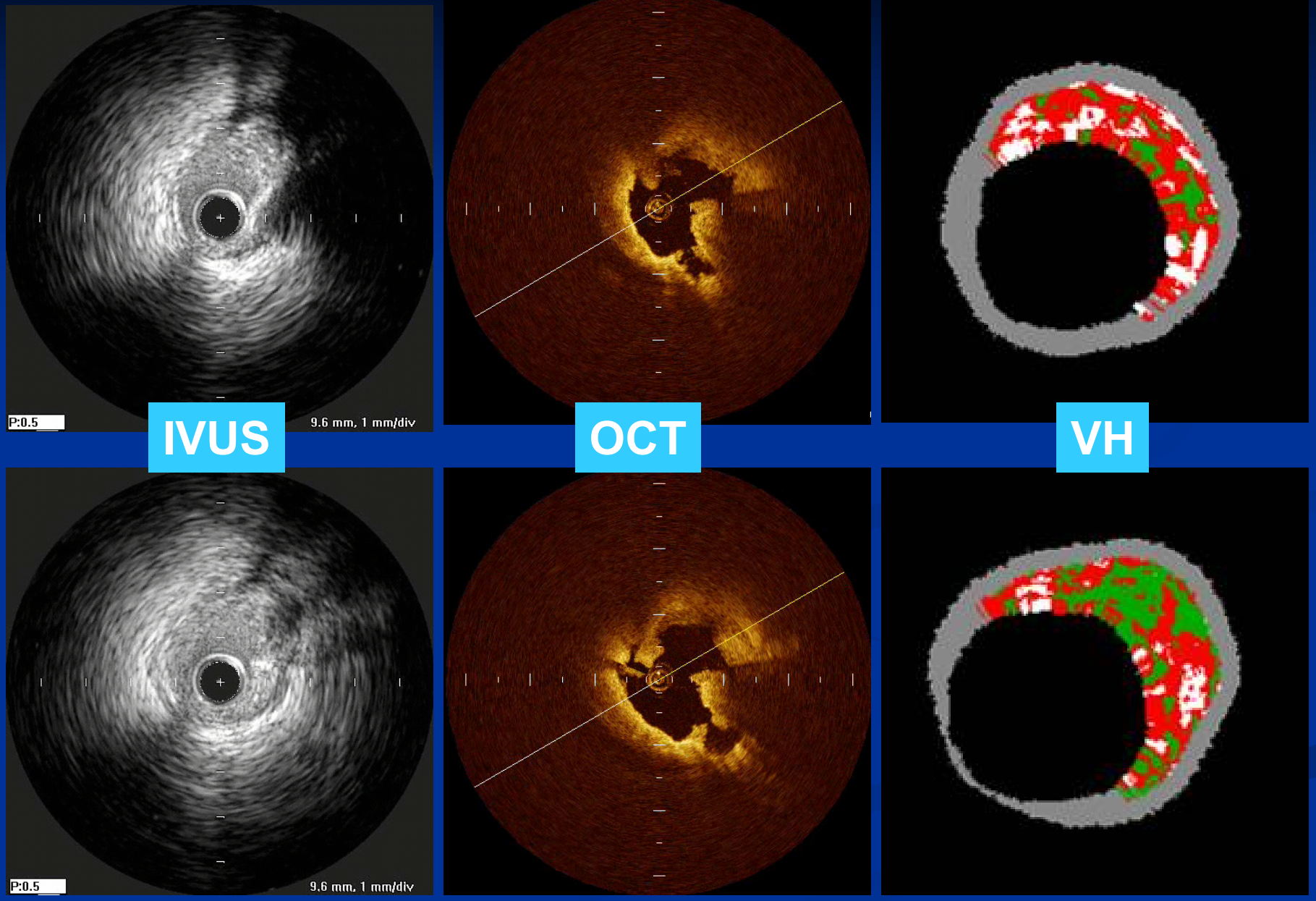
No. of yellow plaques in a coronary artery

Asakura M. JACC 2001;37: 1284-88

Tissue Characterization
IVUS and Virtual Histology



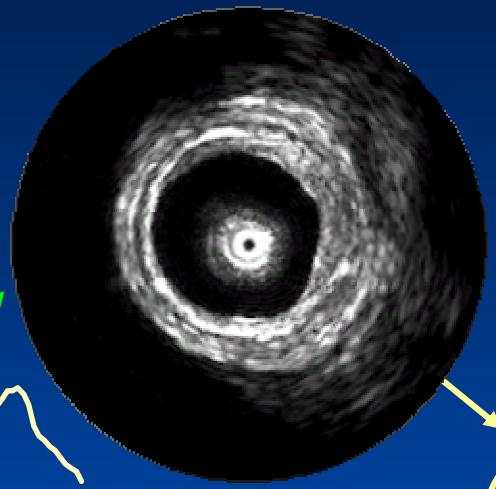
Waxman, Circulation 2006;114:2390-2411



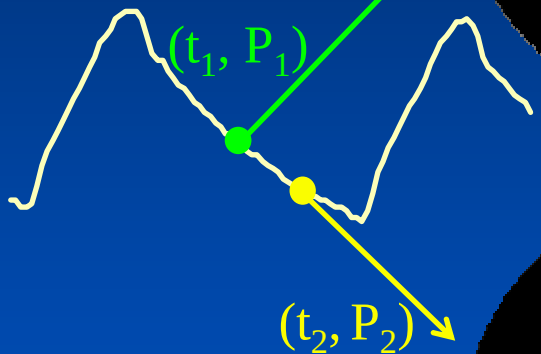
Rupture

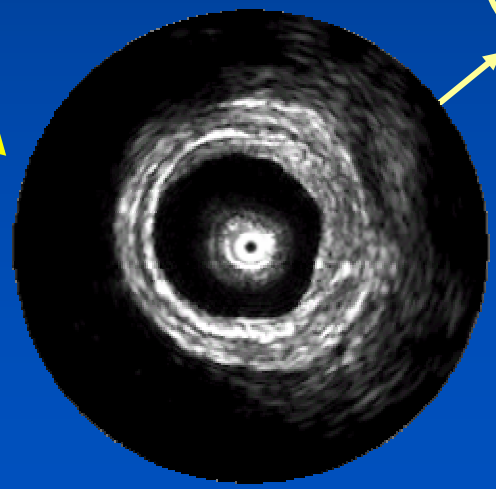
Principles of Palpography

IVUS at 90mmHg

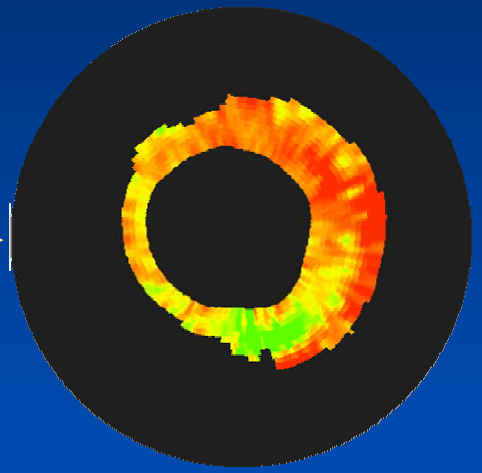


IVUS can be used to assess the deformation of plaques during the change in intracoronary pressure that occur during the cardiac cycle





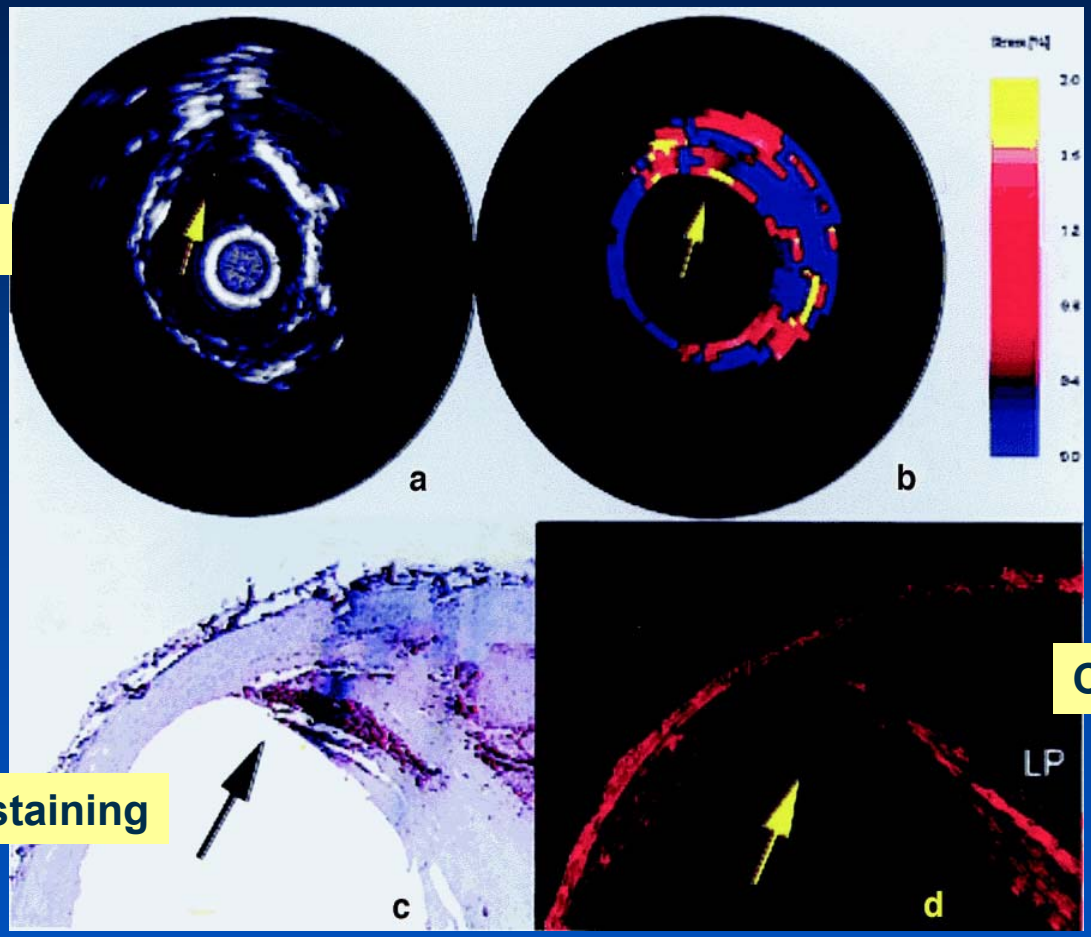
Processing



IVUS elastogram

IVUS at 85mmHg

TCFA: IVUS and Elastography



IVUS

Elastogram

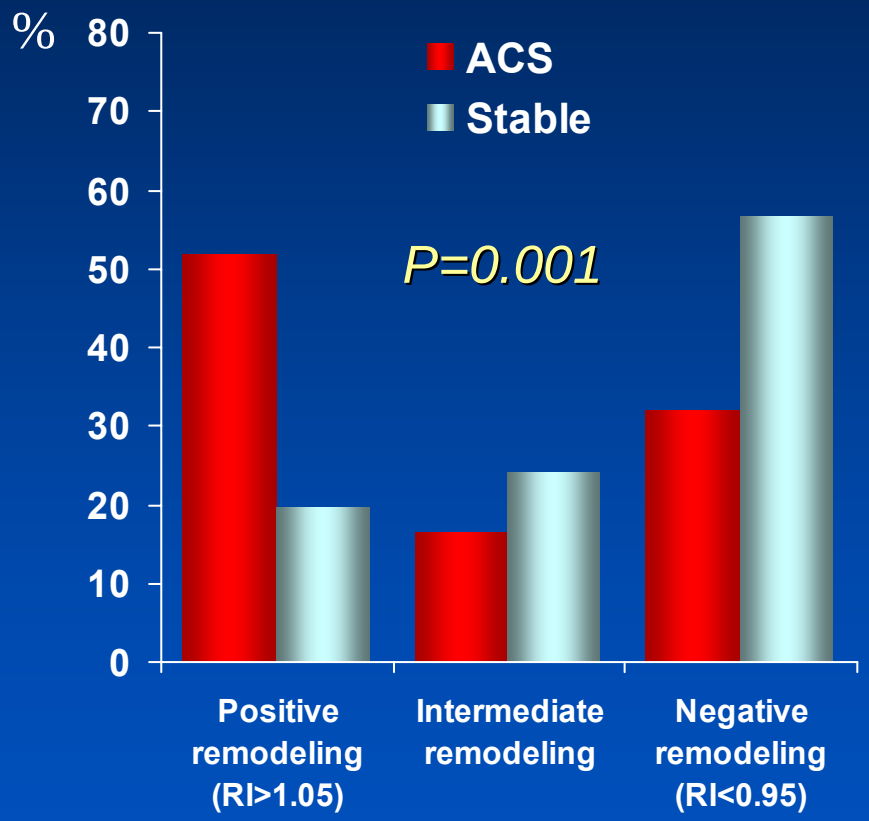
Collagen staining

Macrophage staining

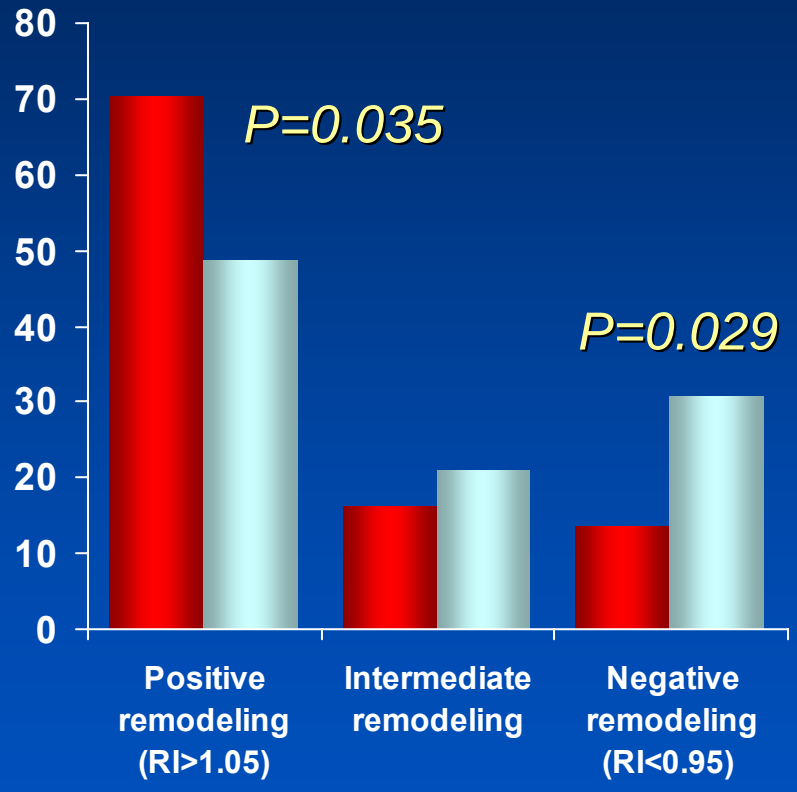
Waxman, Circulation 2006;114:2390-2411

Positive Remodeling and ACS

Positive remodeling is associated with the occurrence of ACS



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



Prati et al. Circulation 2003;107:2320-5

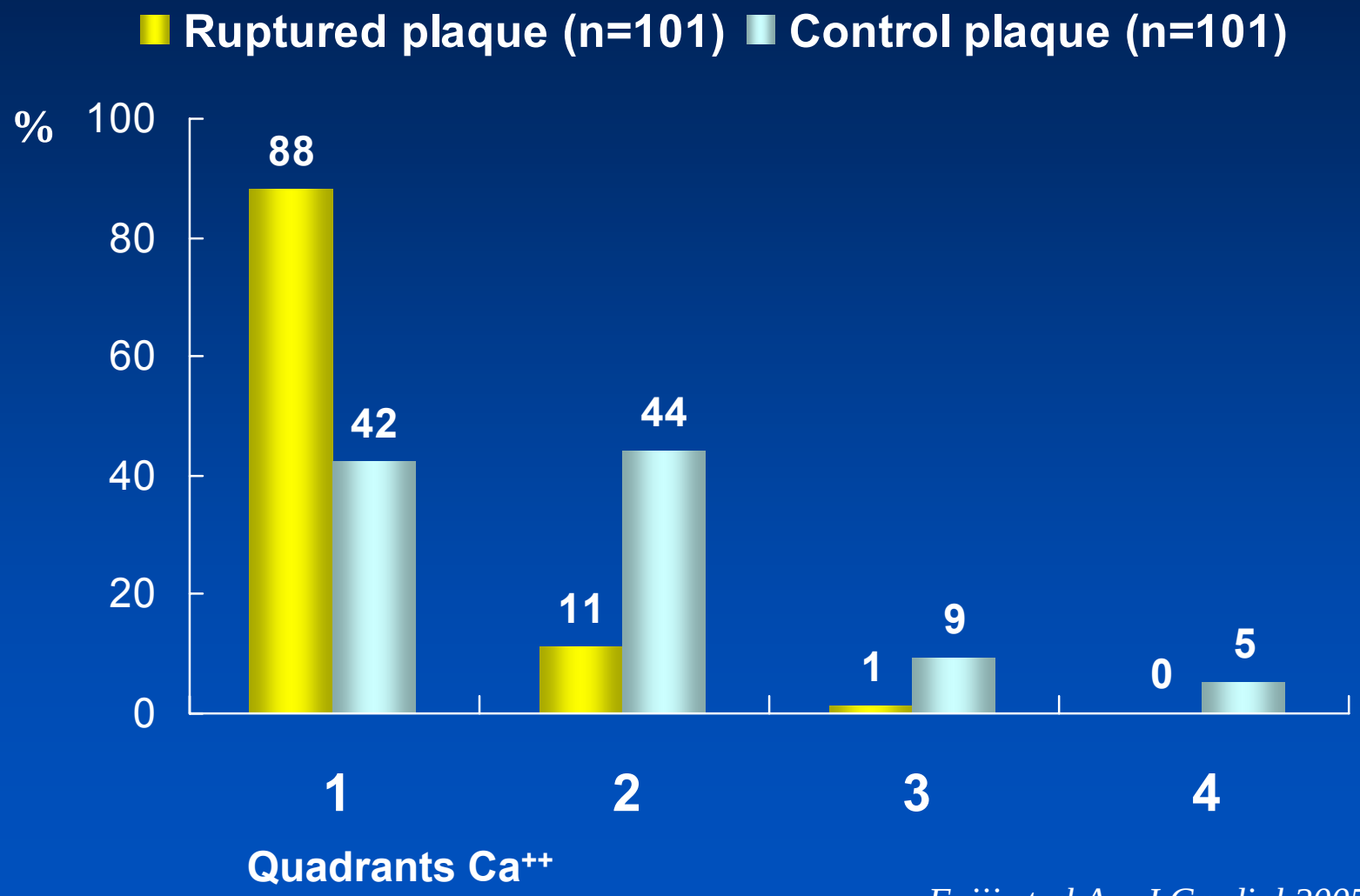
Patterns of Calcification

p<0.0001

	MI (n=61)	UA (n=70)	SA (n=47)
No calcification	26 %	41 %	21 %
Spotty calcification (< 90 °, spotty)	51 %	40 %	30 %
Intermediate calcification (90-180 °)	15 %	16 %	11 %
Extensive calcification (> 180 °)	8 %	3 %	38 %

Ehara. Circulation 2004;110:3424-9

Calcium Contents in ACS



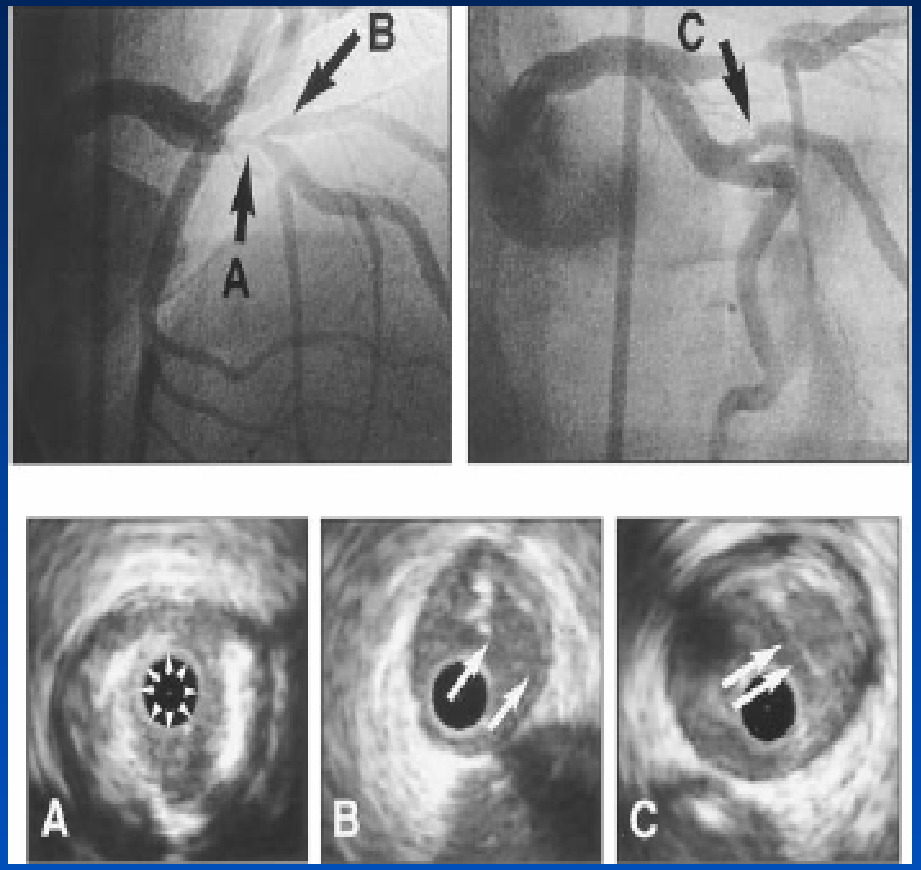
Fujii et al Am J Cardiol 2005;96:352-7

IVUS study: 3-vessel IVUS study

Three-vessel IVUS study in ACS patients:

An incidence of culprit lesion plaque rupture: 37.5% (9/24);

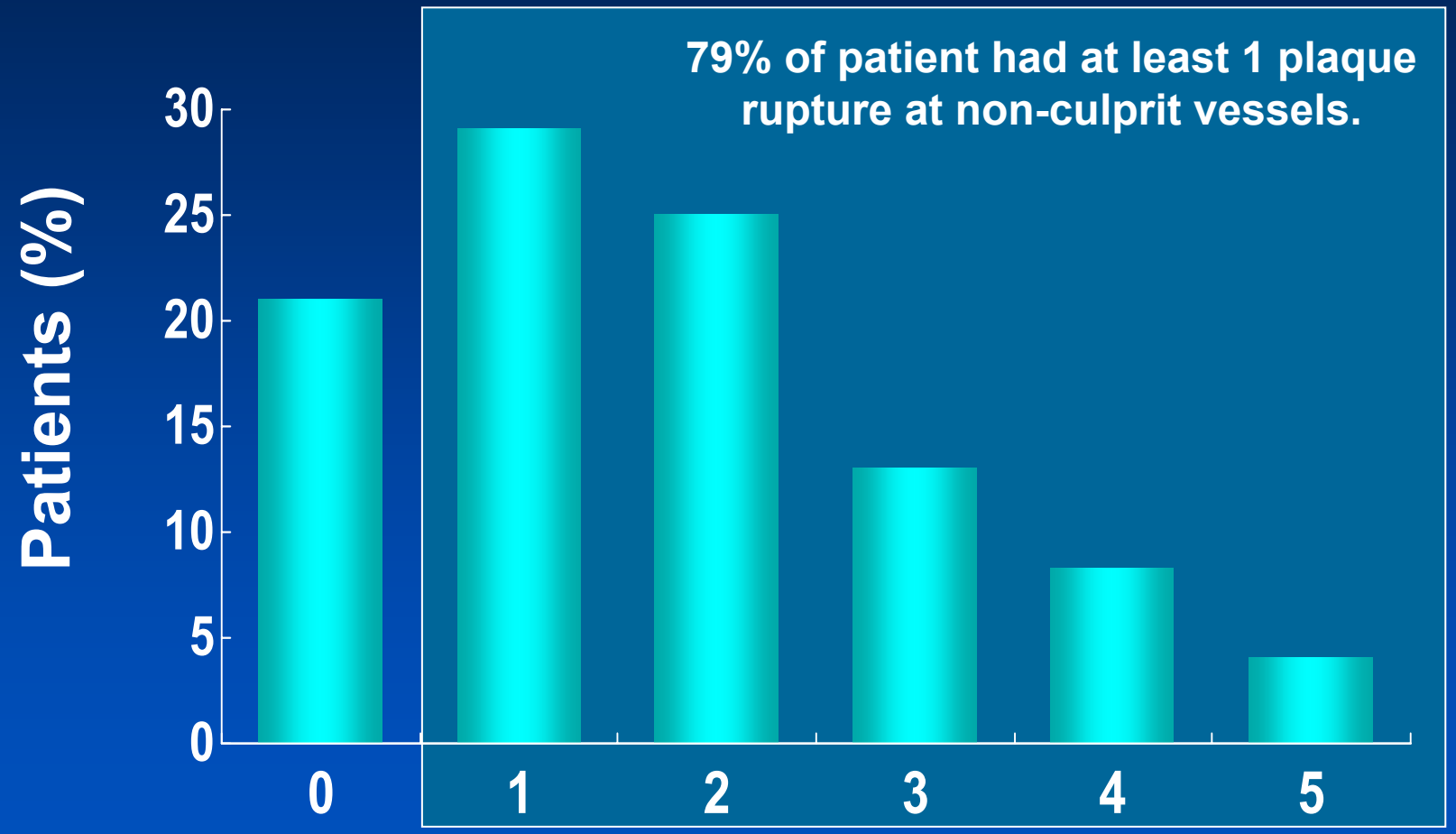
At least one secondary (non-culprit) plaque rupture in 79% (19/24) of the patients



Rioufol G, et al. *Circulation*. 2002;106:804–808.

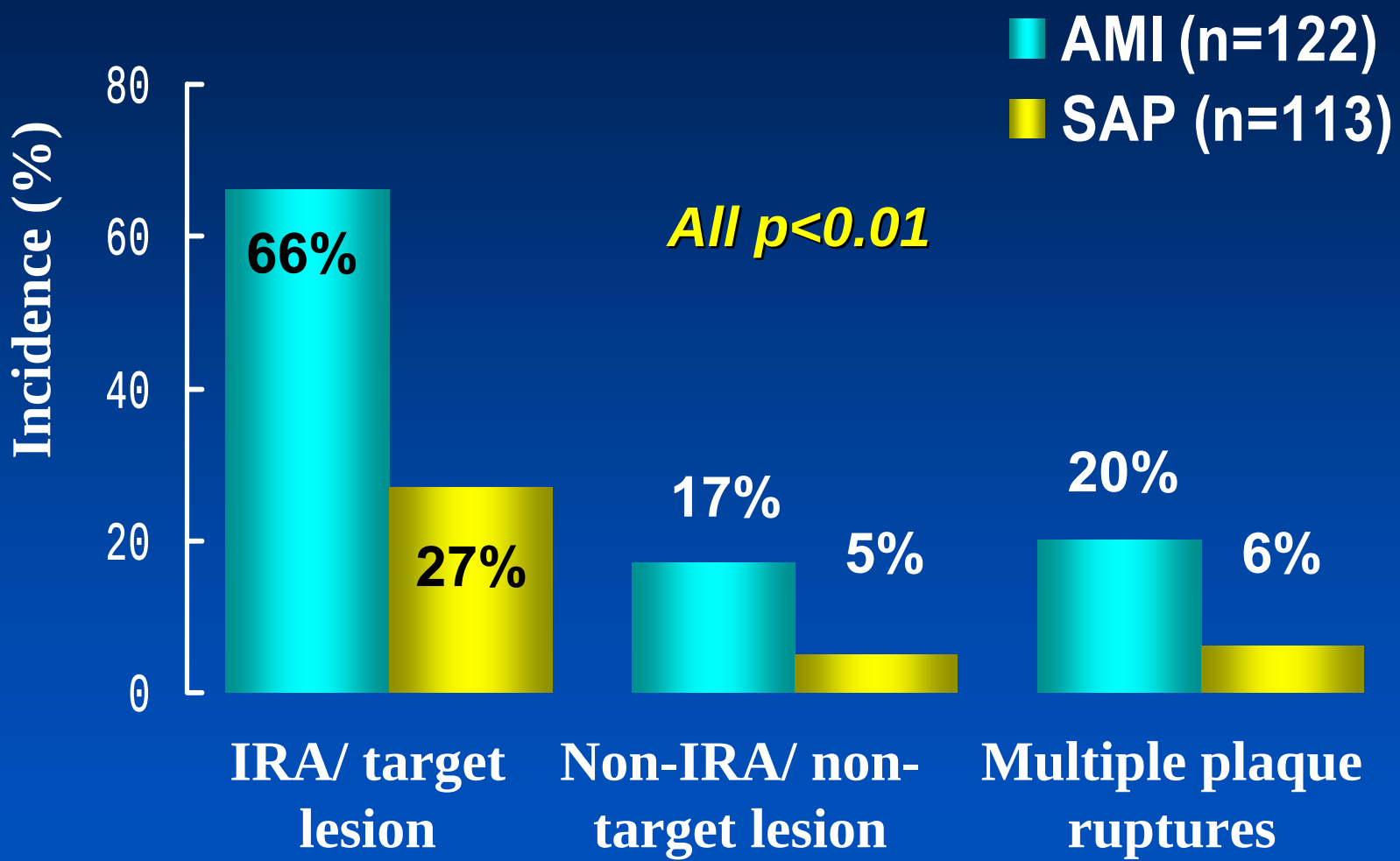
IVUS study for 24 patients

Number of Plaque Rupture at Non-culprit Vessel



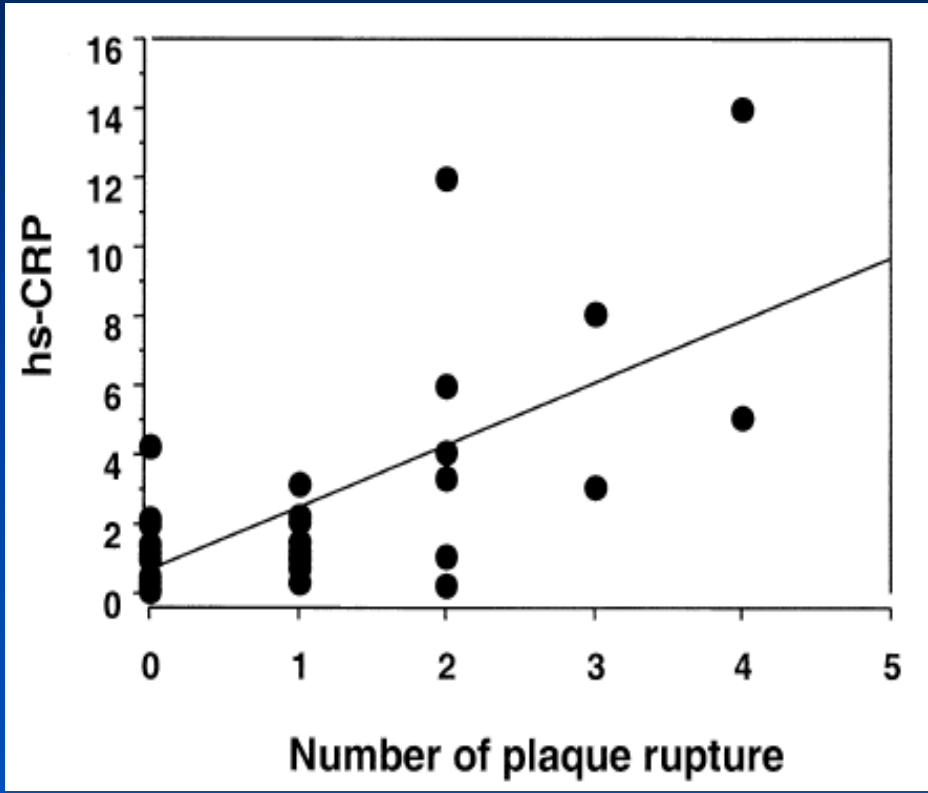
Rioufol G, et al. Circulation. 2002;106:804–808.

Incidence of Plaque Rupture



Hong MK, et al. Circulation 2004; 110: 928-933

“Multiple plaque rupture” and “systemic inflammation”



One previous study using IVUS:

1. The hs-CRP level is correlated with number of plaque ruptures ($p<0.001$) in AMI

2. Patients with plaque rupture in culprit site presented with higher hs-CRP, compared to those without plaque rupture (3.1±0.5 mg/l vs. 1.9±0.4 mg/l, $p=0.04$)

Tanaka A, et al *JACC* 2005;45:1594-9

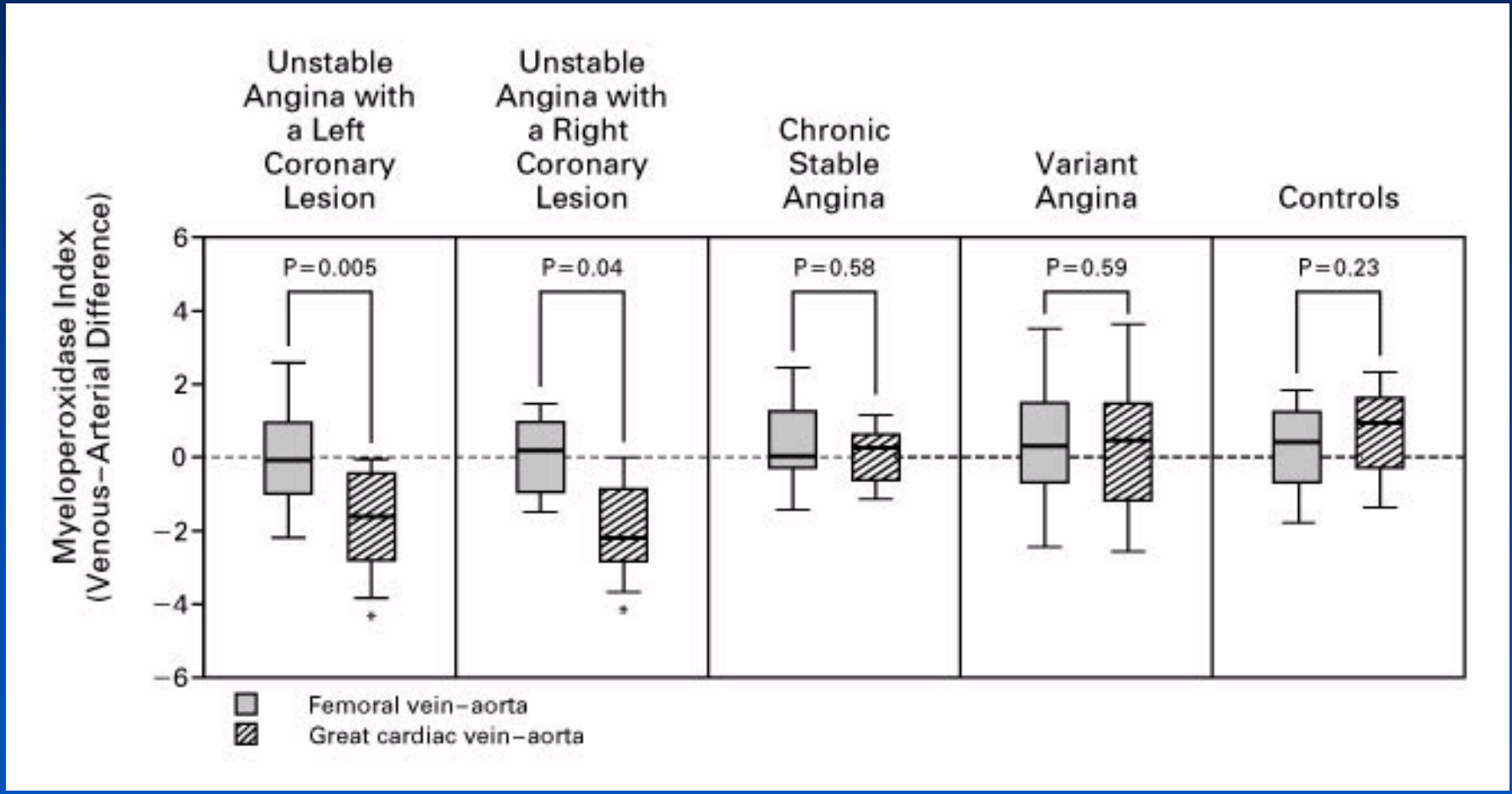
Widespread coronary inflammation in unstable angina

- Neutrophil myeloperoxidase measured in 5 groups of patients
  - LAD (n=24) and RCA (n=9) unstable angina
  - Stable angina (n=13)
  - Variant angina with recurrent ischemia (n=13)
  - Controls (n=6)
- Aorta and great cardiac vein sampling
  - Drains from LAD territory

Buffon et al. New Engl J Med 2002; 347: 5-12

Vulnerable Coronary Arterial Bed

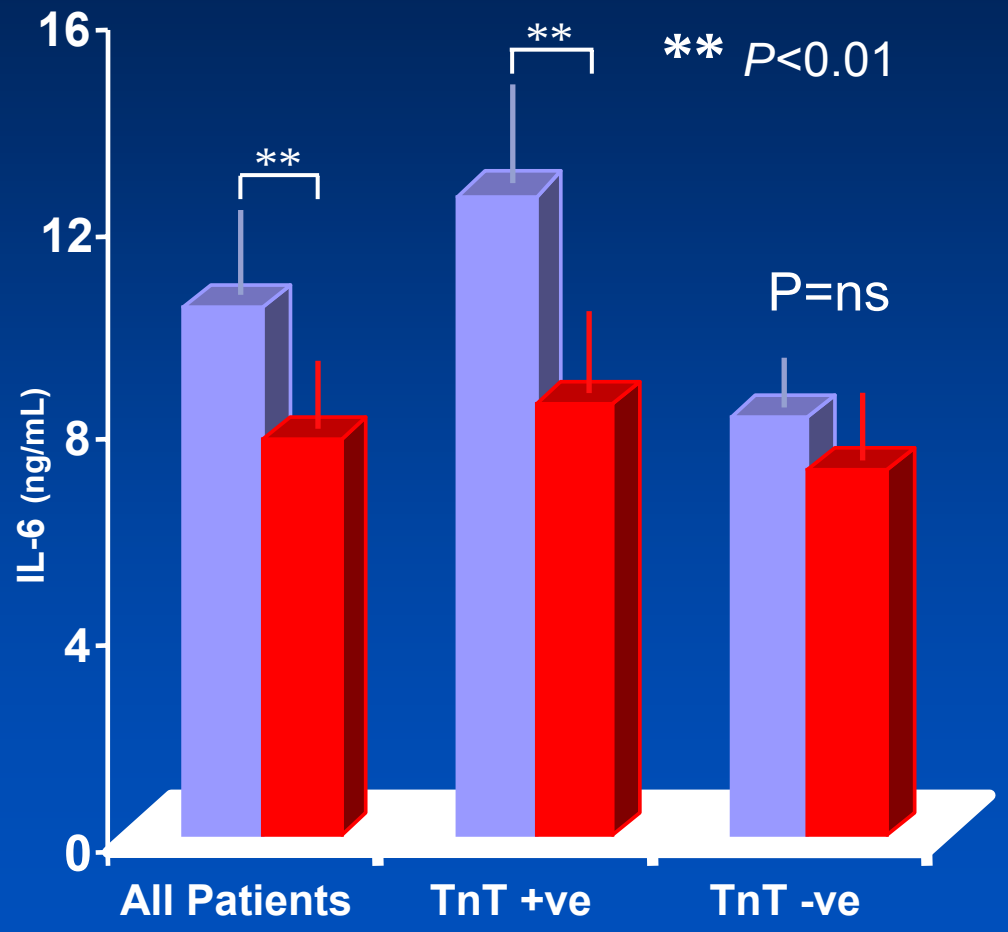
- Sampling in the coronary sinus
- A-V difference in Myeloperoxidase index



Buffon et al. New Engl J Med 2002; 347: 5-12

Transcardiac Cytokine Gradient

- 38 pts with Braunwald IIIb UA
- Time from symptom onset 8.6 ± 5.7 hrs
- Simultaneous aorta and coronary sinus sampling
- Divided according to troponin status



Cusack & Redwood JACC 2002;39:1917-23

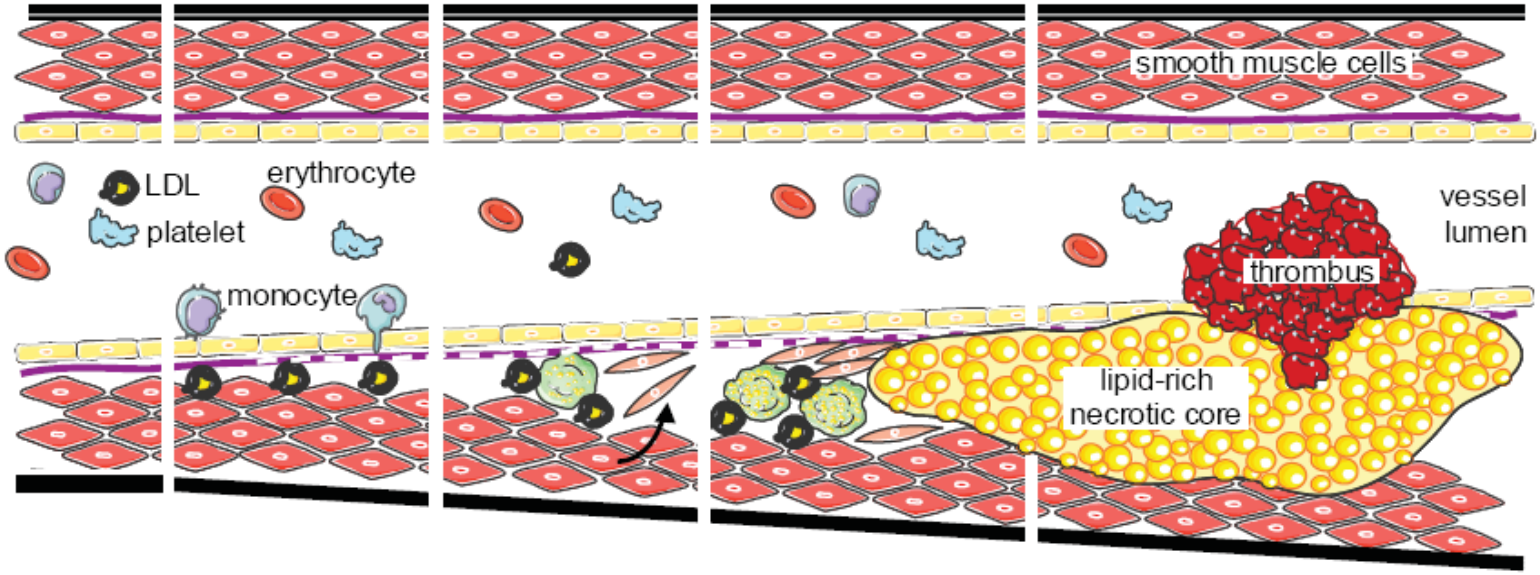
Concept of Vulnerable Plaque

Multiple "vulnerable plaque"

Pan-Coronary Vulnerability

Diffuse inflammatory process !!!!

Multi-biomarker for atherothrombosis



Inflammation	Proteolysis	Thrombosis
sICAM	MMP-1,-2,-9,-10	sCD40L
sVCAM	PAPP-A	sP-Selectin
IL-1 and -6		PAI-1
TNF-α		
MCP-1		
MPO		
LP-PLA$_2$		

Plaque vulnerability

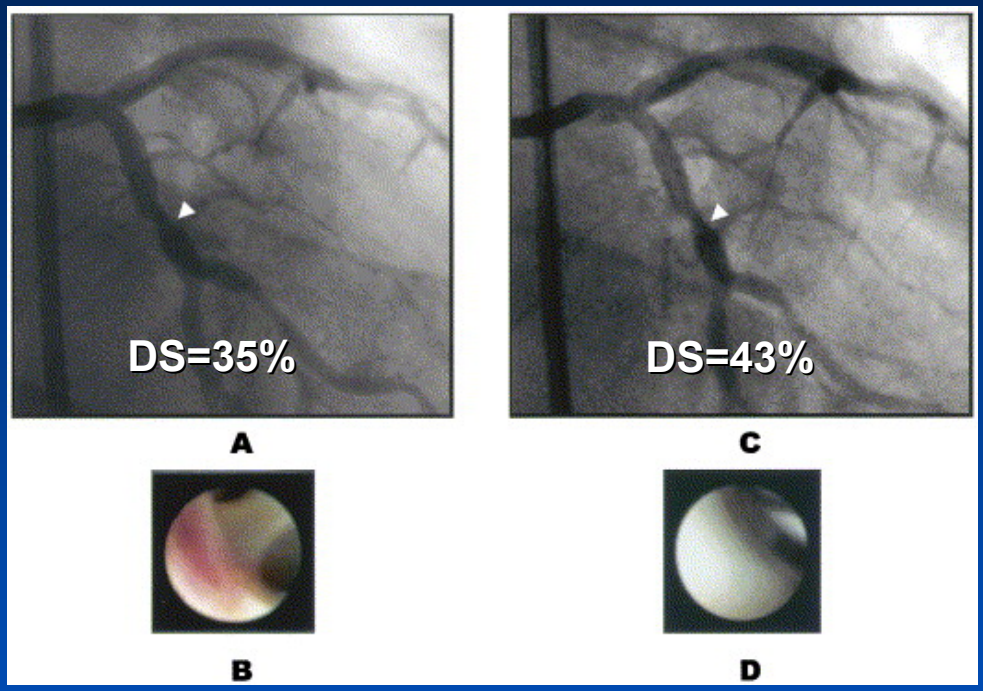
- Although there is no conclusive data, large lipid core, thin cap, and increased macrophage has been implicated as being predictive of future events.

Unfortunately, it is inconclusive to predict which plaque will rupture because of lack of its natural history

- High wall stress in addition to inflammation may trigger the plaque instability

The Fate of “Ruptured Plaque”

Angioscopic F/U of 50 Ruptured Plaques in Non-culprit Lesions.



Pinkish-white thrombus on the yellow plaque

Smooth white intima without thrombus

- Follow-up of 13±9 Mo.
- Remaining of thrombi in 35 (70%)
- Color change of thrombi from red (56%) at baseline to pinkish-white (83%) at follow-up
- Increase of %DS at the healed plaque (12.3% to 22.7%, $p<0.05$)

Takano M et al, J Am Coll Cardiol 2005;45:652– 8

Serial IVUS F/U Studies

	Rioufol et al	Angioscopy	WHC data
No. Patients	14	30	17
No. Lesions	28	50	17
F/U duration (months)	22±13 (IVUS FU)	13±9 (angioscopic FU)	43±25 (Clinical FU)
Healing rate	14/28 lesions (50%)	15/50 lesions (30%)	---
Events	No events	1 Rev.	1 death, 2 Rev
Statin therapy	14 (100%)	Healing (70%), Non-healing (21%)	8 (47%)

Serial IVUS Examination at AMC

- We identified 28 patients from AMC clinical and IVUS core laboratory database with non-target/non-culprit ruptured plaque and without significant stenosis, who underwent baseline and 1-year follow-up IVUS study.

- Statin treatment (n=14, 20mg atorvastatin in 7 patients and 40mg simvastatin in 7 patients) vs.
  non-statin treated group (n=14).

Hong MK et al, Atherosclerosis 2006 (in press)

IVUS Outcome of Plaque Rupture

	Statin (n=14)	No statin (n=14)	P
Complete healing	4 (29%)	0	0.049
Incomplete healing	0	1 (7%)	NS
No significant changes	10 (71%)	10 (71%)	NS
Progression to a focal stenosis requiring PCI	0	3 (21%)	0.11

Changes in Ruptured Plaque Segment

	Statin (n=14)	No statin (n=14)	P
ΔEEM CSA (mm^2)	-0.1±0.1	-0.3±0.7	0.4
ΔLumen CSA (mm^2)	0.4±0.8	-0.6±1.0	0.007
ΔP&M CSA (mm^2)	0.0±0.7	0.6±0.9	0.051
ΔRuptured cavity CSA (mm^2)	-0.5±0.7	-0.3±0.6	0.4

Vulnerable Plaque “natural history”

- In order to investigate natural history of VP and **“estimate the risk”** of clinically significant plaque rupture or ACS over time based on aspects of **plaque morphology**, **plaque thermography**, **palpography**, or **biochemical markers**, we would need a prospective longitudinal cohort study

PROSPECT

Providing Regional Observations to Study Predictors of Events in the Coronarv Tree

Natural history study in pts with ACS

700 pts with ACS

UA (with ECGΔ) or NSTEMI or STEMI >24º

1-2 vessel CAD undergoing PCI

at up to 40 sites in U.S., Europe

Biomarkers
- **-Hs CRP**
- **-IL-6**
- **-sCD40L**
- **-MPO**
- **-TNFα**
- **-MMP9**
- **-Lp-PLA2**
- **-HgBA1C**
- **-Insulin**
- **-others**

PCI of culprit lesion(s)

Successful and uncomplicated

Formally enrolled

3-vessel imaging post PCI

Culprit artery, followed by non-culprit arteries

Angiography (QCA of entire coronary tree)

IVUS

Virtual histology

Palpography

Proximal 6-8 cm of each coronary artery

?± Thermography (EU subset only)

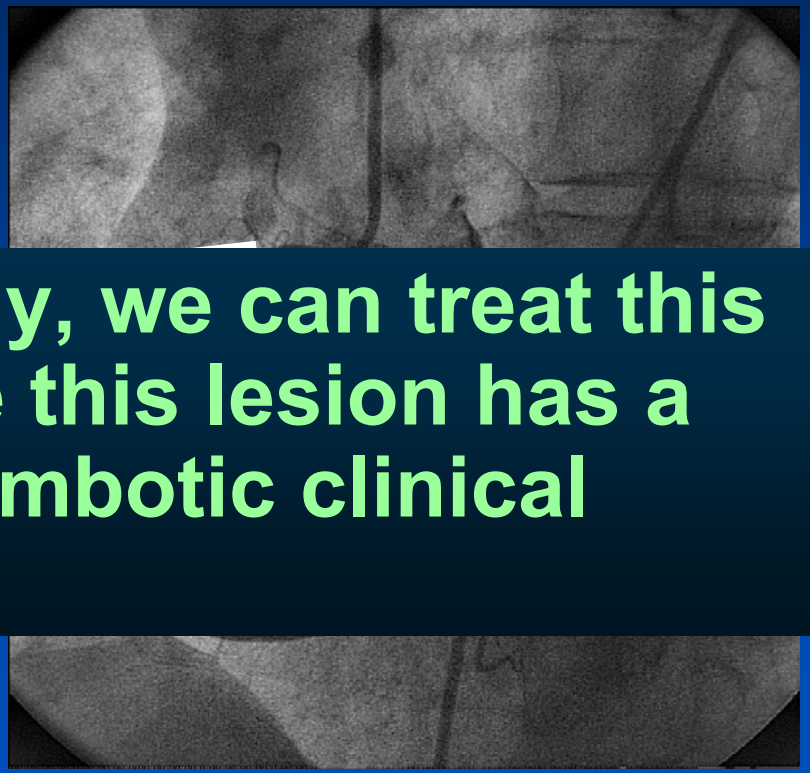
Meds rec
Aspirin
Plavix 1yr
Statin

F/U: 1 mo, 6 mo, 1 yr
2 yr, ±3-5 yr
(event driven)

Repeat imaging in pts with events

PROSPECT

Providing Regional Observations to Study Predictors of Events in the Coronary Tree



At the end of the study, we can treat this lesion or not because this lesion has a X % risk causing thrombotic clinical event within a year

Potential Treatment of Vulnerable Plaques (Systemic Therapy)

- Therapies to lower LDL cholesterol
- Therapies to increase HDL cholesterol
- Anti-inflammatory therapy (Inhibitor of lipoprotein-associated phospholipase-2): IBIS-2 Trial

Potential Treatment of Vulnerable Plaques (Local Therapy)

- Treatment of coronary artery risk based on location for culprit lesions.
- Stents for the treatment of vulnerable coronary plaques and arteries.
- Stenting for intermediate stenoses that are not flow limiting. (Prevail study)
- Photodynamic therapy.
- Cooling, heating, and sonotherapy.

Optimum Approach in Patients with Vulnerable Plaque….

- Act “locally” with appropriate revascularization, and
- Act “globally” with systemic treatments to address the multicentric plaques and their inflammatory basis.

Libby, JACC 2005


REUTERS