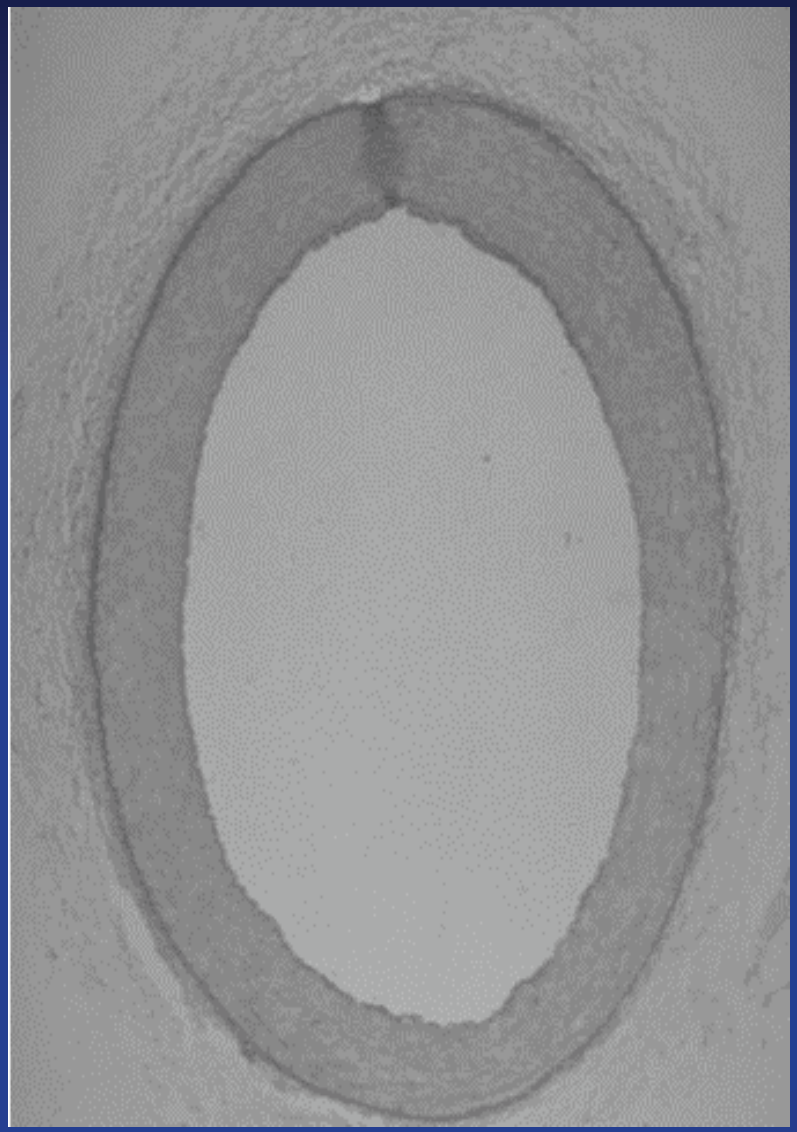
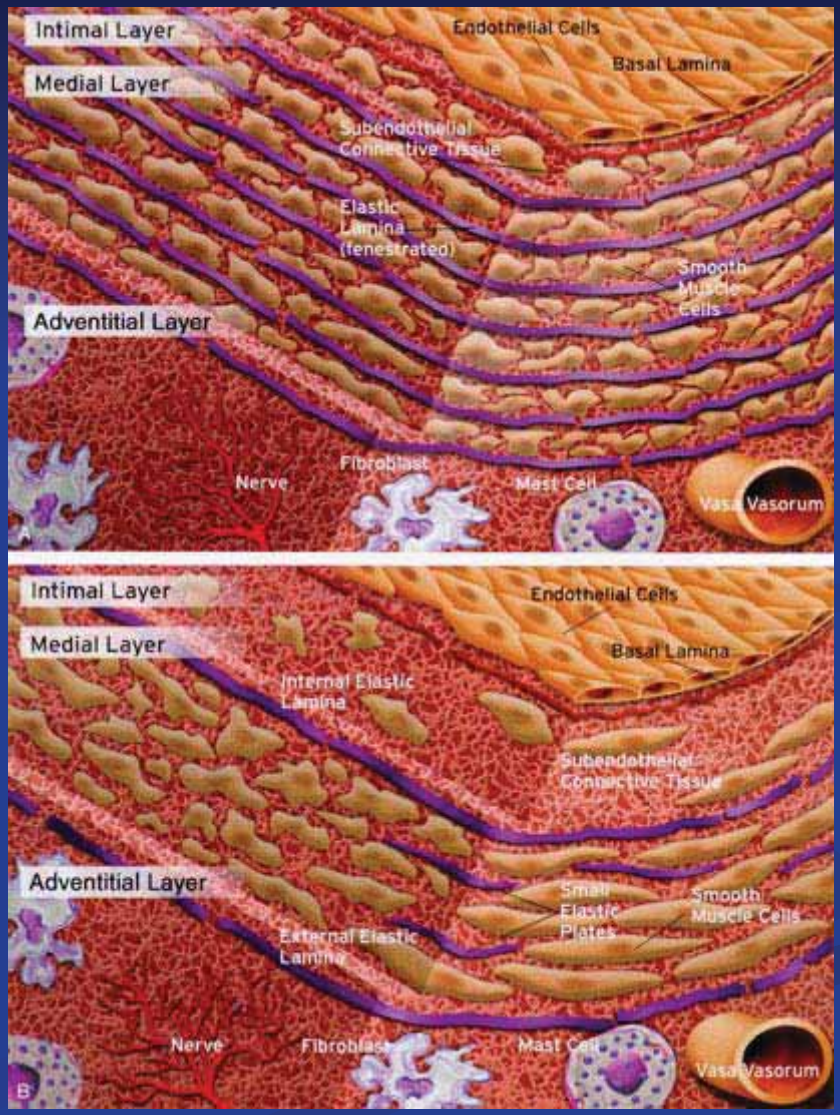
Struggles to Stabilize Vulnerable Plaques

Angioplasty Summit

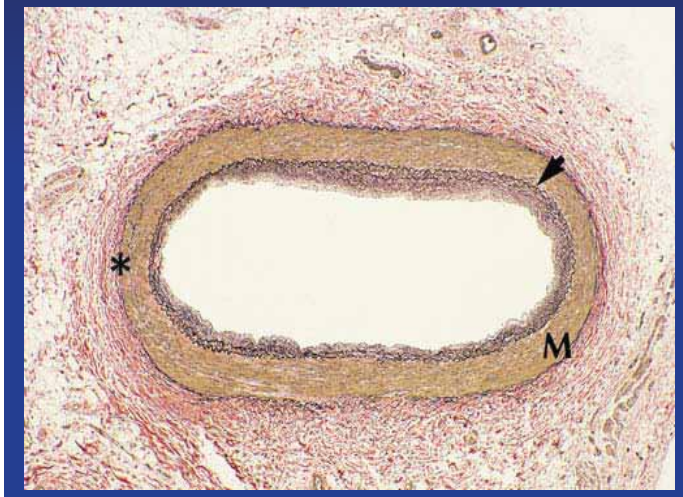
Introduction

Normal Coronary Artery and Its Histology

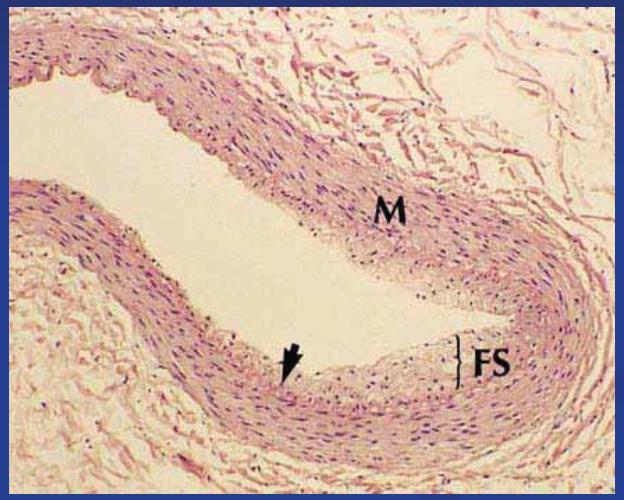




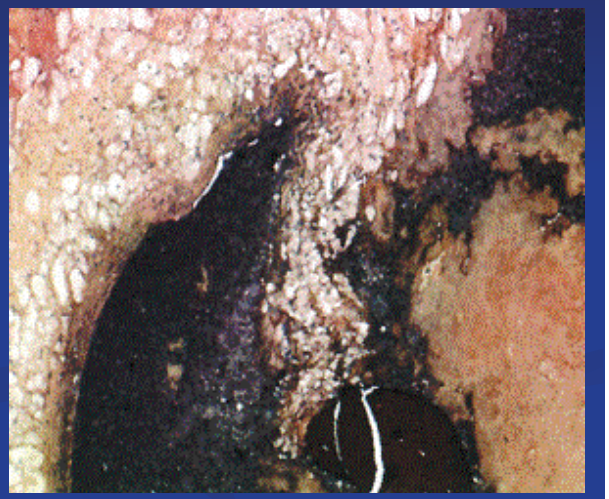
Coronary Arteries in Each Stages



Normal coronary artery



Fatty streak (FS)



Ruptured plaque

Risk Factors

Major

Cigarette smoking
Elevated blood pressure
Elevated total cholesterol
(and LDL-C)
Low serum HDL-C
Diabetes mellitus
Advancing age
Obesity
Physical inactivity

Predisposing

Family history of premature CHD
Ethnic characteristics
Psychological factors

Conditional

Elevated serum triglycerides
Small LDL particles
Elevated serum homocysteine
Elevated serum lipoprotein(a)

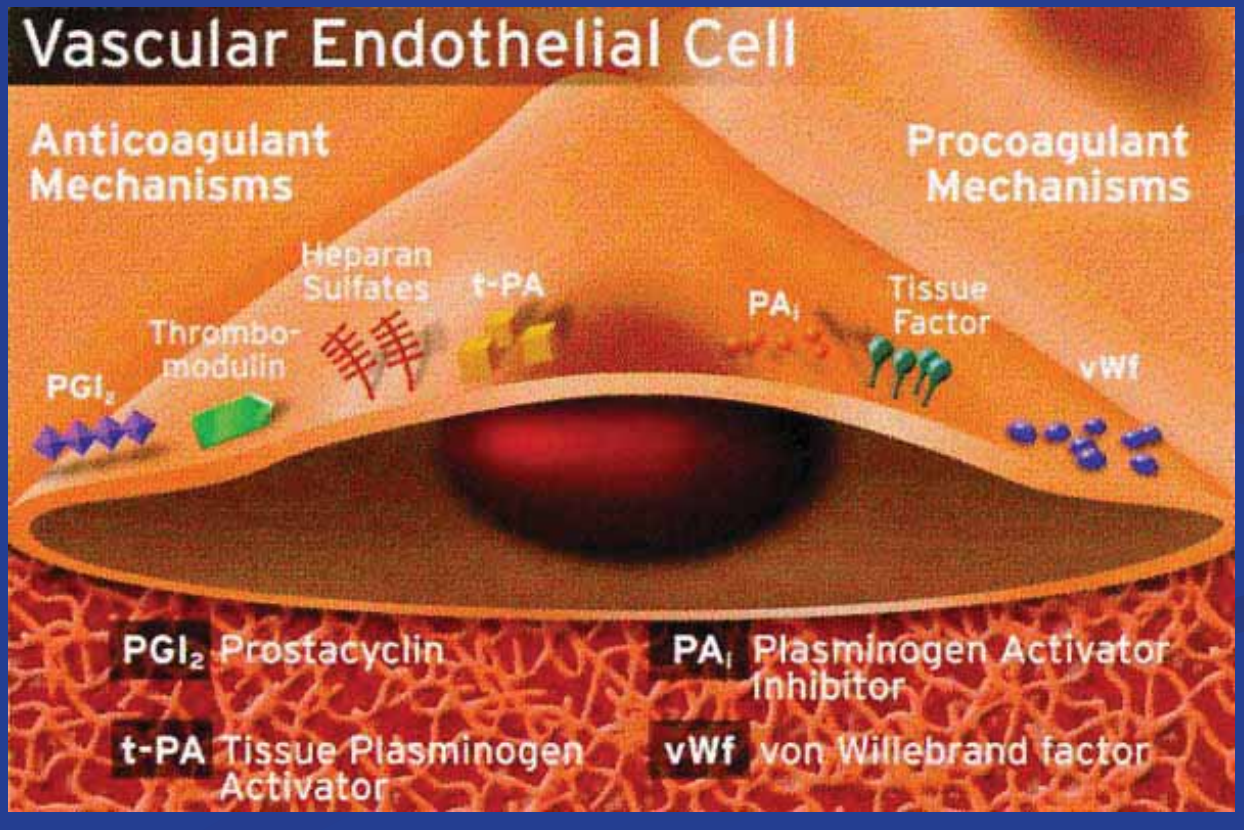
? ←

Prothrombotic factors (eg, fibrinogen, TF)
Inflammatory markers (eg, CRP)

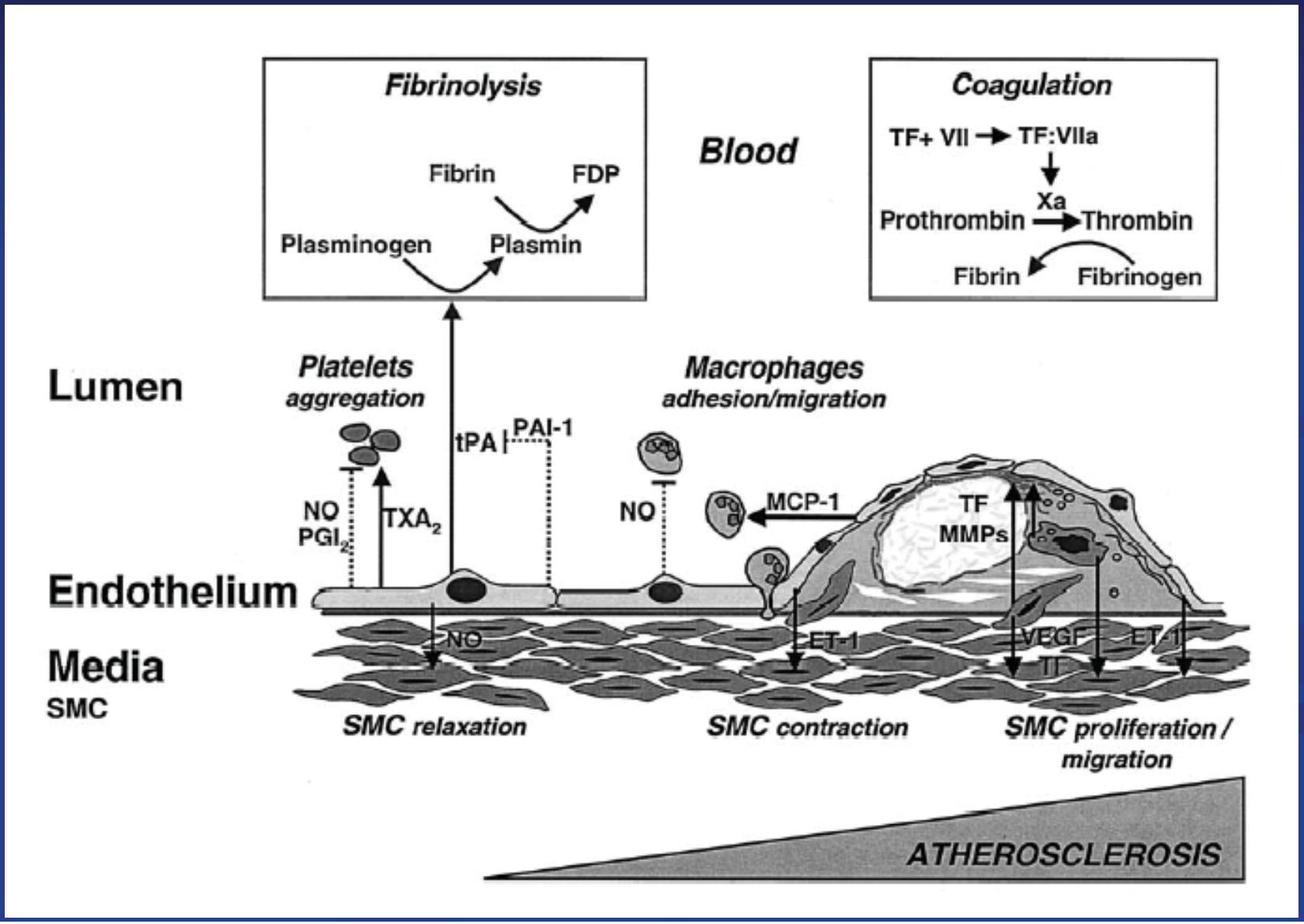
Fuster V, Gotto A. *Circulation* 2000; 102:IV-94
(Framingham, AHA)

Table 1. Functions of the Normal Endothelium

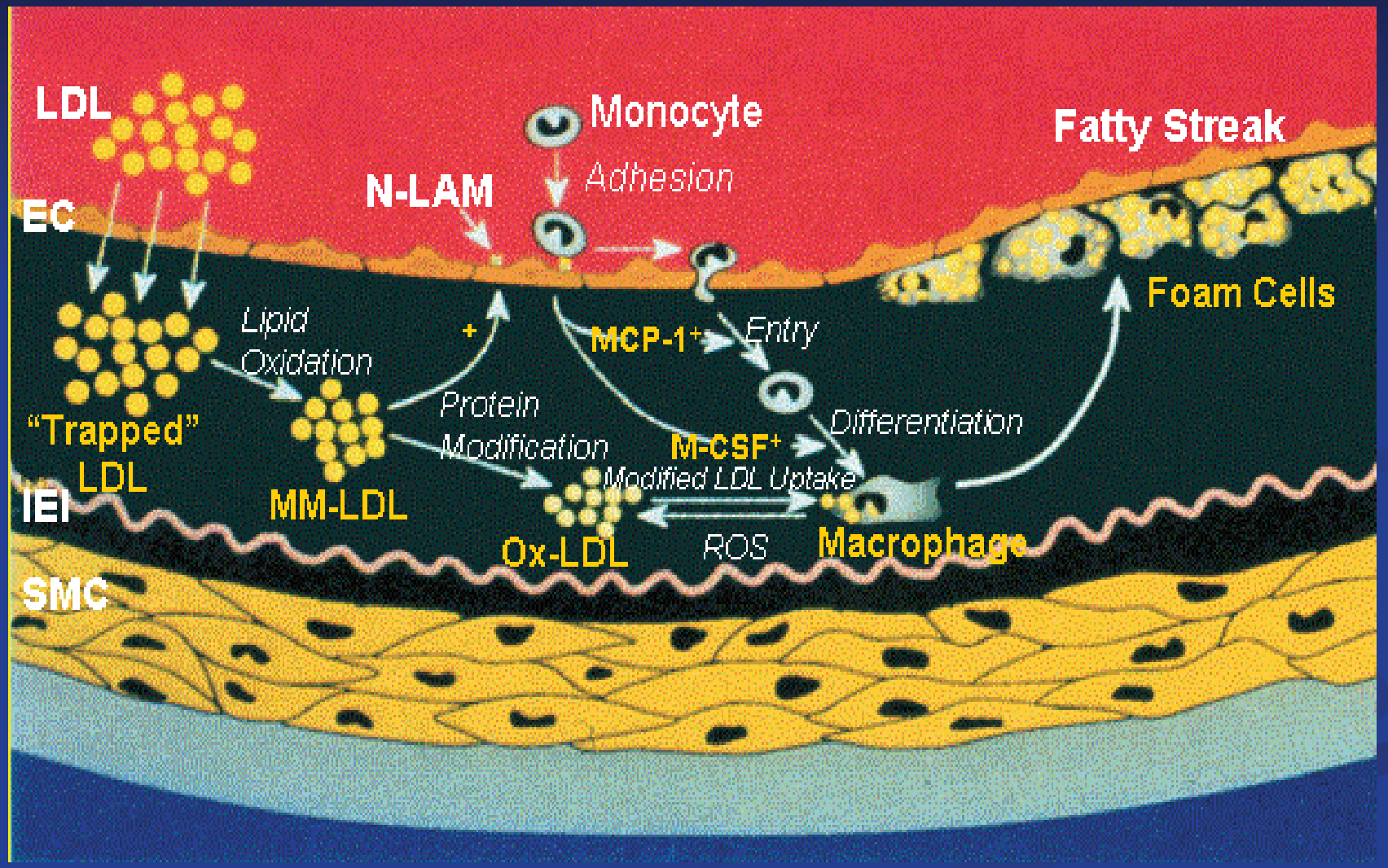
Permeability barrier
Production of thrombogenic and nonthrombogenic products
Metabolism of vasoactive substances
Production of cytokines and growth factor
Synthesis of leukocyte adhesion molecules
Synthesis of basement membrane constituents
Lipid metabolism



Thrombotic and antithrombotic properties of the endothelium

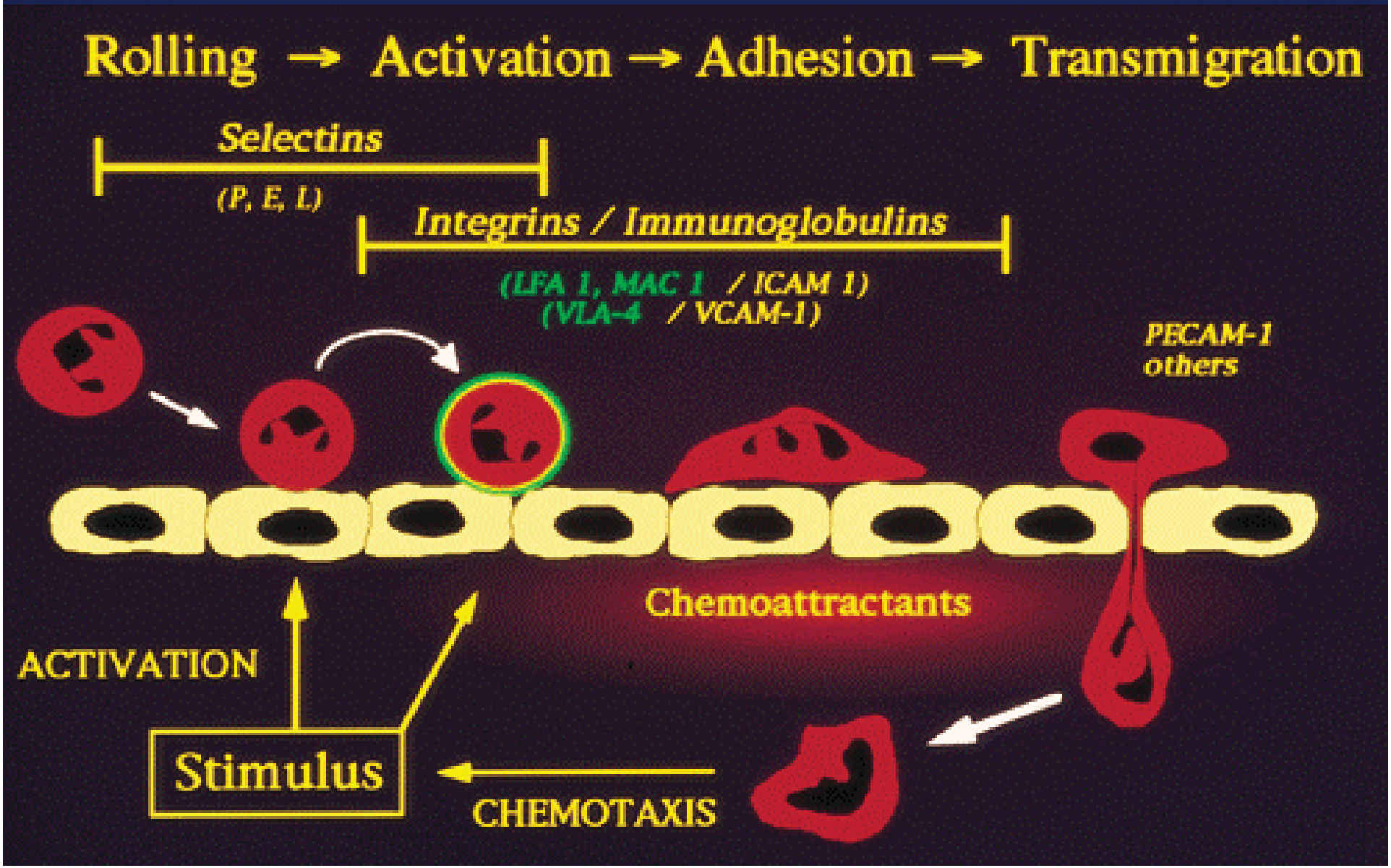


Development of Atherosclerotic Plaque

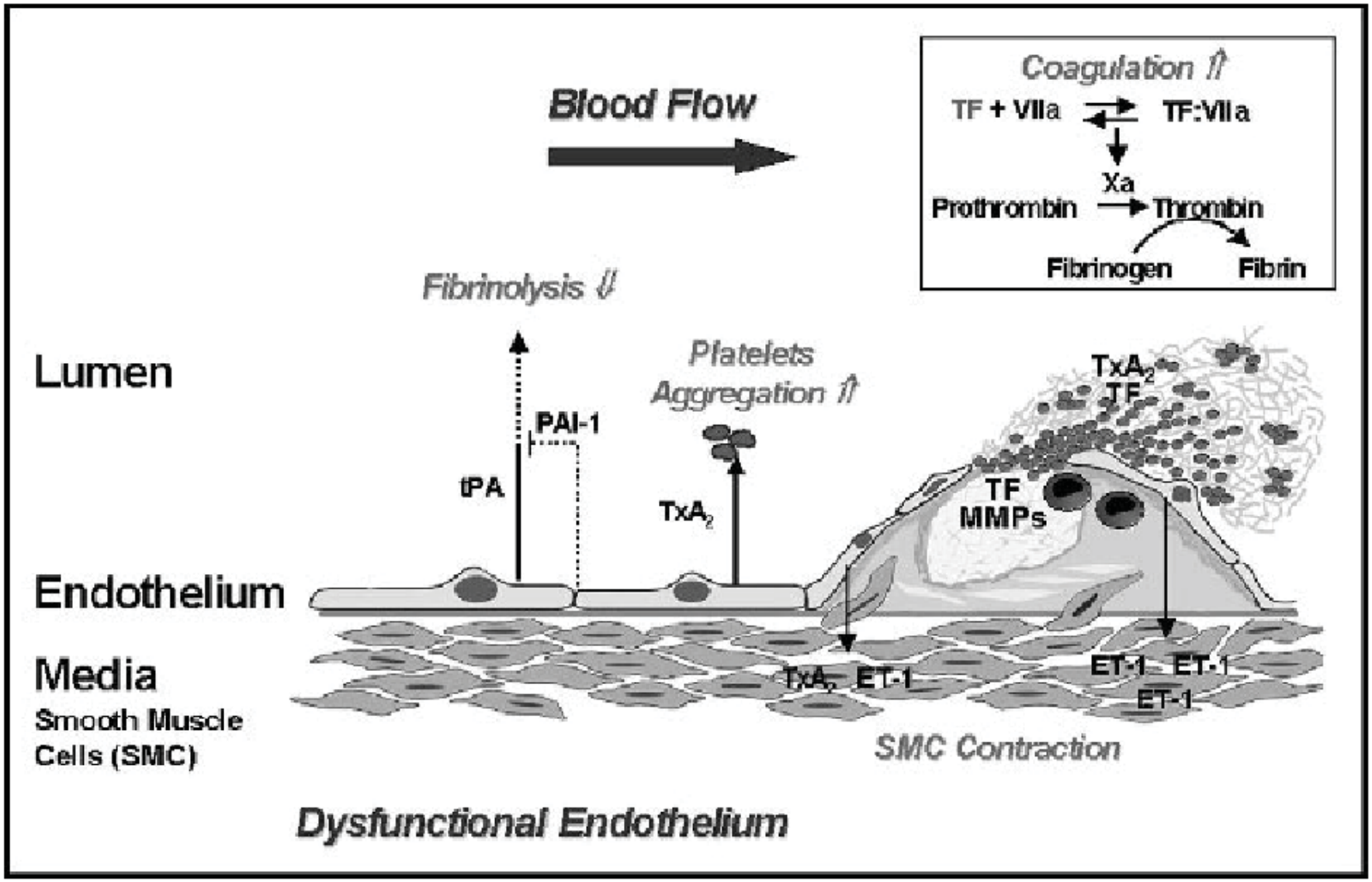


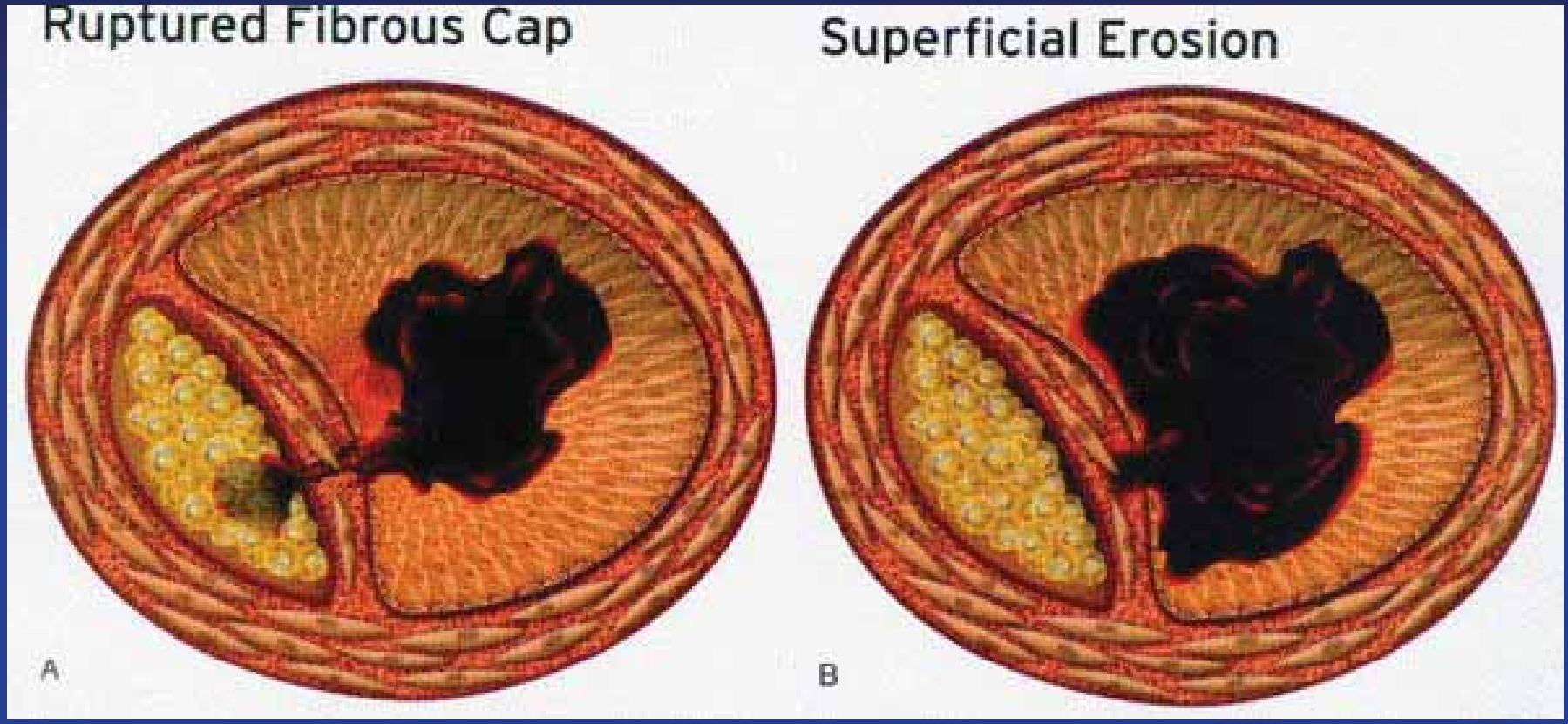
Berliner et al, Circulation 1995;91:2488-2496

Sequence of Leukocytic Events in Inflammation



Atherosclerotic Plaque Progression and Disruption



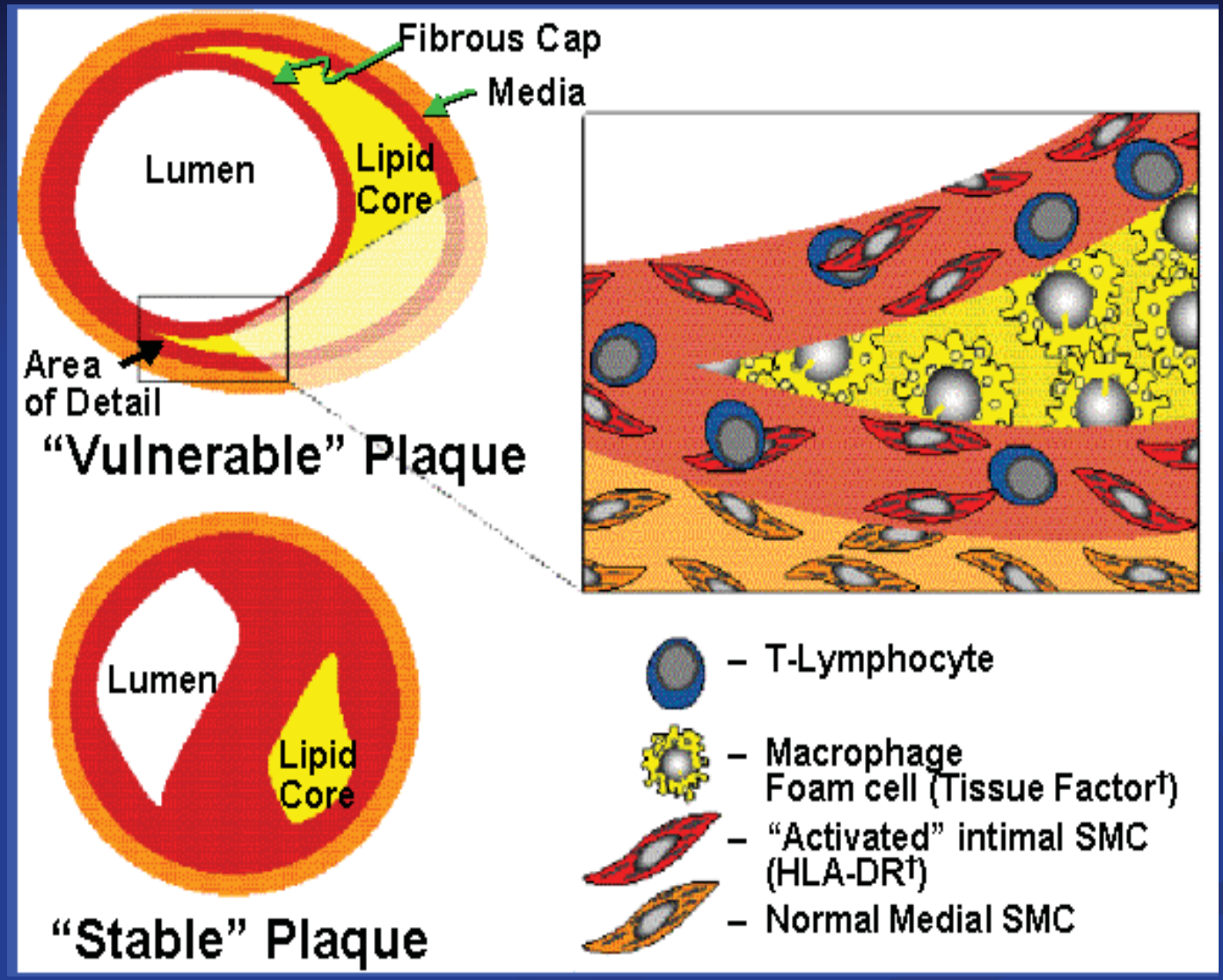

Ruptured Fibrous Cap
Superficial Erosion
A
B

Proposed Histopathological and Clinical Criteria for Definition of Vulnerable Plaques

Major Criteria:

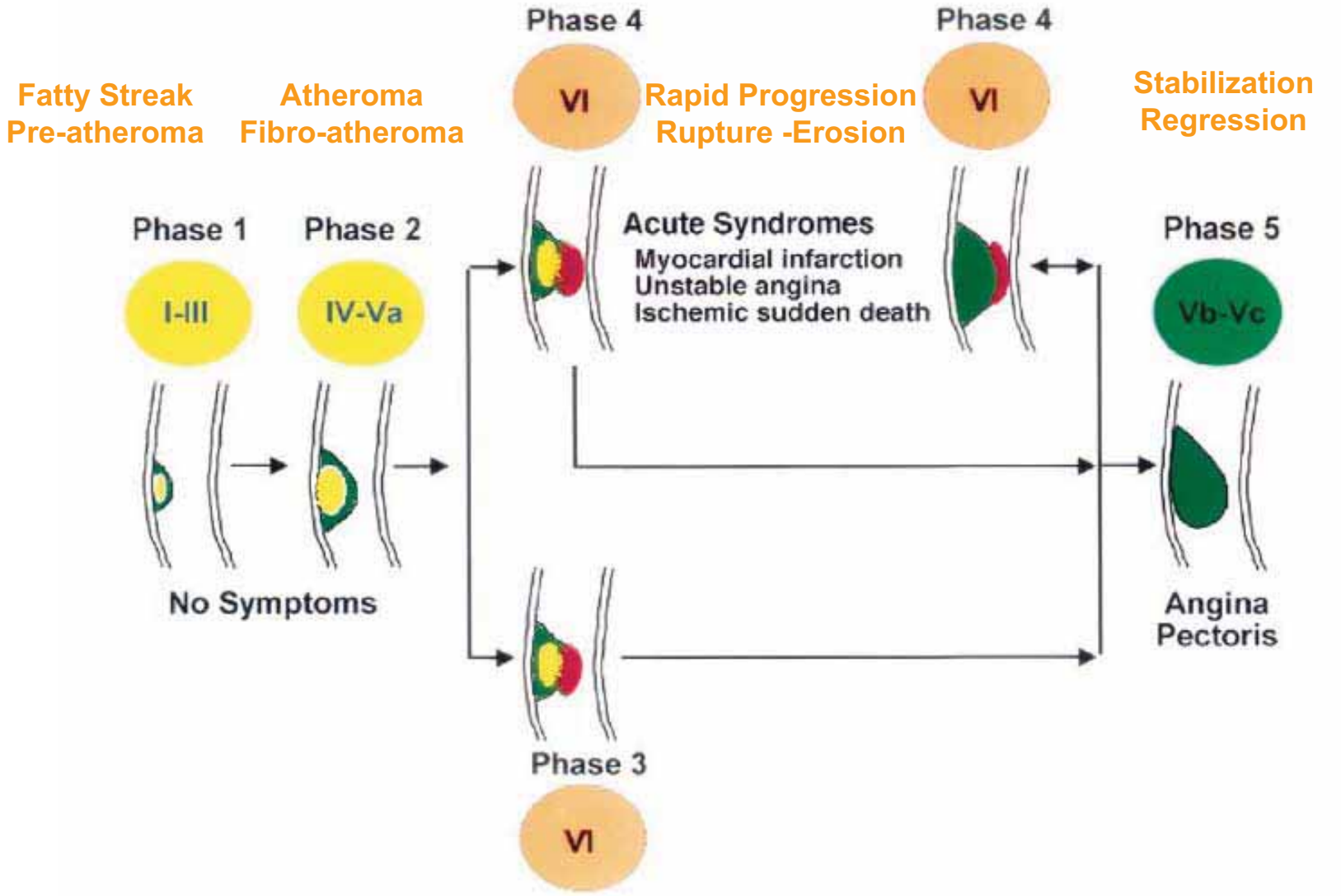
1. Active inflammation (monocyte/macrophage infiltration)
2. Thin cap (<65μm) with Large Lipid Core (>40%)
3. Endothelial Denudation with Superficial Platelet Aggregation
4. Fissured / Wounded Plaque

Characteristics of Plaque Prone to Rupture



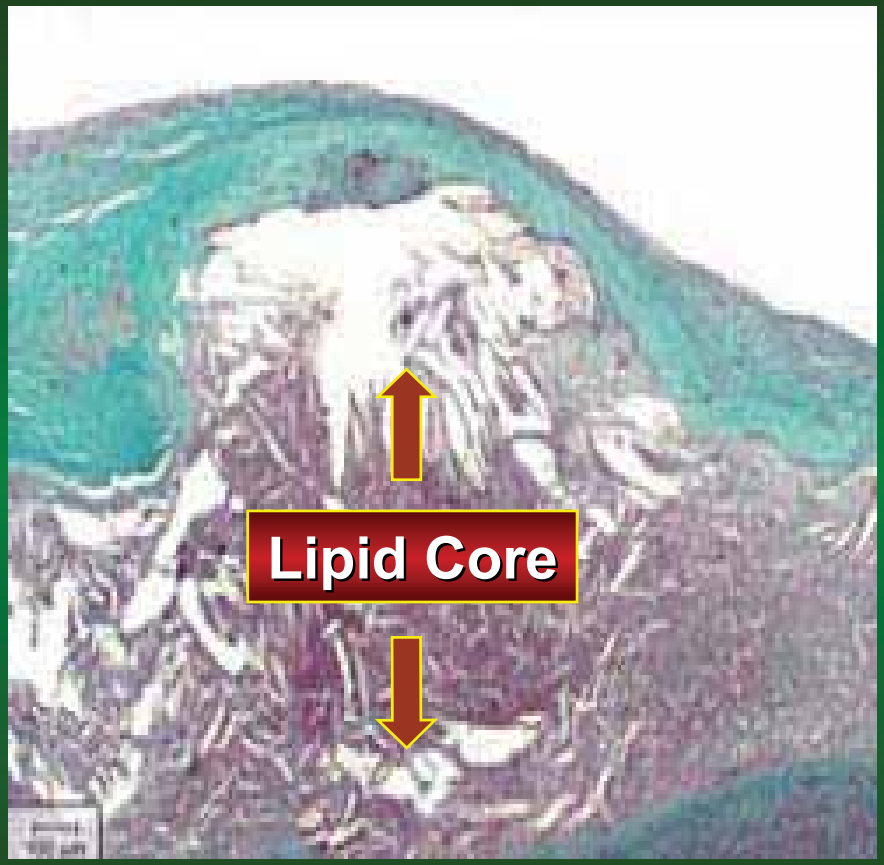
Libby P, *Circulation*.1995;91:2844

Phase and Lesion Morphology of Progression of Coronary Atherosclerosis

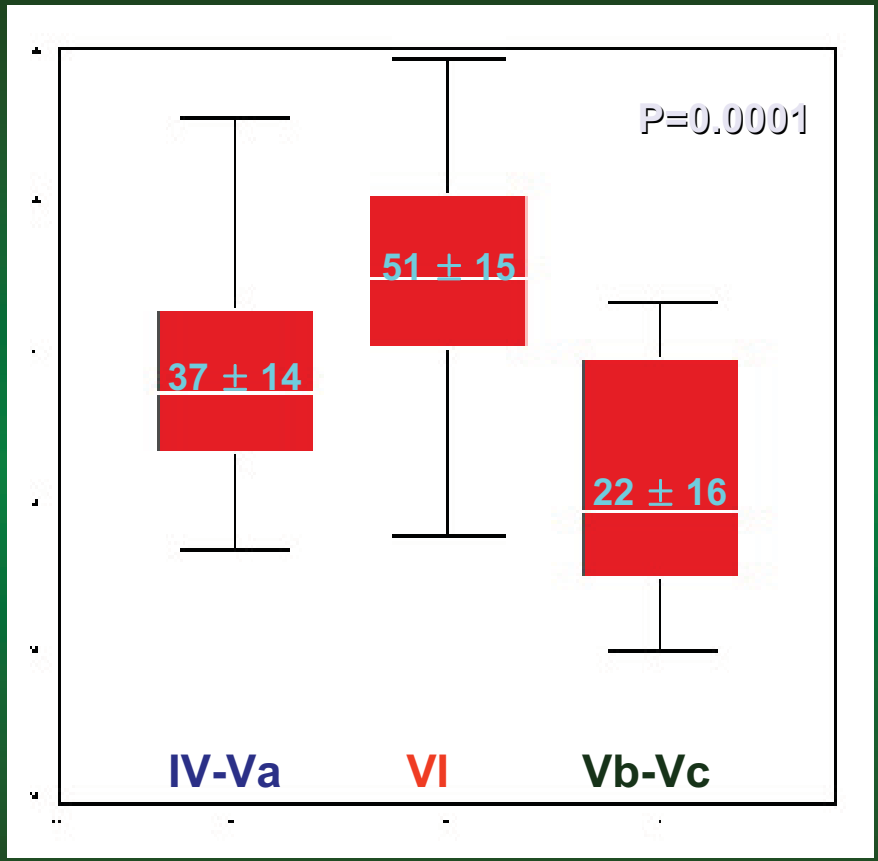


High-Risk, Disrupted and Fibro-Calcific Plaques

Percent Lipid Core Area



Elastic Trichrome Stain

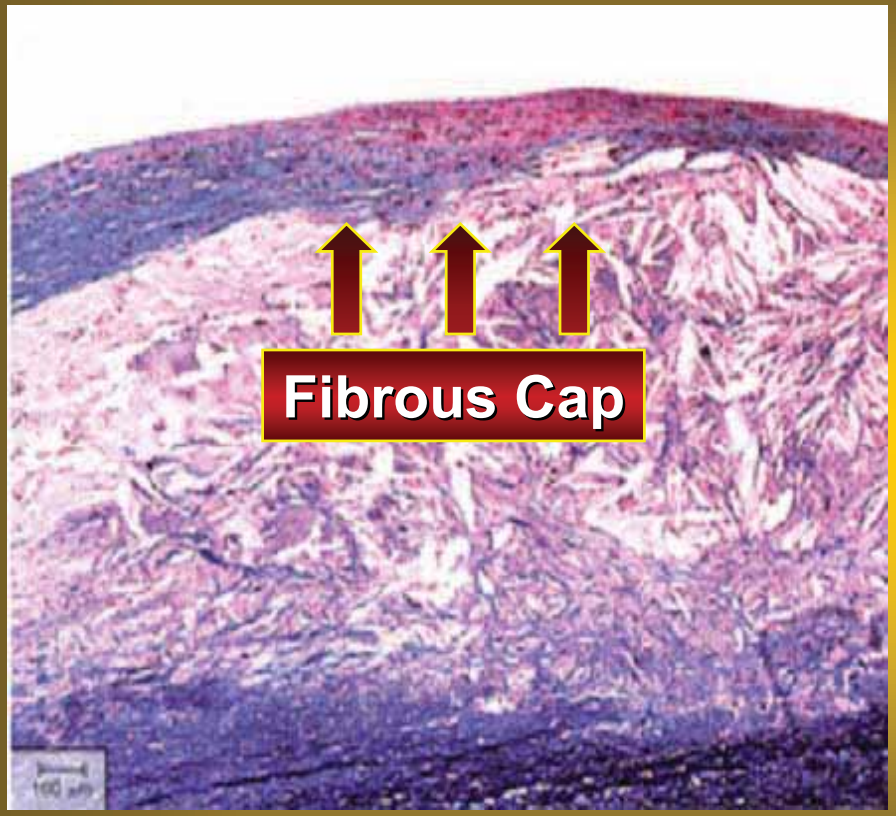


High-Risk (n=89) | Disrupted (n=55) | Fibro-Ca++ (n=18)

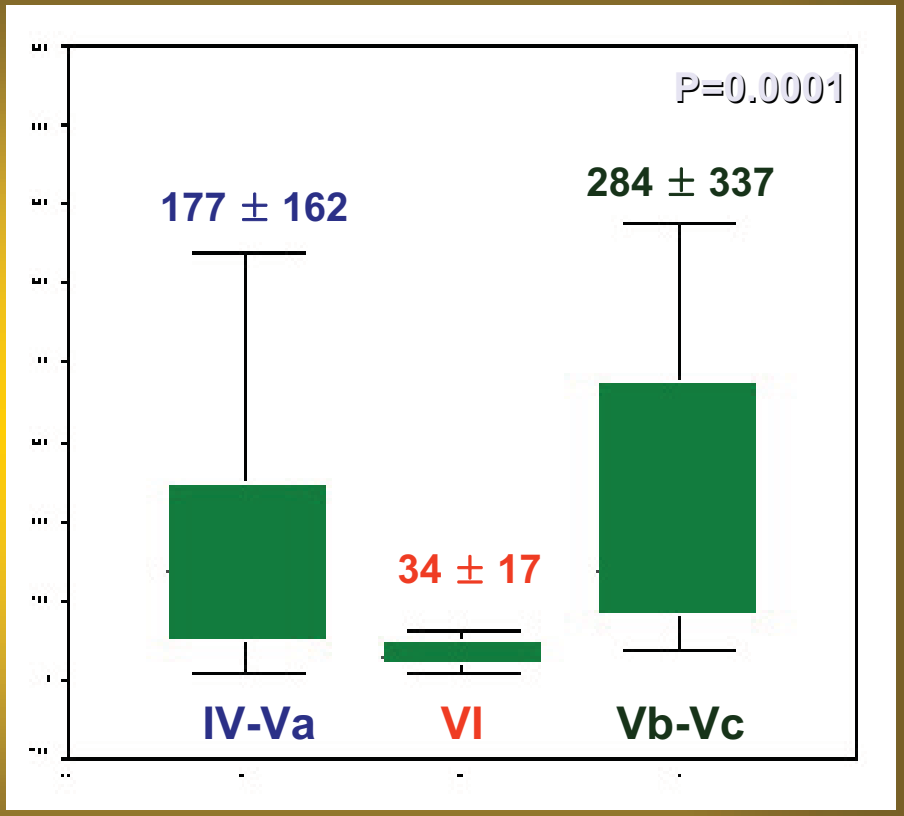
Moreno PR, et al. Circulation 2002;106:II-703

High-Risk, Disrupted and Fibro-Calcific Plaques

Fibrous Cap Thickness (microns)



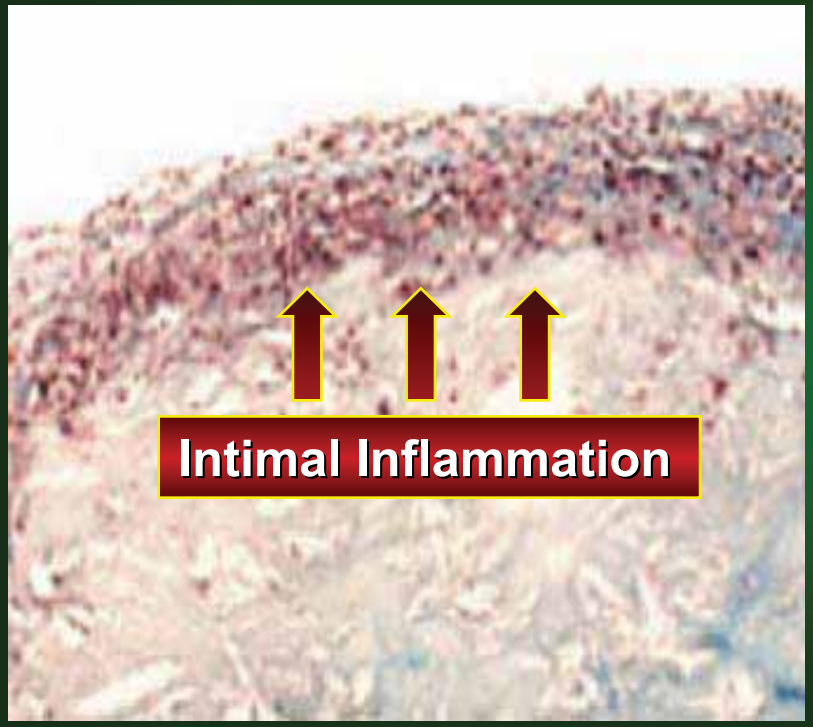
Elastic Trichrome Stain

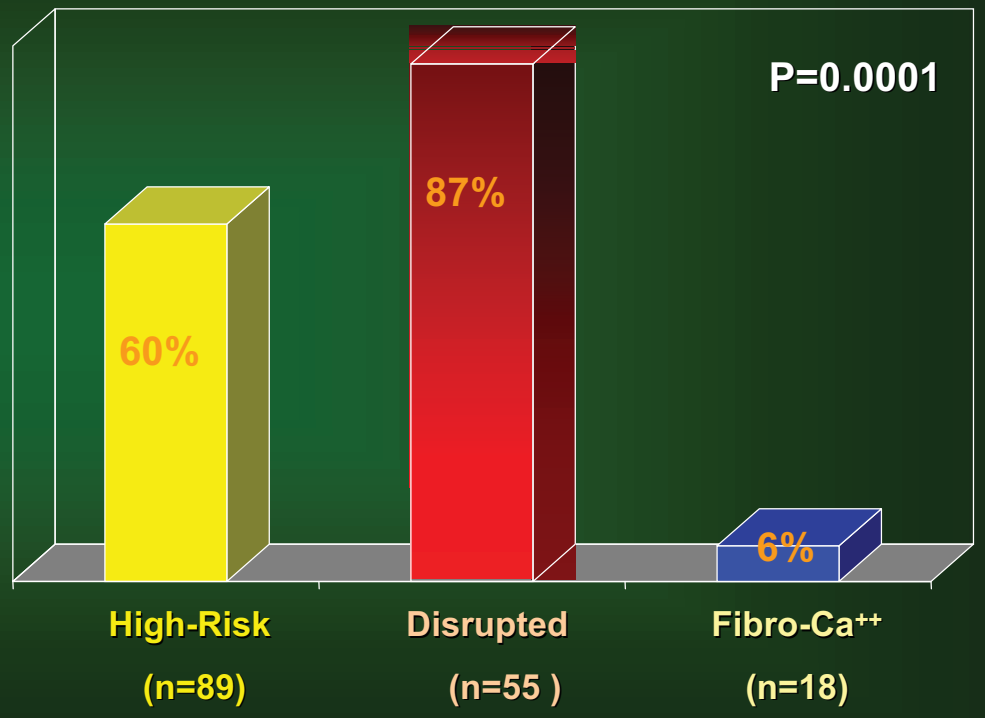


Moreno PR, et al. Circulation 2002;106:II-703

High-Risk, Disrupted and Fibro-Calcific Plaques

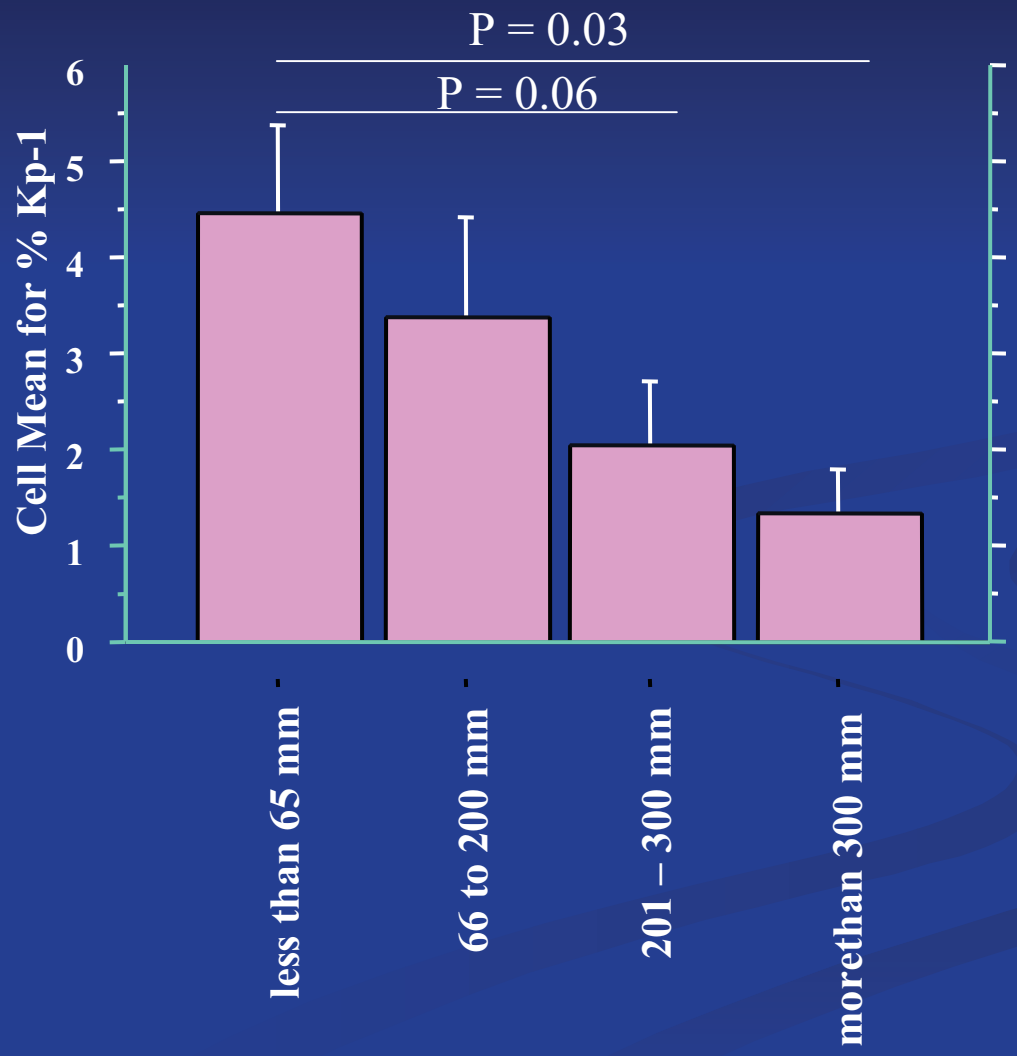
Inflammation: Tunica Intima





Moreno PR, et al. Circulation 2002;106:II-703

Relationship of Fibrous Cap Thickness to Macrophage Infiltration



Proposed Histopathological and Clinical Criteria for Definition of Vulnerable Plaques

Minor Criteria:

1. Superficial Calcified nodule
2. Glistening Yellow
3. Intraplaque Hemorrhage
4. Critical Stenosis
5. Positive Remodeling?

VP in Acute Coronary Syndromes

Coronary Syndromes	No.	Thrombus Frequency
Acute Myocardial Infarction	n=15	
Plaque Rupture	9 (60%)	80%
Plaque Erosion	3 (20%)	
Stable Plaque	3 (20%)	
Sudden Death	n=126	
Plaque Rupture	38 (30%)	49%
Plaque Erosion	21 (17%)	
Calcified Nodule	3 (2%)	
Stable Plaque	64 (51%)	

Detection of Vulnerable plaque

Diagnosis and Screening –Plaque Level

- Plaque inflammation (macrophage density or rate of monocyte infiltration
- Matrix digesting enzyme activity in the cap (MMP 2, 3, 9, etc)
- Endothelial denudation or dysfunction (local NO production, anti/pro-coagulation properties of the endothelium)
- Superficial platelet aggregation and fibrin deposition (residual mural thrombus)
- Plaque cap thickness with a resolution of <65~100 micron
- Collagen content, lipid core size, mechanical stability (stiffness and elasticity)

Diagnosis and Screening –Plaque Level

- Calcification burden and pattern (nodule, scattered, intimal, deep)
- Angiogenesis, leaking vasa vasorum, and intraplaque hemorrhage
- Presence of certain microbial antigens
- Rate of apoptosis (apoptosis protein markers, coronary microsatellite, etc)
- Shear stress imaging (flow pattern throughout coronary artery)

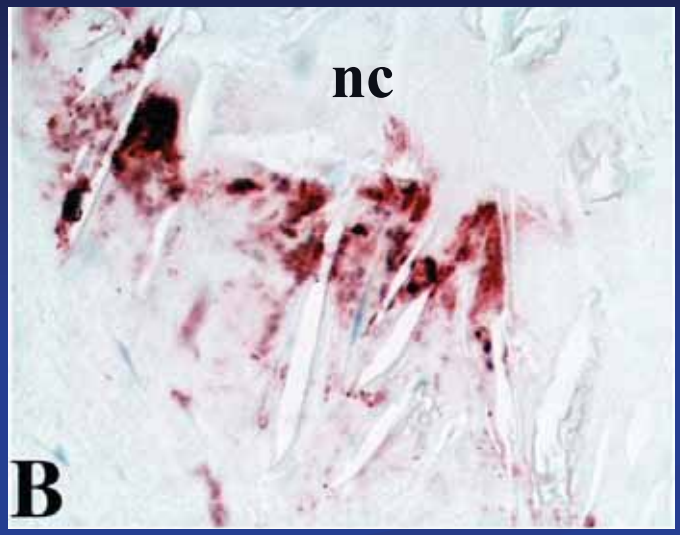
Diagnosis and Screening–Systemic Level

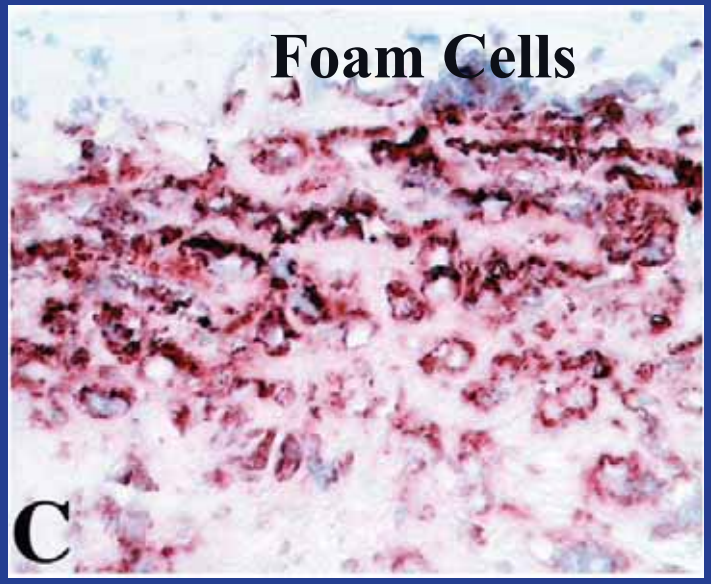
- Markers of blood fibrinolysis
- Markers of lipid-peroxidation
- PAPP-A, pregnancy associated plasma protein-A
- Plaque specific markers of immune activation (anti-LDL ab)

Diagnosis and Screening–Systemic Level

- CRP, CD 40L, ICAM-1, VCAM, and other serological markers of inflammation
- MMPs and acidic digesting proteinases and their inhibitors such as TIMMPs and cystatin
- Circulating apoptosis markers
- Markers of blood hypercoagulability

Immunolocalization of CRP in Coronary Artery Section





Burke A, et al.
Circulation. 2002;105:2019

Serum hs-CRP Correlated with Immunohistochemical Staining Intensity

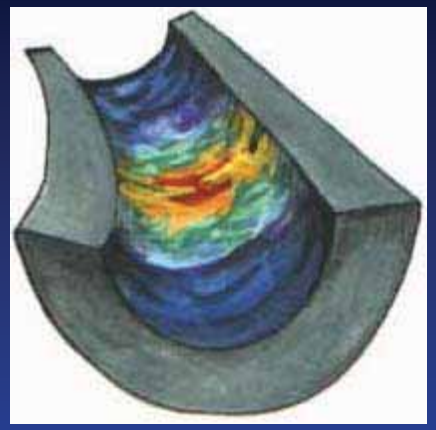
CRP	CRP staining intensity of plaques*	Mean number of thin cap atheroma
Low CRP group (<1.0mg/mL)	2.9 ±0.5	0.95 ±0.22
High hs-CRP group (>3.2mg/mL)	6.2±0.6	3.0 ±0.3

*Grading of staining intensity was assessed on macrophages and Lipid core. A quantitative score of 0 to 4 was applied to each. A sum of the 2 scores resulted in overall grading system of 0 to 8

Imaging the Vulnerable Plaque

- **Two Important Features;**
  - degree of luminal obstruction
  - composition of the plaque
- **Invasive Techniques**
  - angiography
  - intravascular ultrasound
  - angioscopy
  - optical coherence tomography
- **Noninvasive Techniques**
  - B-mode ultrasound
  - MDCT, MRI, Scintigraphy

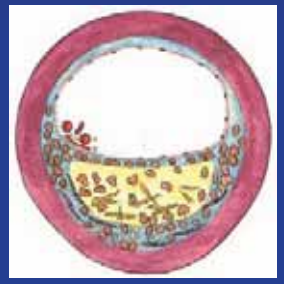
Morphology vs. Activity Imaging



Thermography,
Spectroscopy, MRI with
targeted CM

Activity

Active and
inflamed
plaque



Inactive and
non-inflamed
plaque

Morphology

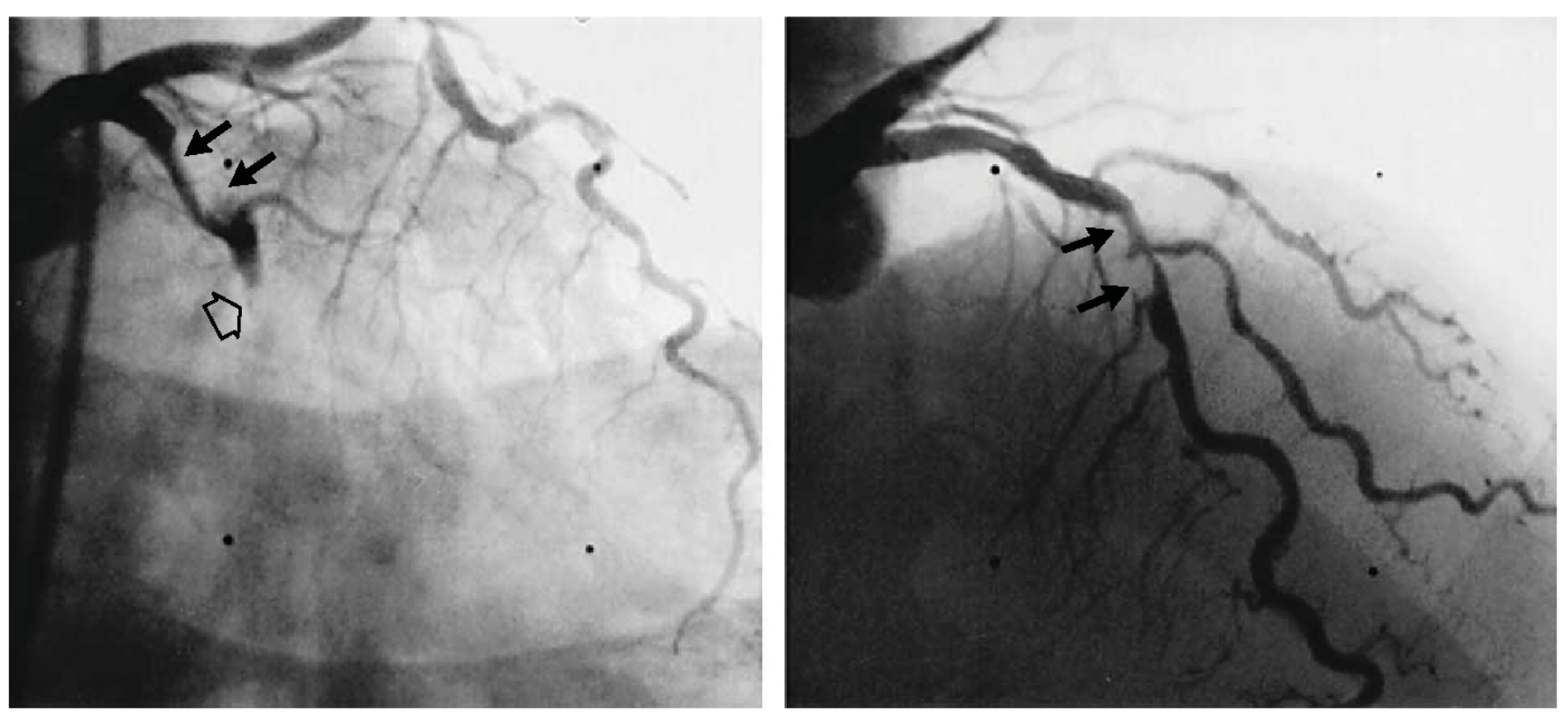
IVUS

OCT

MRI
w/o CM

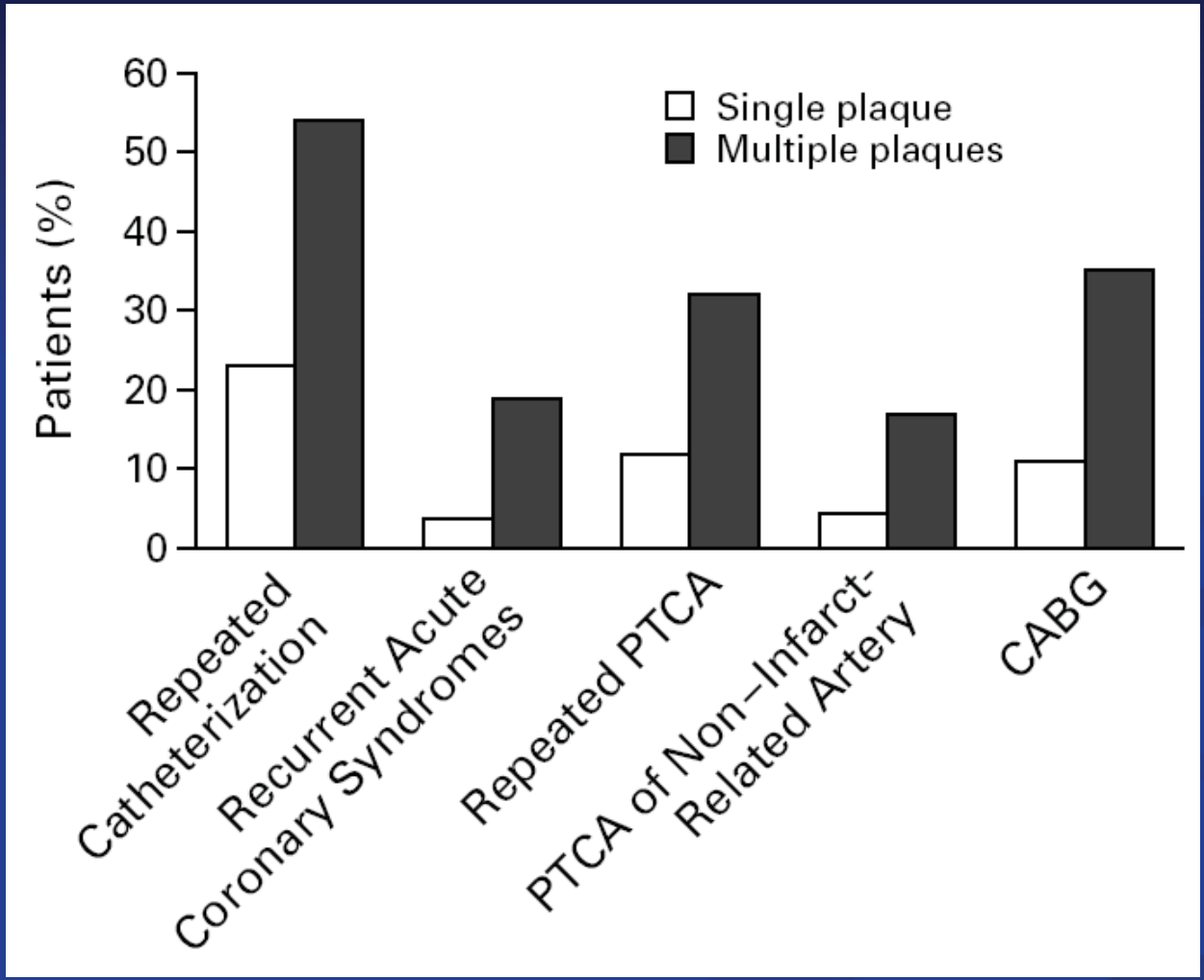
Angiography

Thrombus, Ulceration, Plaque Irregularity, Impaired Flow



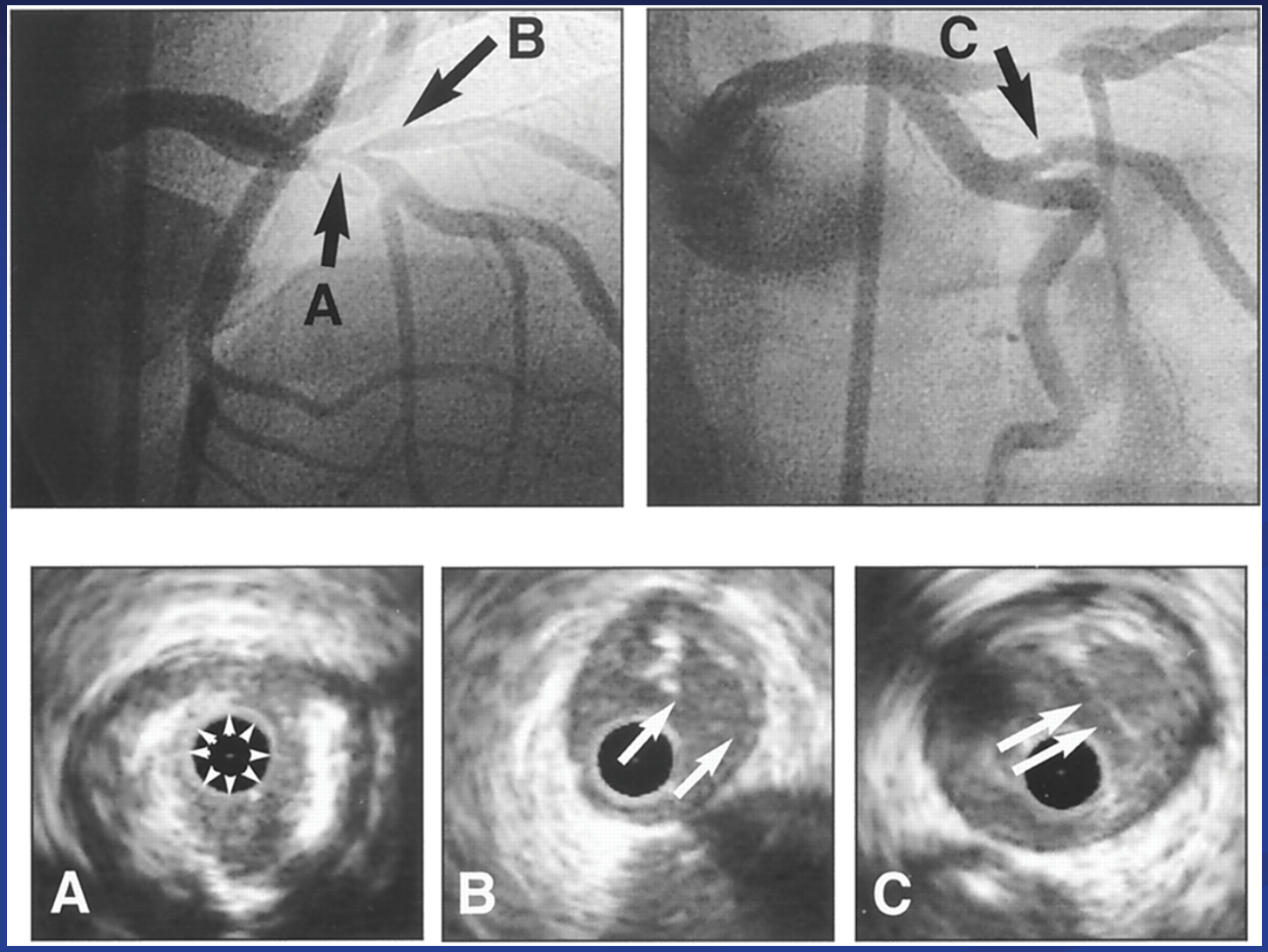
Goldstein JA, N Engl J Med 2000;343:915-22

Angiography



Goldstein JA, N Engl J Med 2000;343:915-22

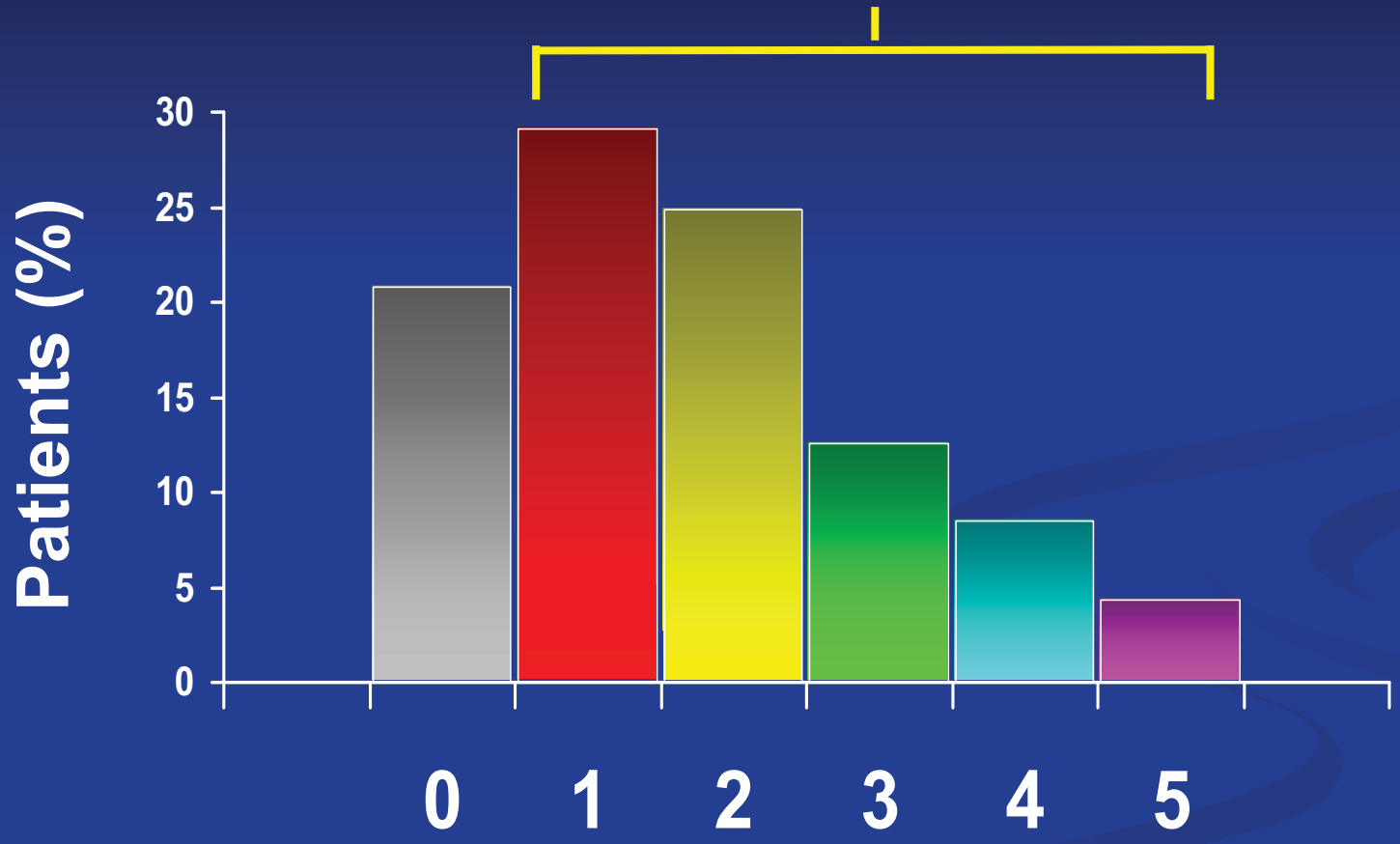
Multiple Atherosclerotic Plaque Ruptures Detected by IVUS



Rioufol et al. Circulation 2002; 106:804-808

Vulnerable Plaques in ACS

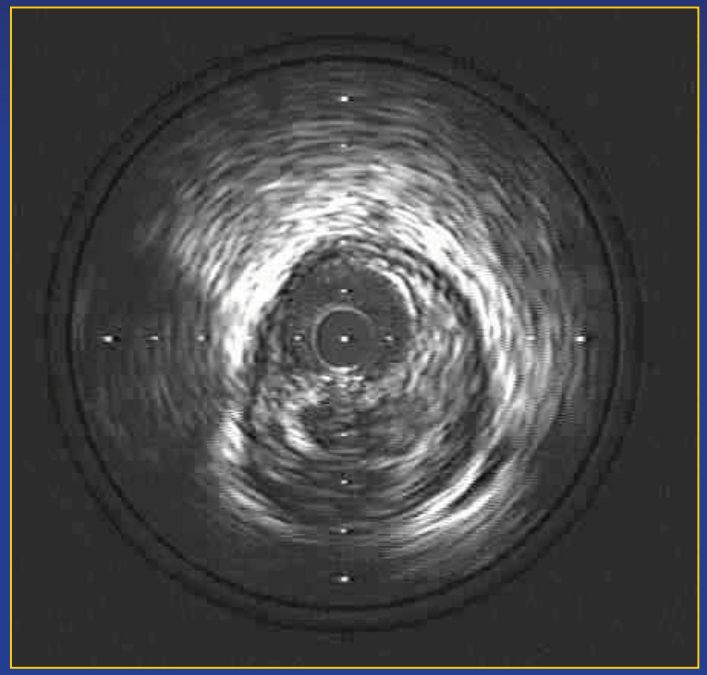
79% of ACS patients have > 1 ruptured plaque

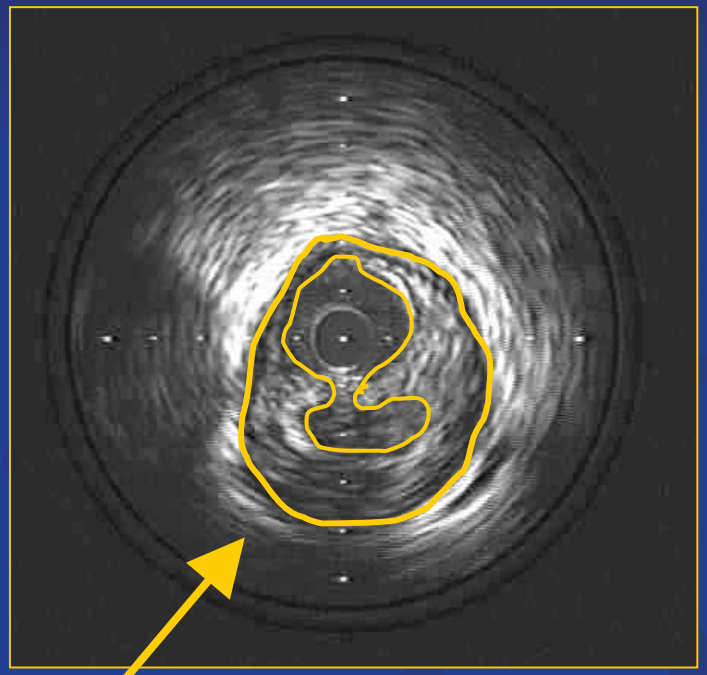


 # Ruptured plaques in addition to culprit lesion

Rioufol et al. Circulation 2002; 106:804-808

IVUS Imaging of VP





Ruptured plaque

Angioscopy

- Characterize plaque morphology directly

  Yellow plaque: presence of lipid-laden atheroma

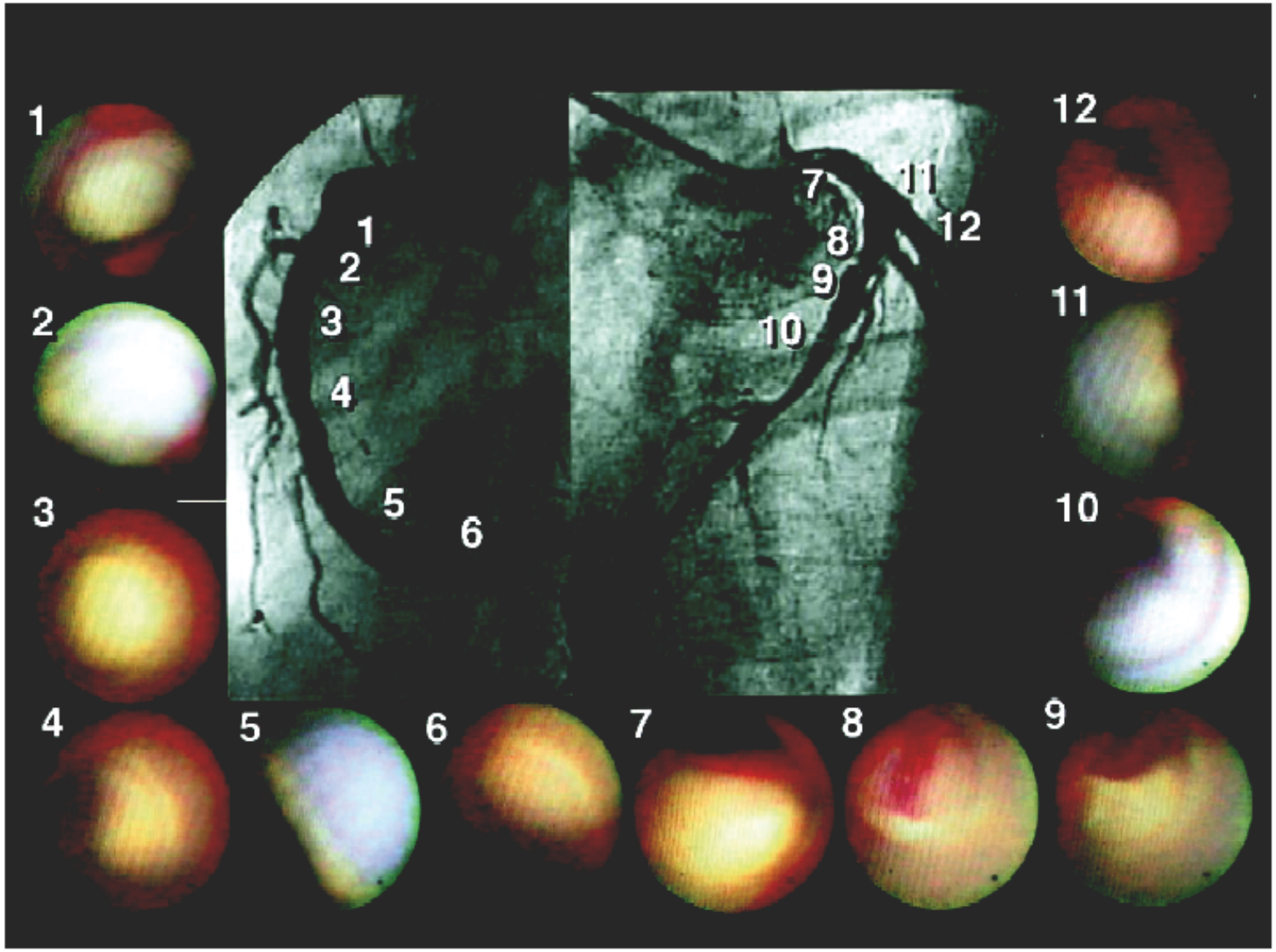
  Gray-yellow plaque: degenerated or fibrous plaque

  Gray-white plaque: fibrous plaque without degeneration

- Considered the gold standard for the detection of thrombus and luminal dissection *in vivo*

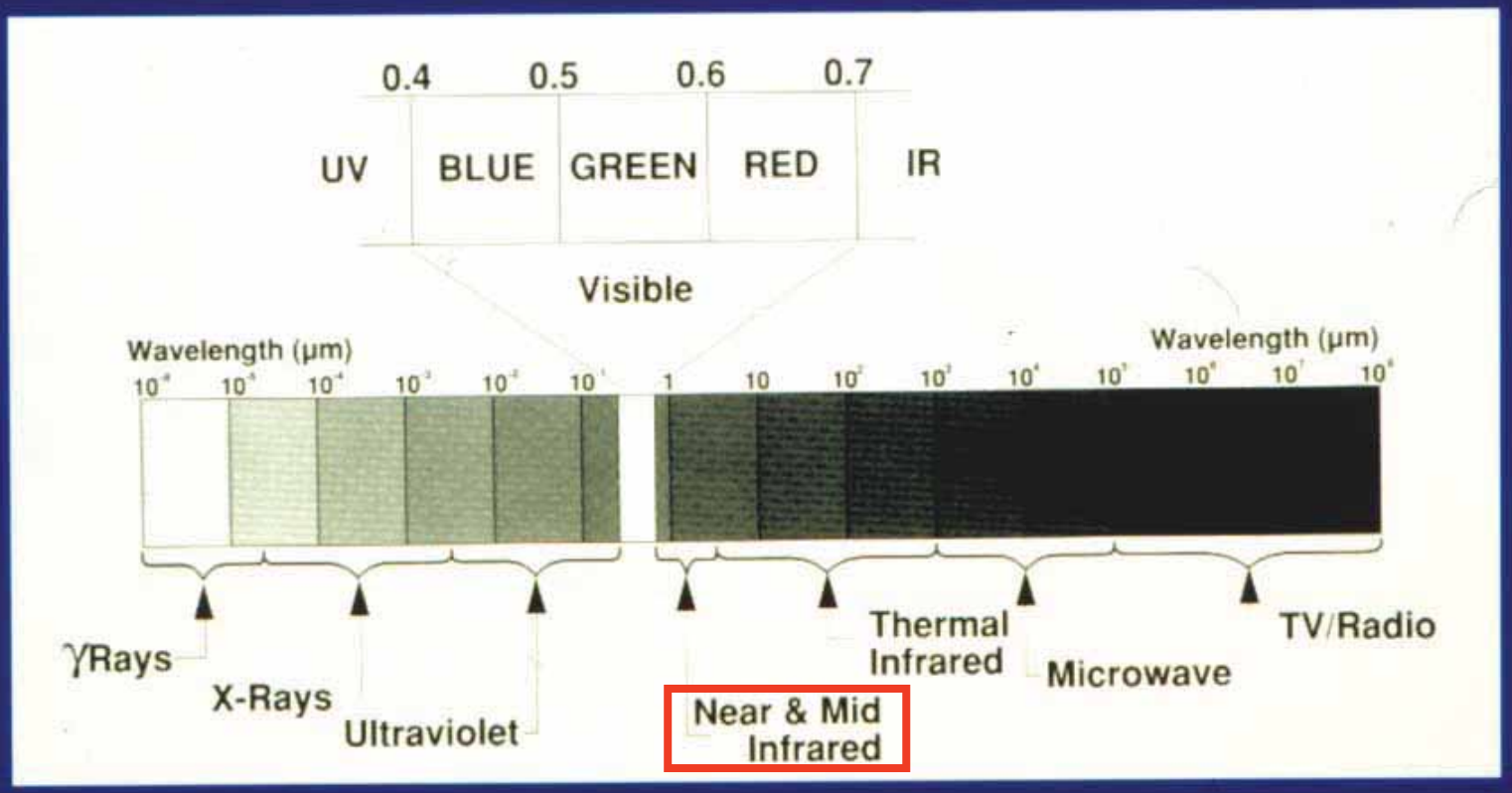
- *But, **Invasive** and **Subjective***

Angioscopy



Asakura M, et al JACC 2001;37:1284-8

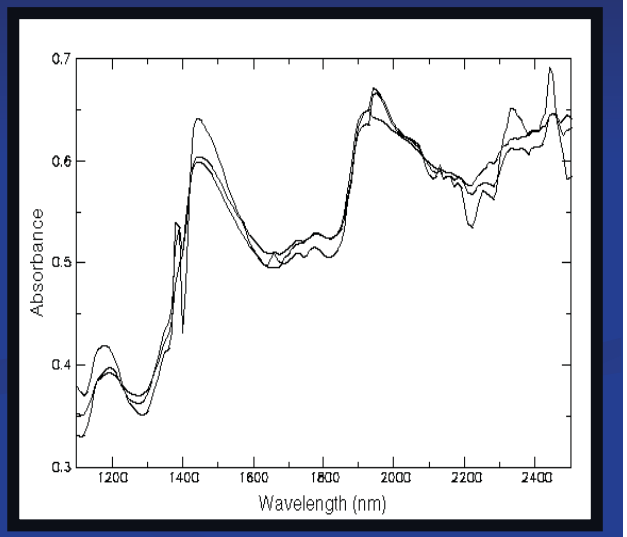
ELECTROMAGNETIC SPECTRUM



InfraReDx

- Biological tissues have unique absorbance in the NIR wavelength range
- NIR light has enough penetration that may obtain spectra through blood

Tissue Evaluation by Near-IR Spectroscopy



Absorbance peaks are caused by:

Combinations of fundamental bonds (C-H, C=C, C=O)

Electron transitions in the heaviest atoms

Advantages of Near-IR Spectroscopy For Vulnerable Plaque Research

- Analysis under 1 second
- Simultaneous, multi-component, non- destructive analysis
- Chemical, biological and molecular information
- Automated predictions using computer algorithms
- Detection limits can be very low (from picograms to planets)
- Cost per analysis is minimal (no reagents used)

Dempsey RJ et al. Applied Spectroscopy 1996;50:18A-34A

Coronary Composition by NIR Spectroscopy

147 Human Coronary Sections

Hypothesis

- Lipid pool in coronary plaques

Methods

- Spectrometer: Foss/NIRSystems
- H & E and Trichrome staining

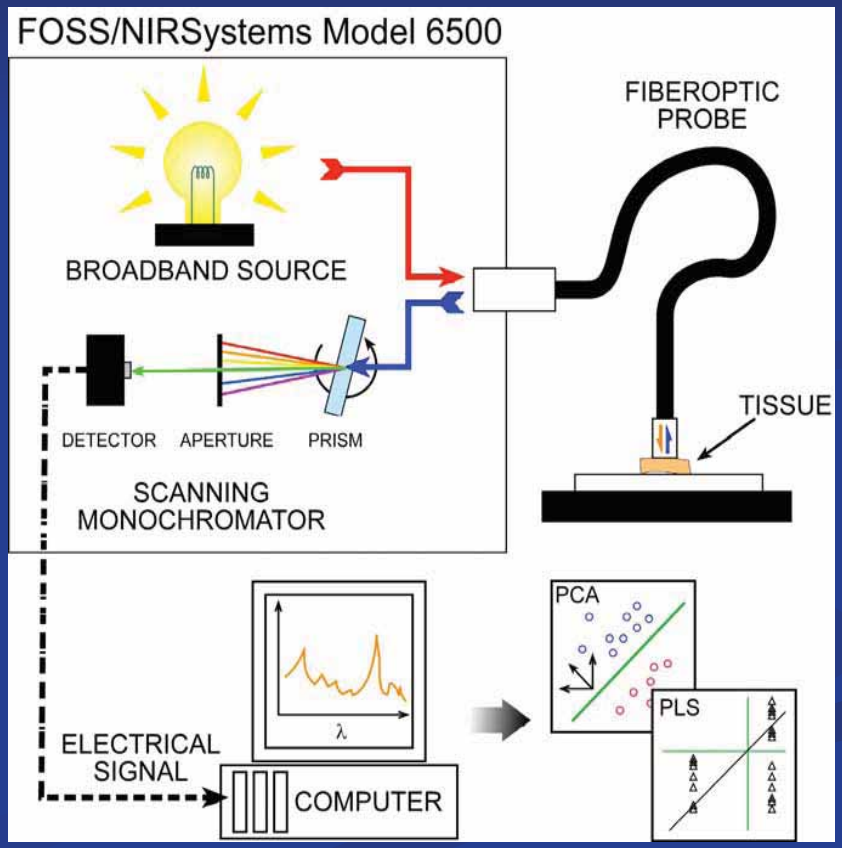
Identification Algorithm Model

- Training Set (76 sections)

Blinded prediction

- Validation set (70 sections)

Spectrometer



Moreno PR, et al. JACC 2001;37:356A

Coronary Plaque Lipid Pool Detection by Near-IR Spectroscopy

Validation set (70 sections)

NEAR-INFRARED SPECTROSCOPY	HISTOLOGY +	HISTOLOGY -
+	21	2
-	1	46

- Sensitivity (%) 95
- Specificity (%) 96
- PPV (%) 91
- NPV (%) 98

Moreno PR, et al. JACC 2001;37:356A

Optical Coherence Tomography

- Analogous to ultrasonography, measuring the intensity of **back-reflected infrared light** rather than sound.

- **Characteristics**

  First, its resolution, at 4 to 20μm, is higher than that of any currently available imaging technology.

  Second, acquisition rates are near video speed.

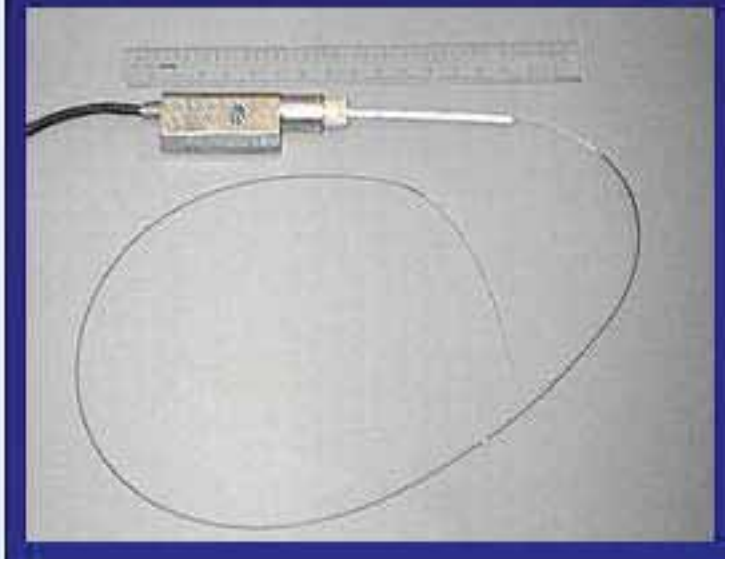
  Third, OCT catheters consist of simple fiber optics and contain no transducers within their frame (catheters are slim and inexpensive).

  Fourth, OCT systems are compact and portable

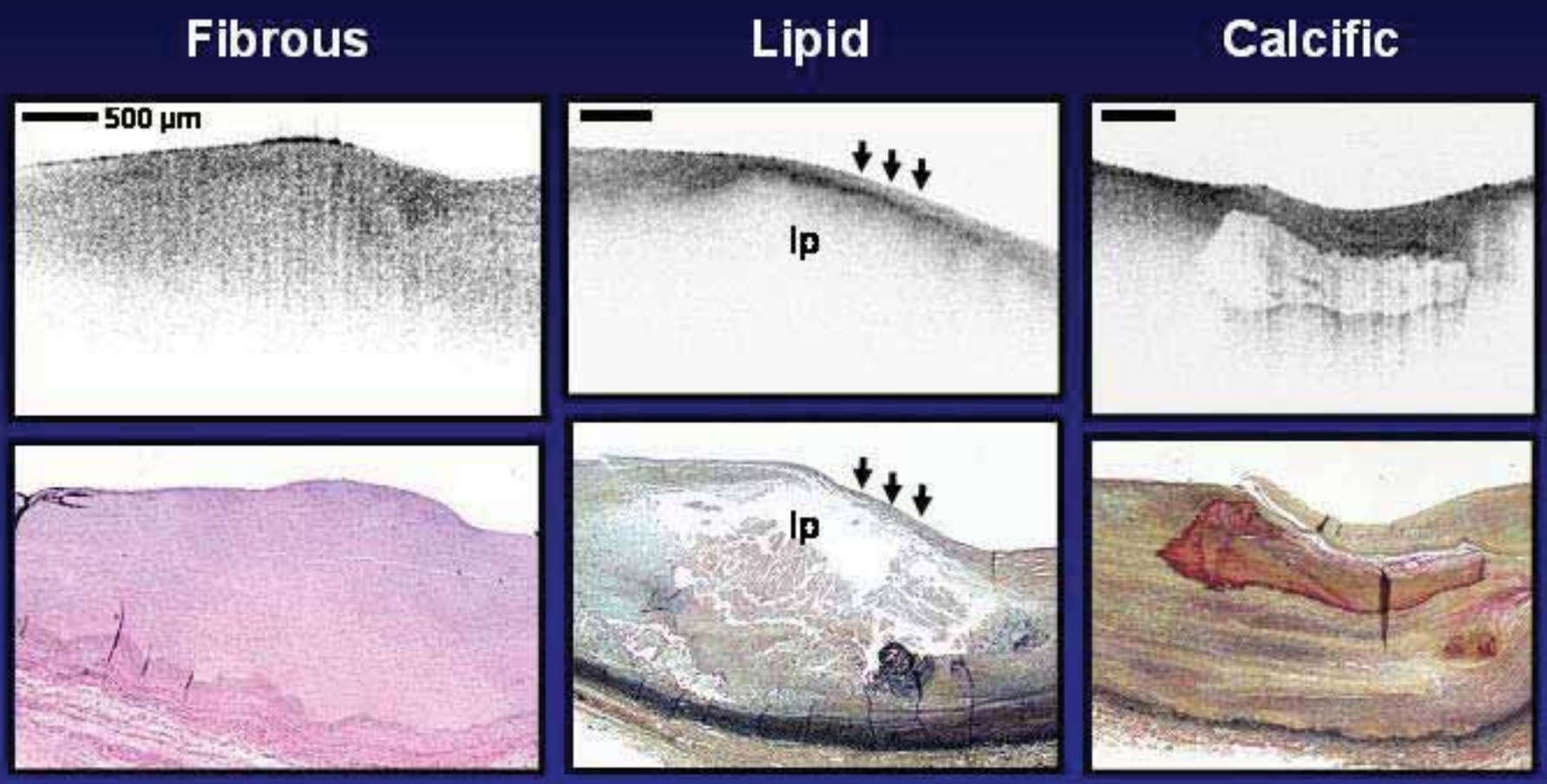
MGH OCT System

Technical Data

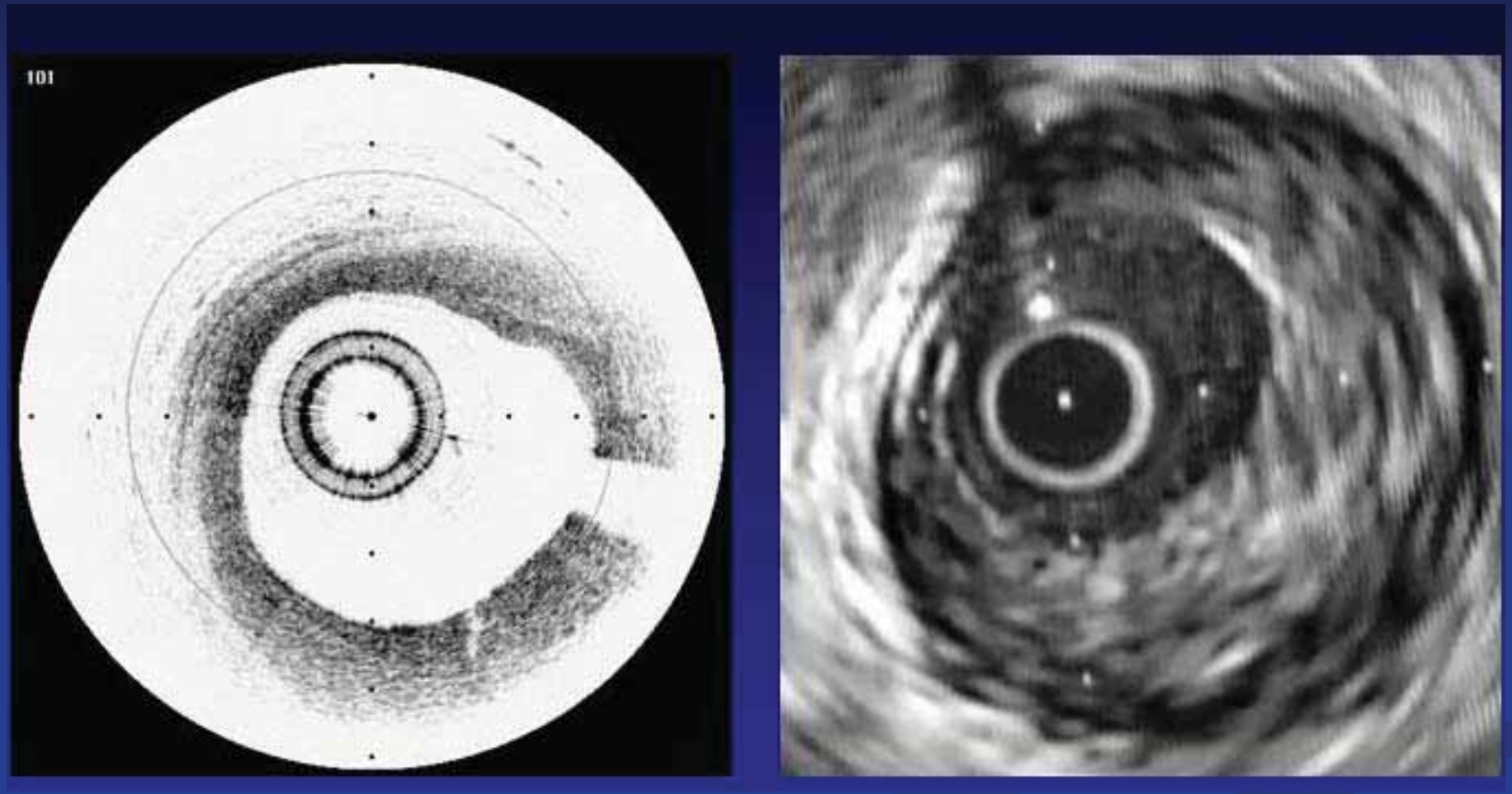
Optical wavelength :	1300 nm
Image acquisition rate :	4-8 images / sec
Catheter:	3.0 F
Axial Resolution :	10 μm
Transverse Resolution :	25 μm
Data storage :	Digital



OCT Characteristics



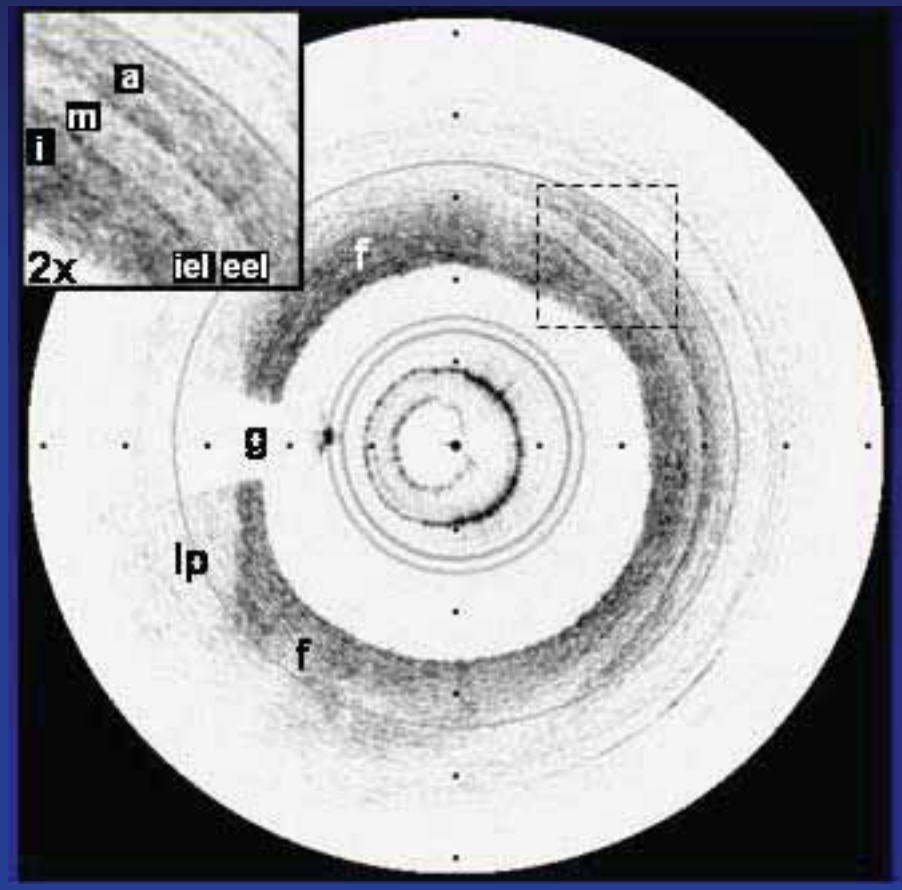
OCT vs IVUS: Fibrous Plaque



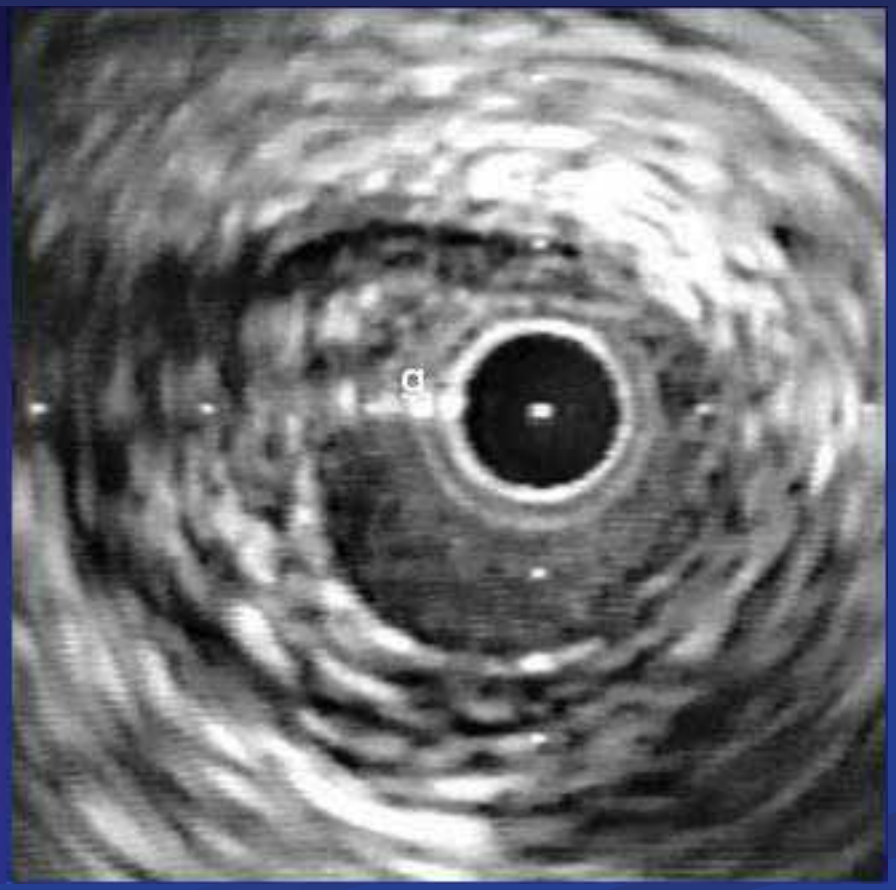
OCT

IVUS

OCT vs IVUS: Lipid Rich Plaque



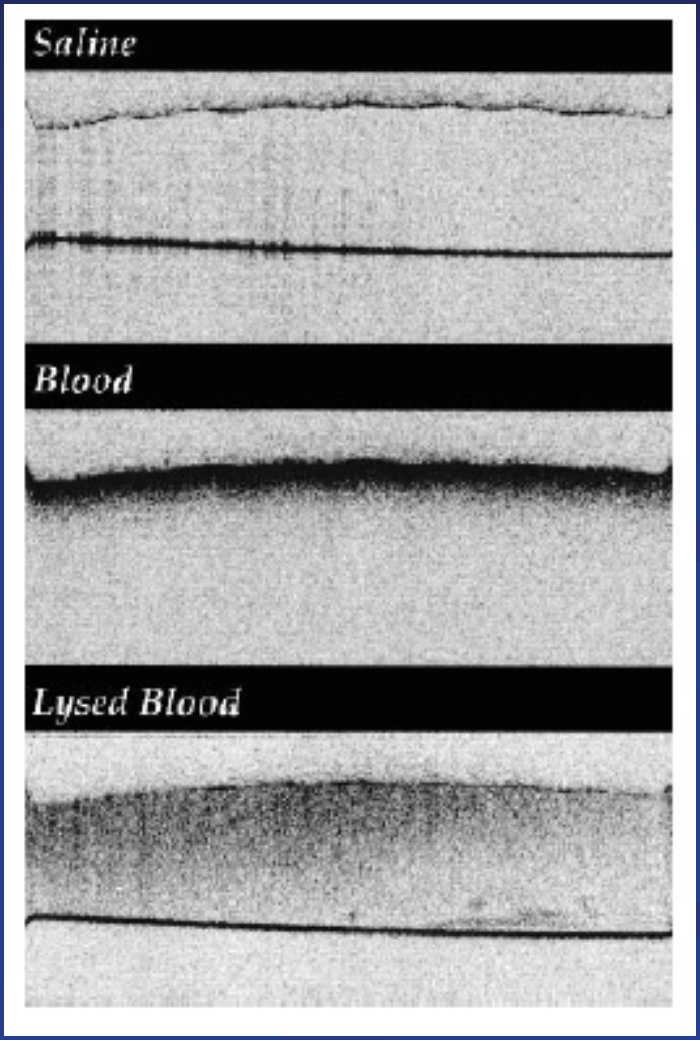
OCT



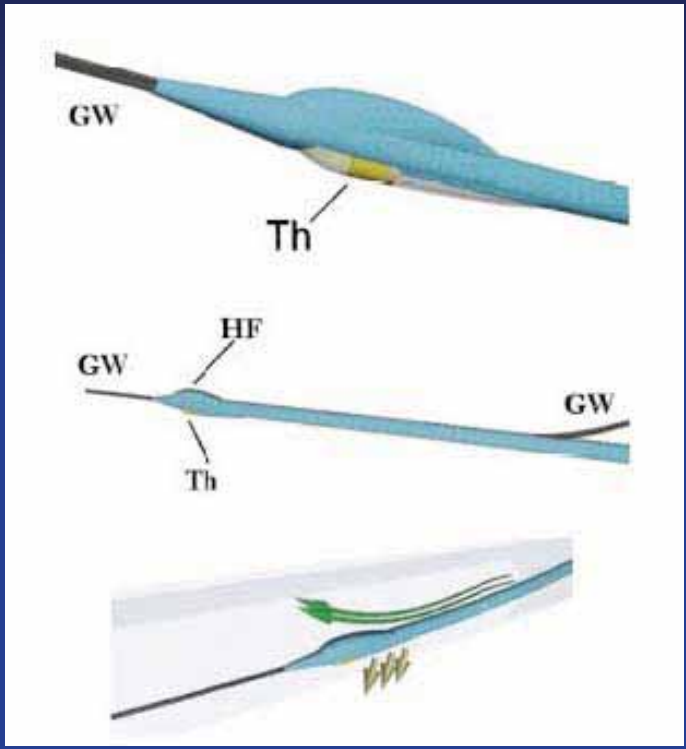
IVUS

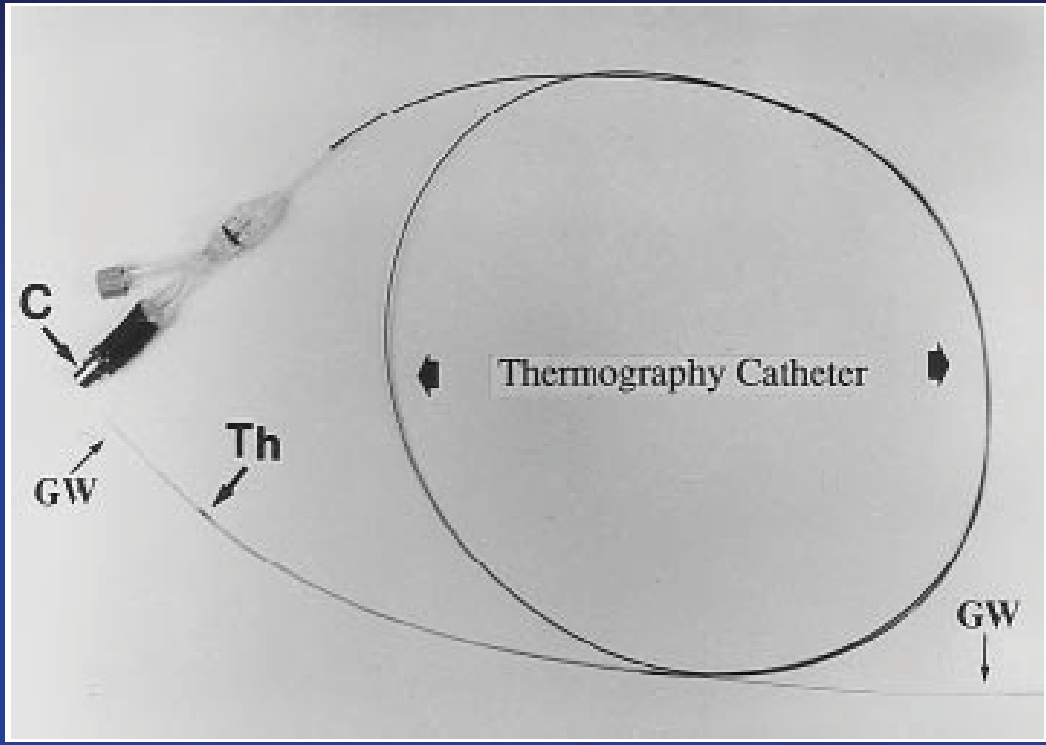
Optical Coherence Tomography

- But, Light scattering occurs from RBCs, saline flushes were required during imaging at 2~3mL/s

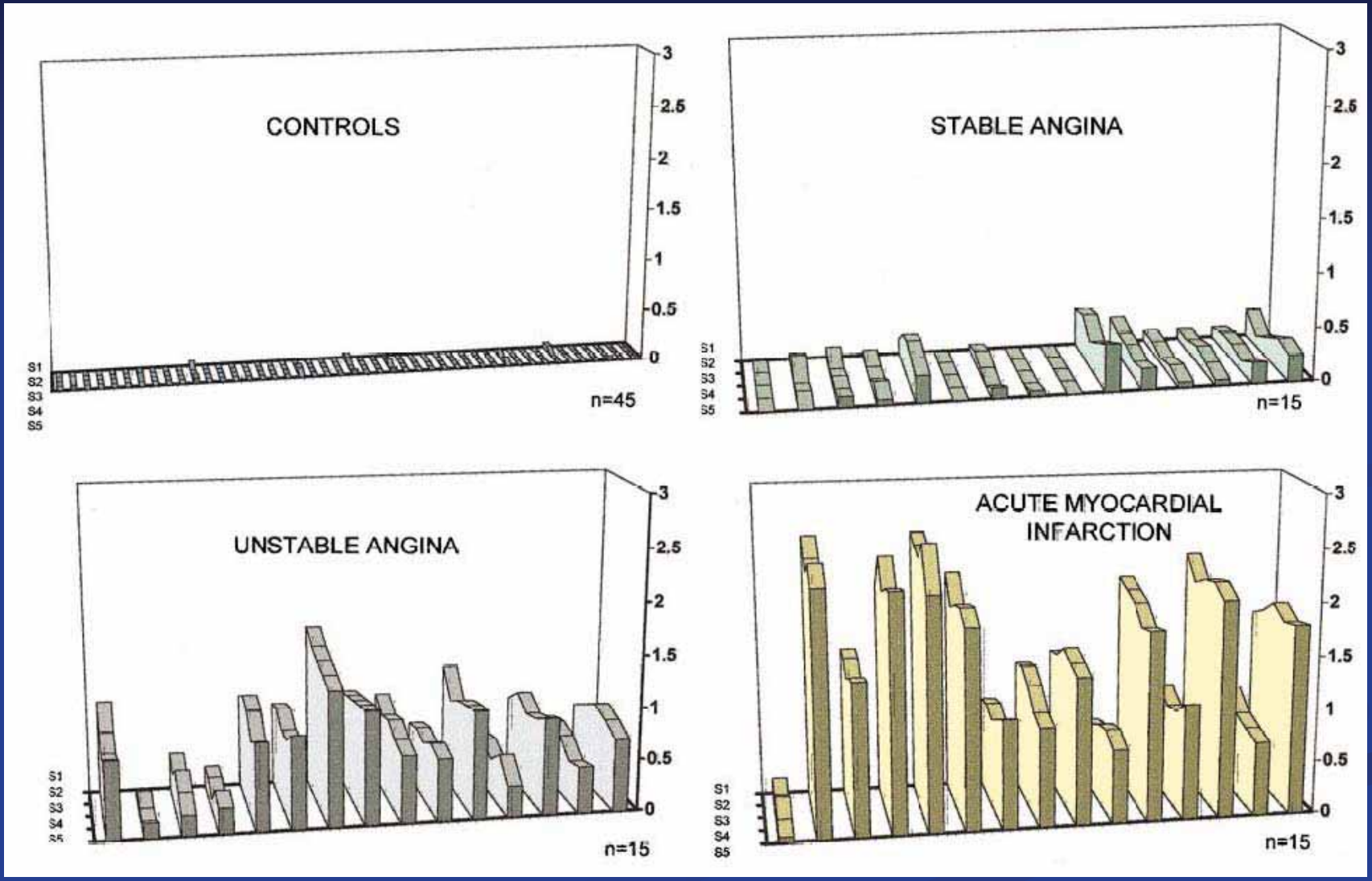


Thermography



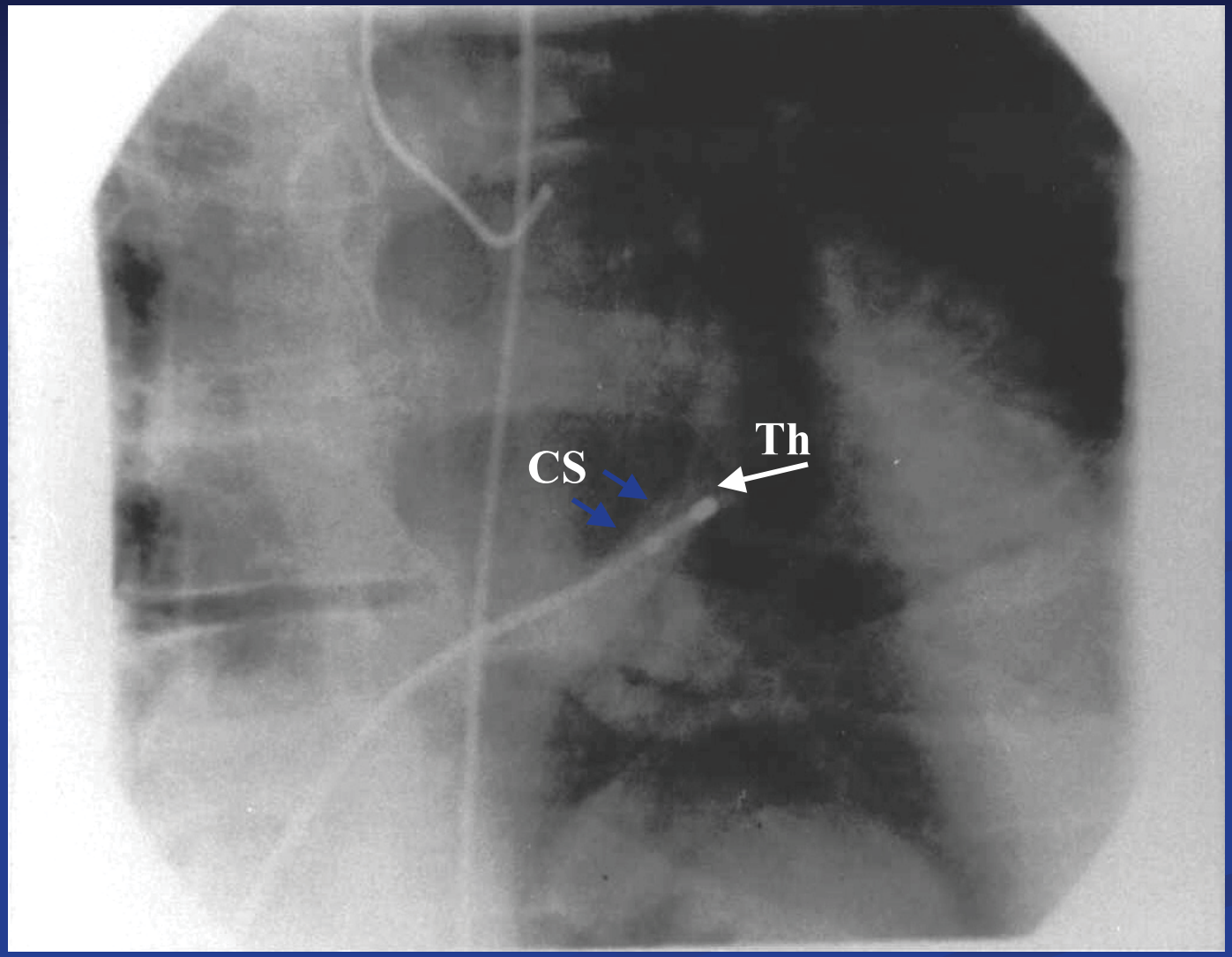


Thermography

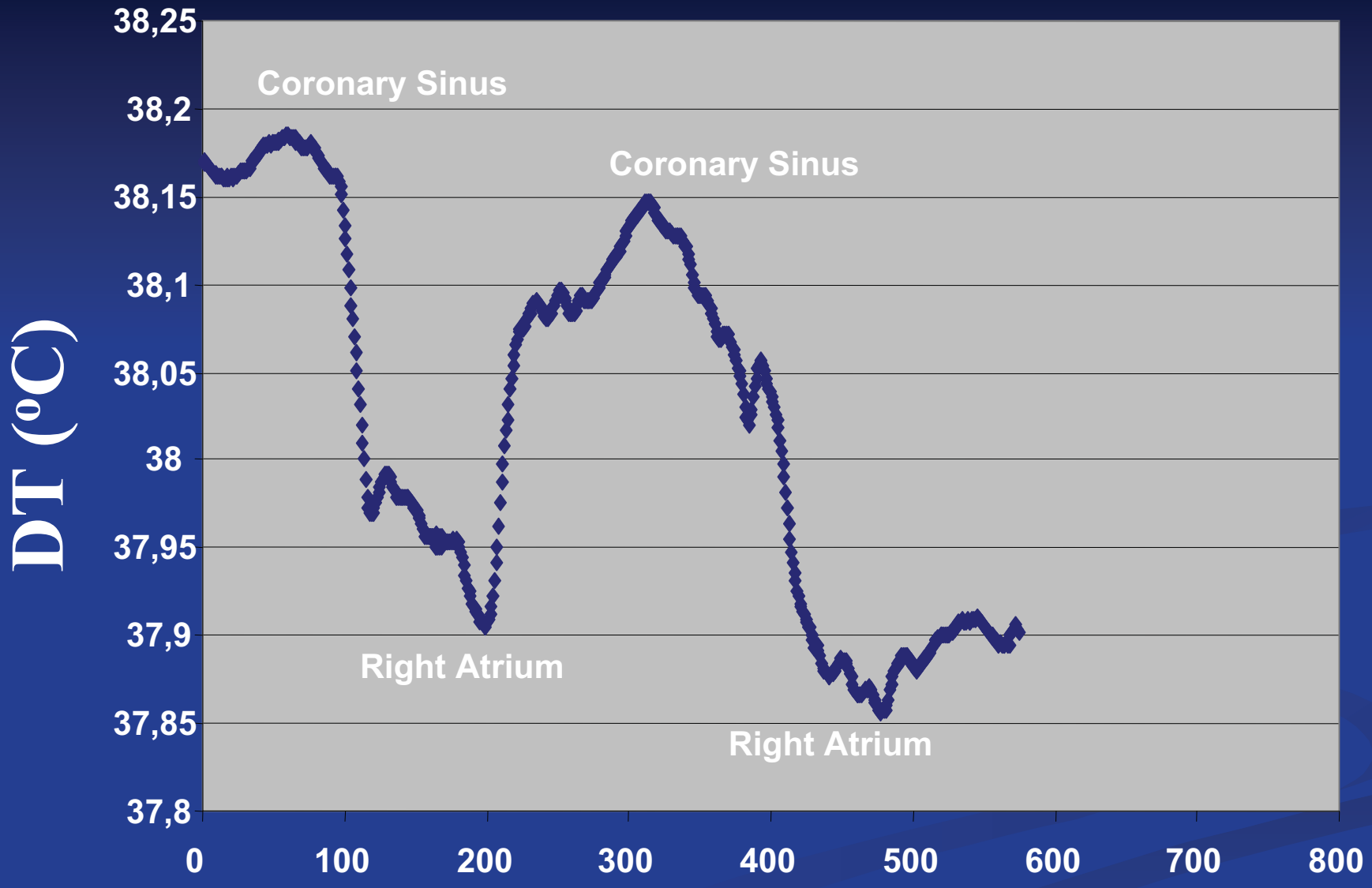


Stefanadis et al Circulation, 1999;99:1965-1971

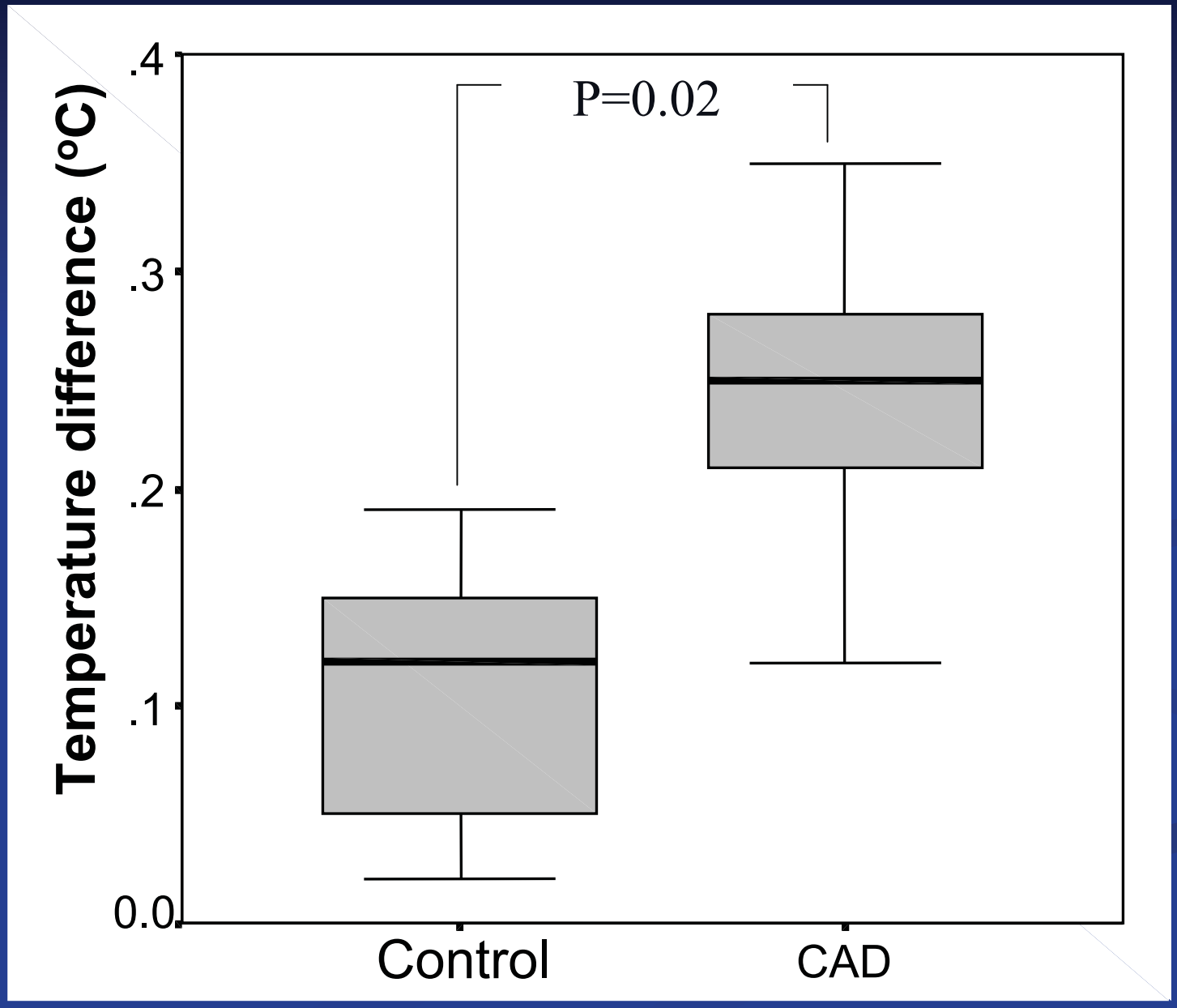
In Vivo Coronary Sinus Thermography



In Vivo Coronary Sinus Thermography

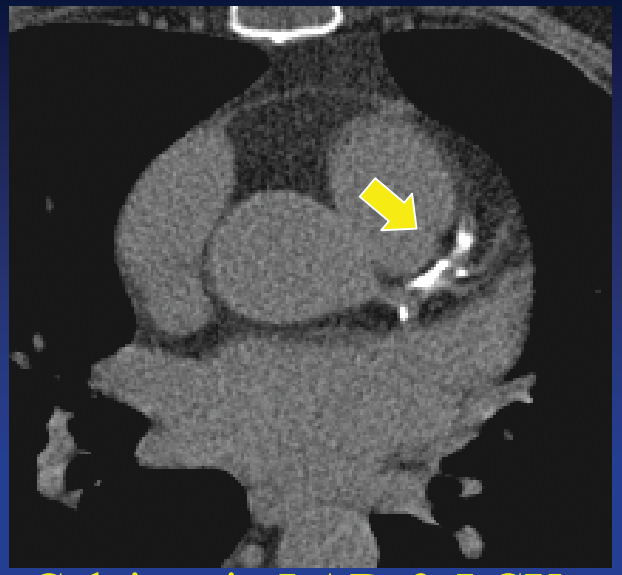


Results of Thermography

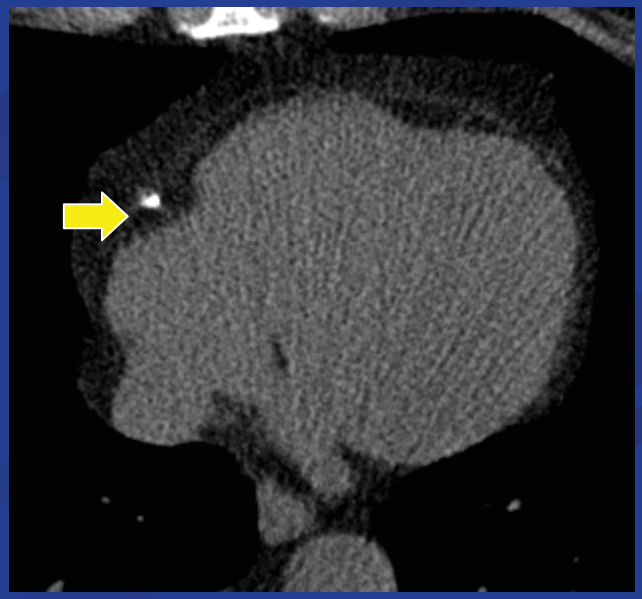


EBCT

Electron beam tomography permits the sensitive detection and quantification of coronary artery calcification.



Calcium in LAD & LCX

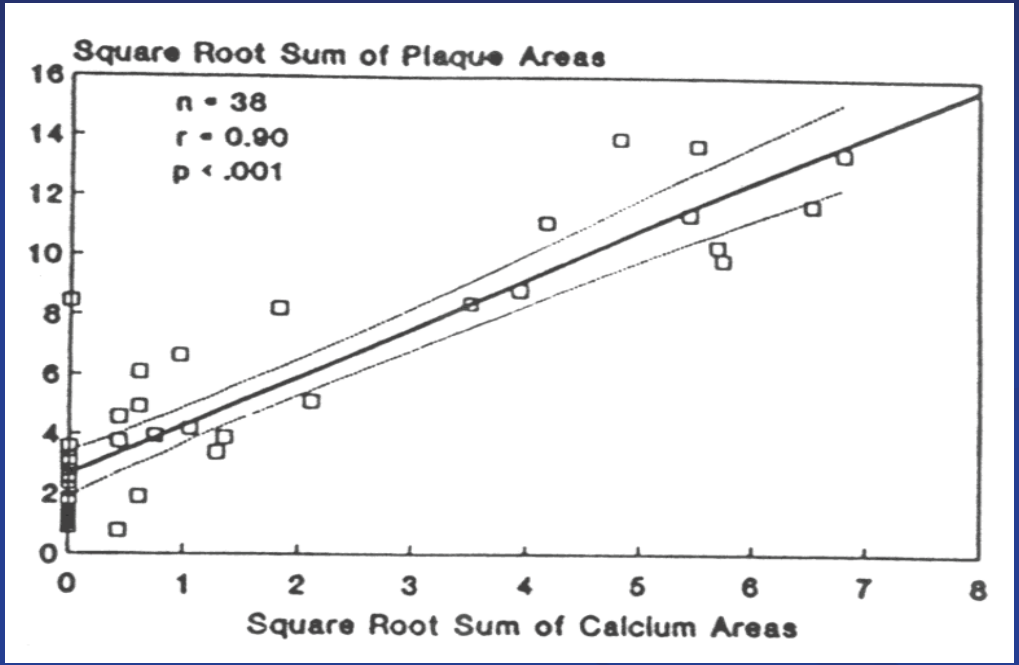


Calcium in RCA

EBCT

Coronary calcium vs Overall Plaque burden

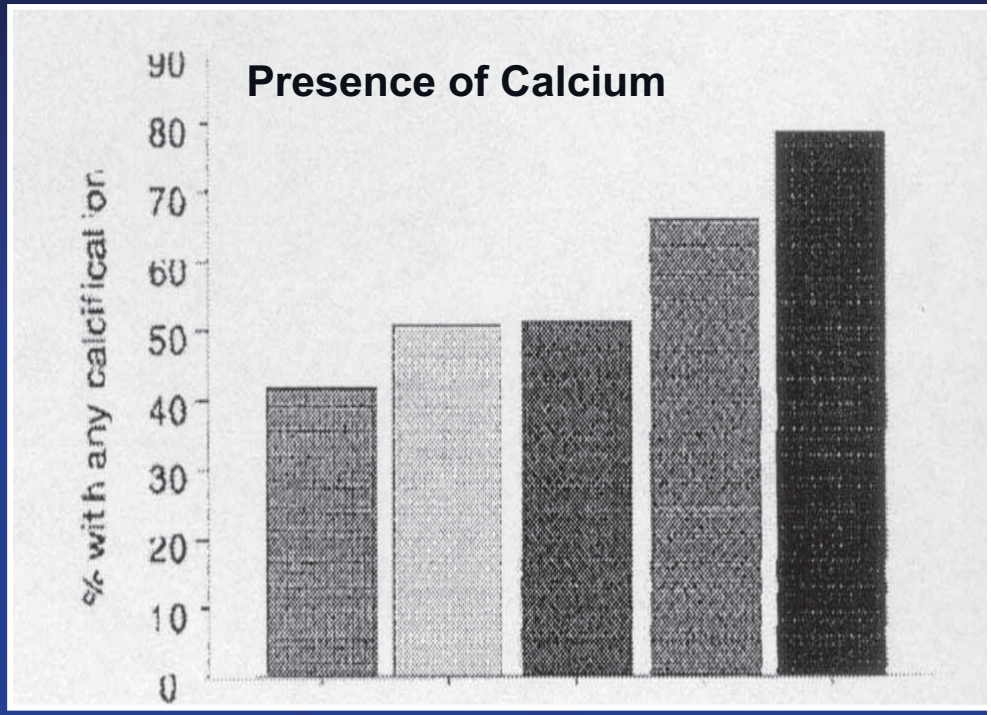
The amount of calcium correlates to overall plaque burden



However, no close relationship between calcium in a vessel segment and degree of luminal stenosis.

EBCT

Even though calcium does not permit to specifically detect *vulnerable* plaque, it is wrong to assume that calcified plaques are stable or more frequently stable than non-calcified plaques.



EBCT

632 asymptomatic patients
32 +/- 7 months follow-up
myocardial infarction and death

Annual event rate:

0.1% for calcium score of 0
2.1% for calcium score 1-99
4.1% for calcium score 100-400
4.8% for calcium score > 400

70% of events in 25% of patients with highest calcium score

Raggi et al, Circulation 2000;101:850-855

What is the potential clinical role of coronary calcium detection?

In clinical practice, cleary low-risk and clearly high-risk individuals probably do not need further testing for risk stratification.

Intermediate risk patients, however, might profit:

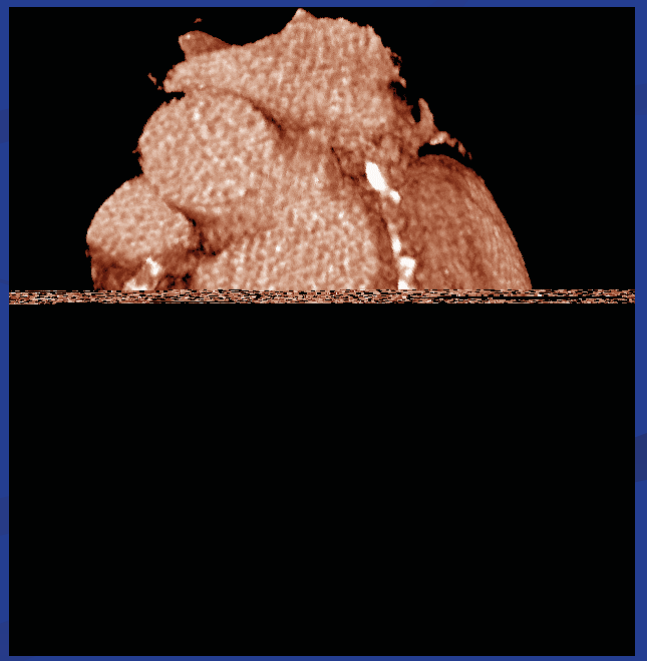
ACC/AHA: selected use of coronary calcium scores when a physician is faced with the patient with intermediate coronary artery disease risk may be appropriate

Role of EBCT in risk stratification?

Coronary calcium, even though it does not permit to detect the „*vulnerable plaque*“, permits to identify the patient with high plaque burden.

The detection of coronary calcium therefore permits identification of patients at increased risk for coronary artery events.

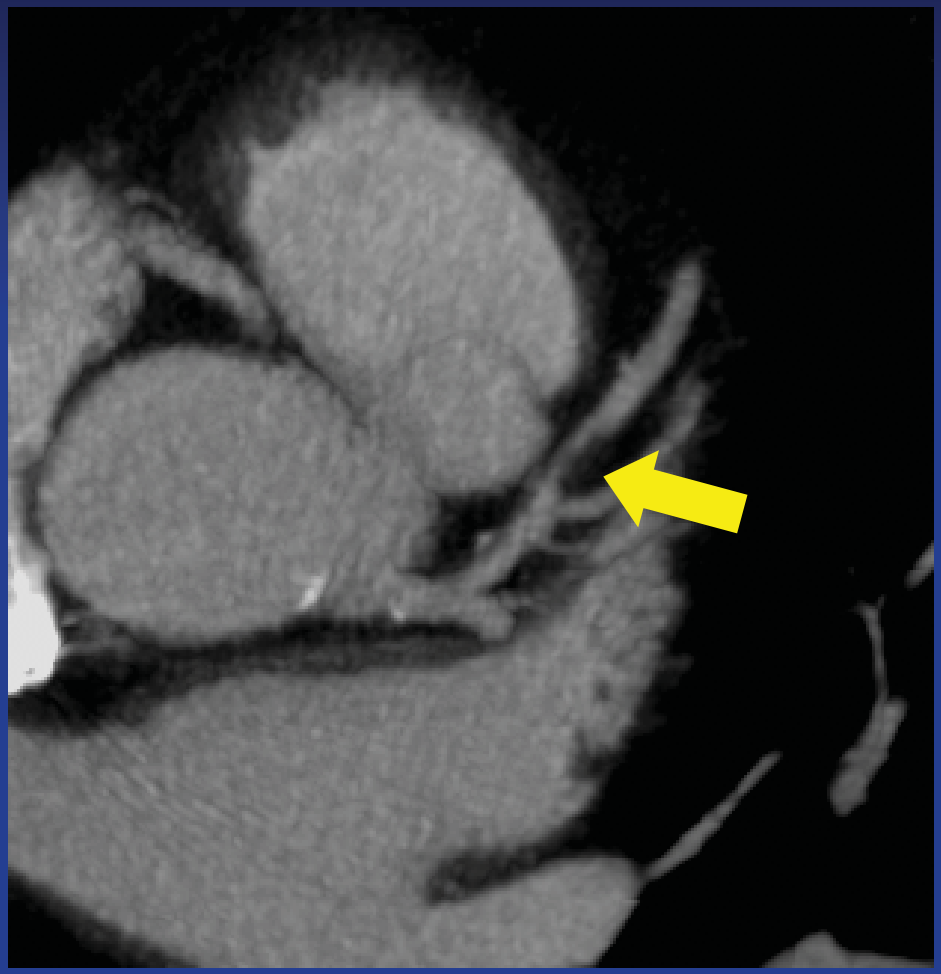
It may be beneficially applied in patients who seem to be at „intermediate“ risk.

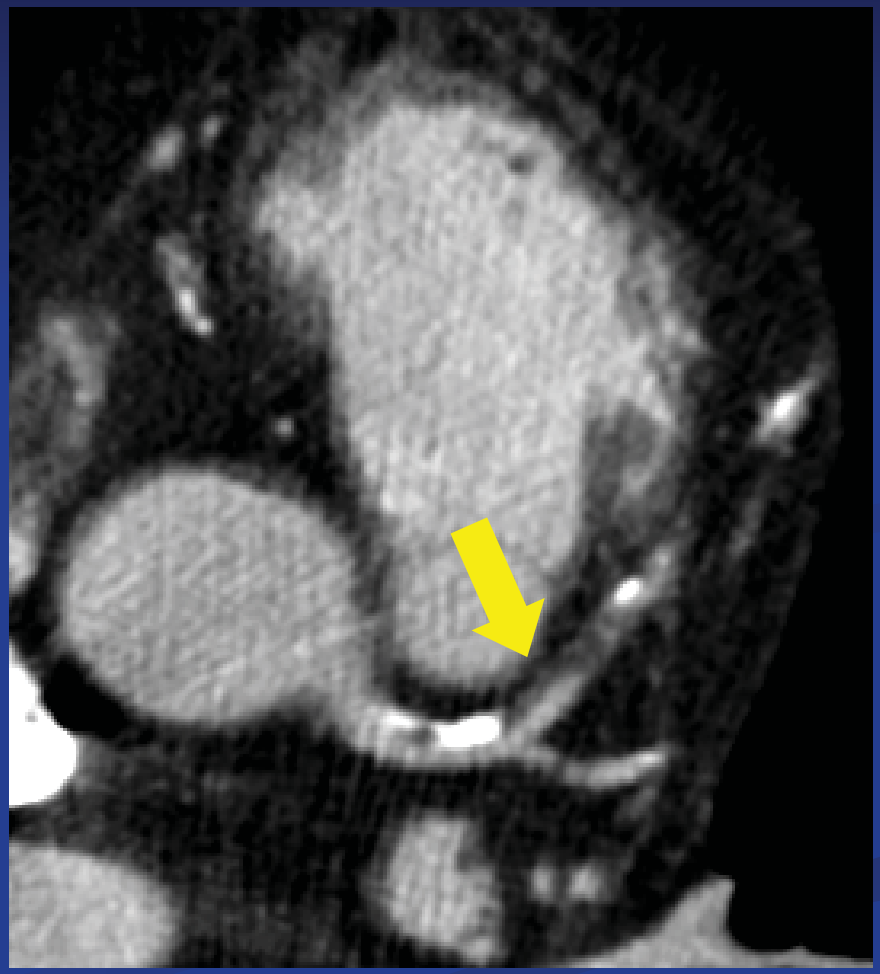


MSCT

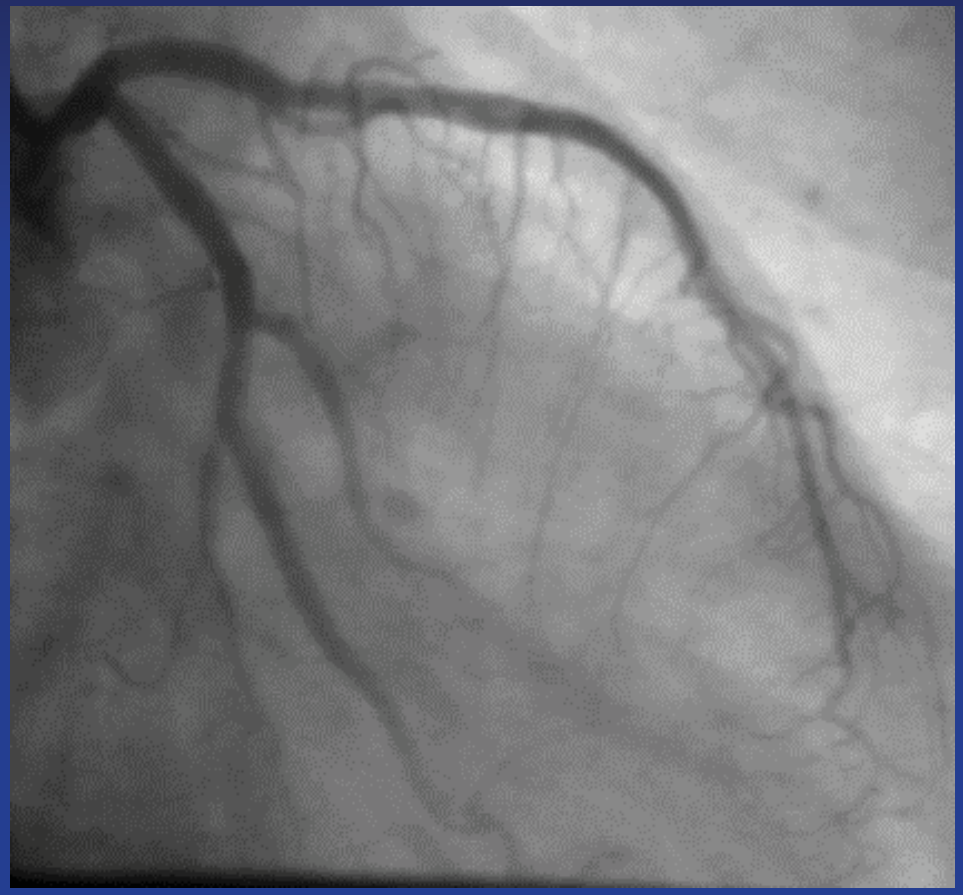
- **Detection of stenoses**
  - Calcium
  - Small vessels
- **Characterization of plaques**
  - Identify atheromas
  - Follow up under therapy
- **Acute coronary event**
  - Intracoronary thrombus
  - Myocardial infarction

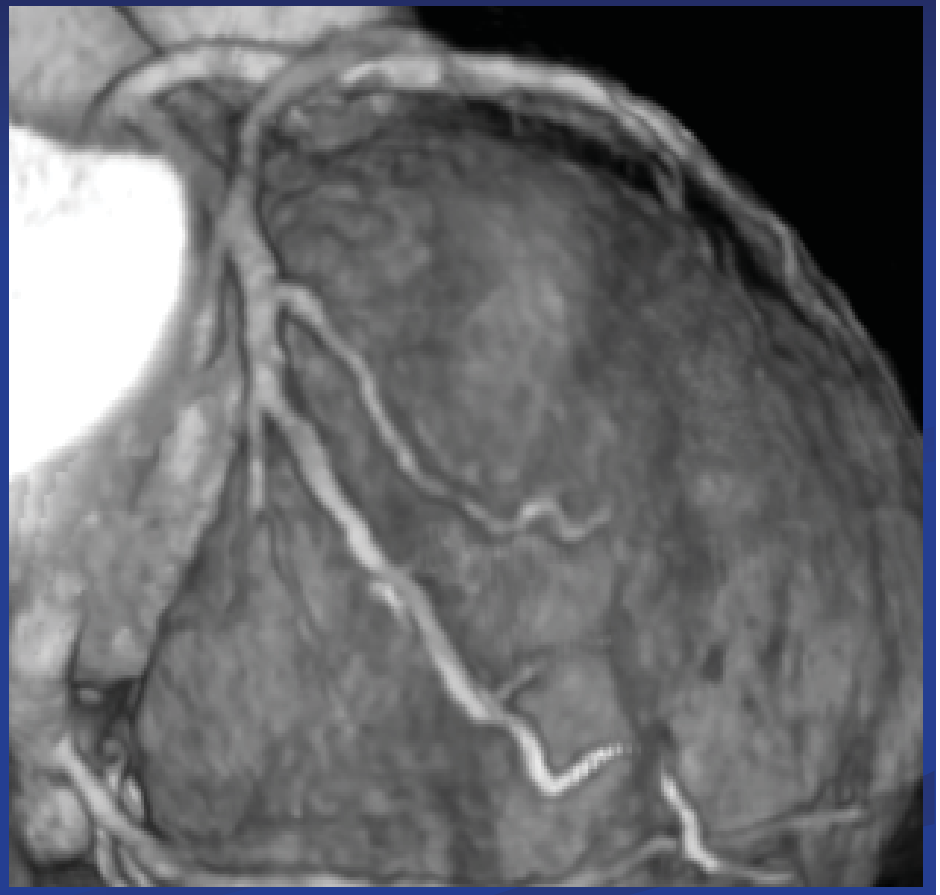
Non-calcified Plaque in MSCT:





Left Coronary Artery (RAO)

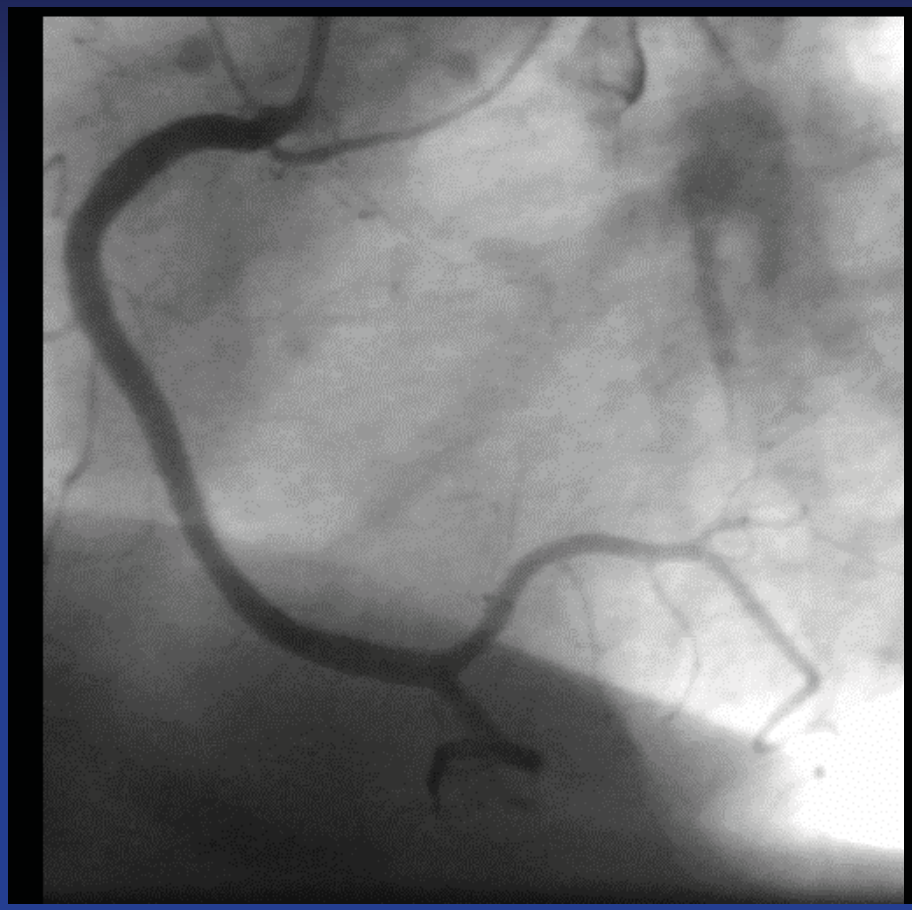


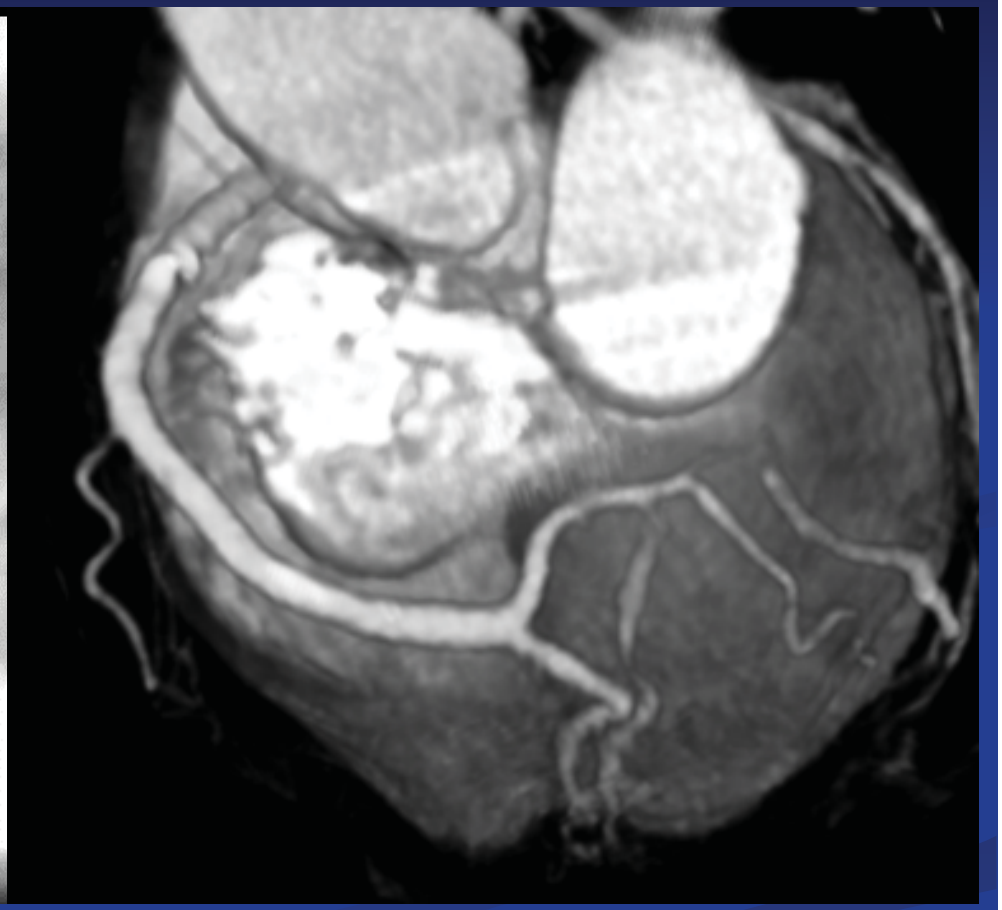


Coronary Angiography

MDCT & VRT

Right Coronary Artery (LAO)



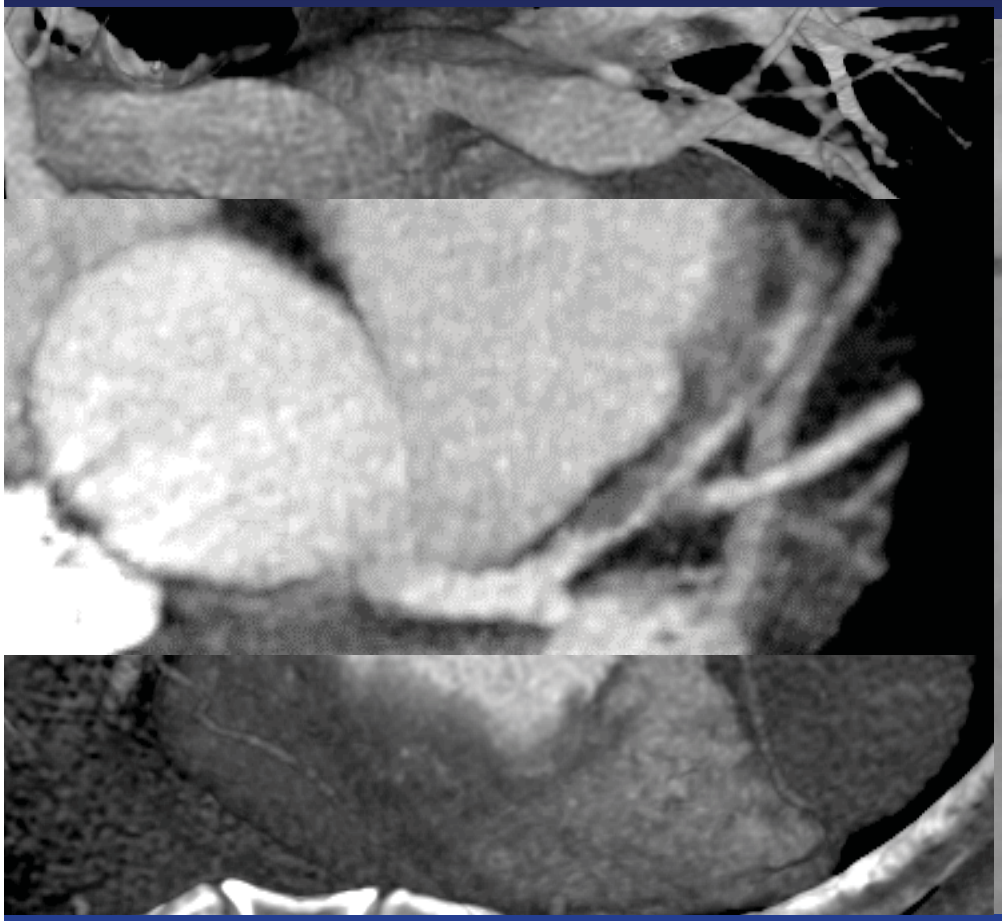


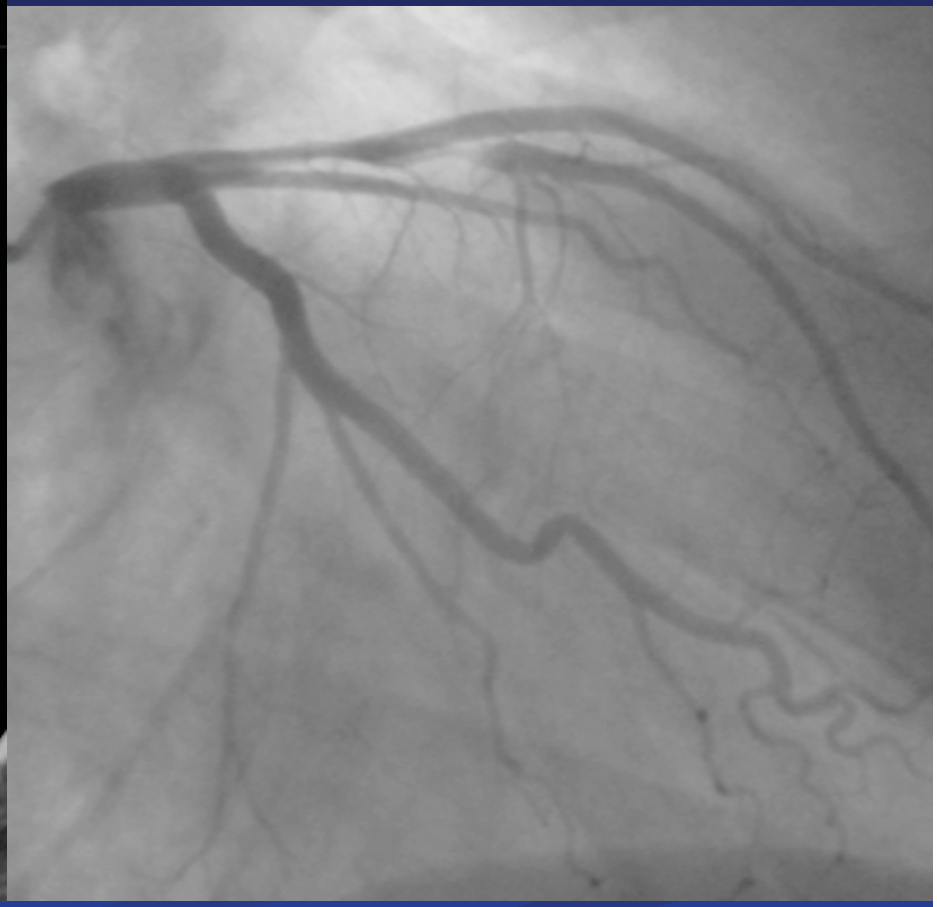
Coronary Angiography **MDCT & VRT**

Coronary Stenoses
CT Angio & Angiography

Author	Journal	PPV	NPV	n.a.	n
Niemann	Lancet 2001	81%	97%	30%	35
Achenbach	Circulation 2001	59%	98%	32%	64
Mean/sum		70%	98%	31%	99

Coronary Plaque Imaging

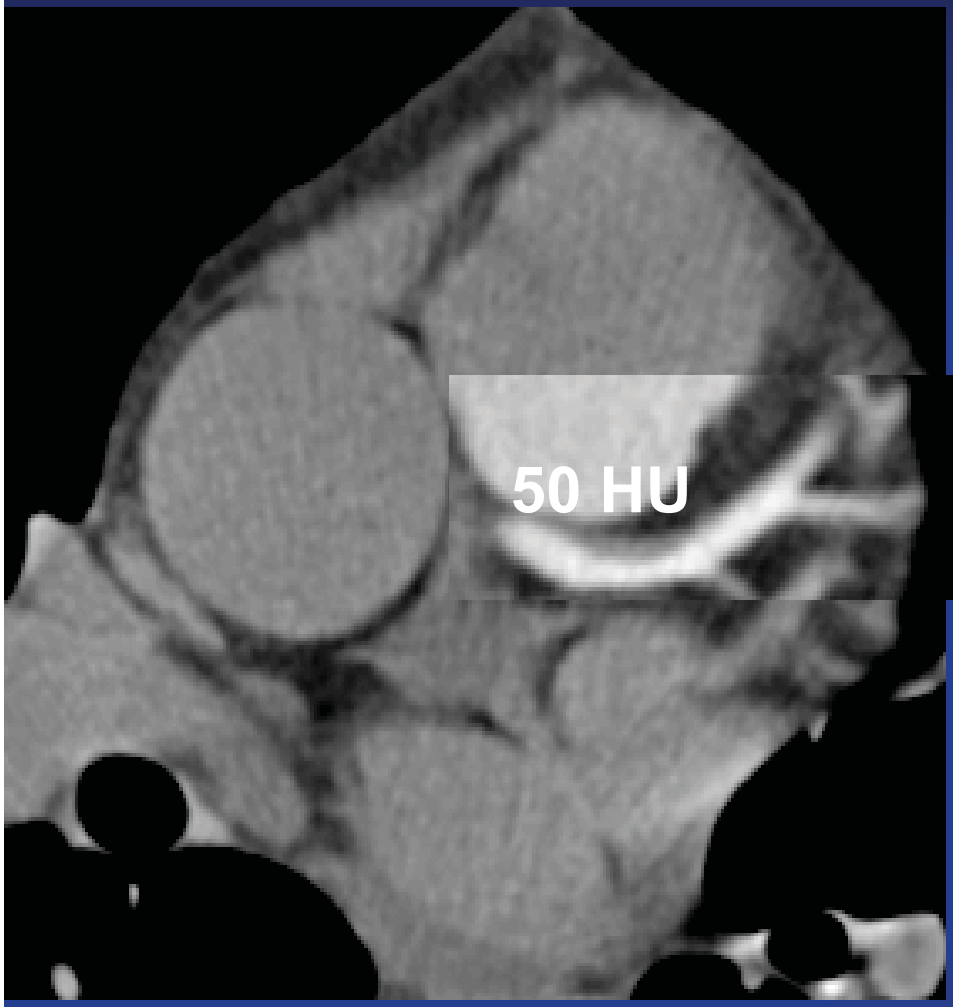


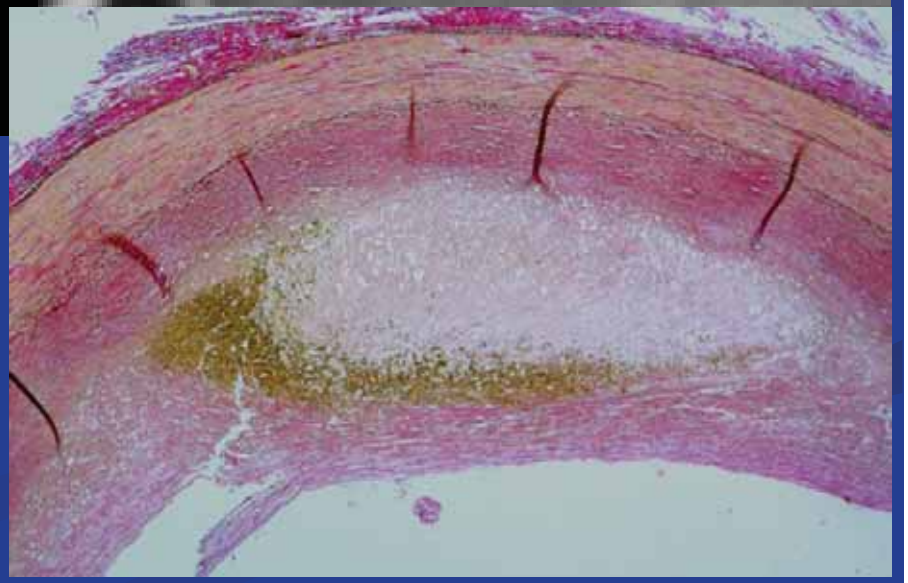


MDCT

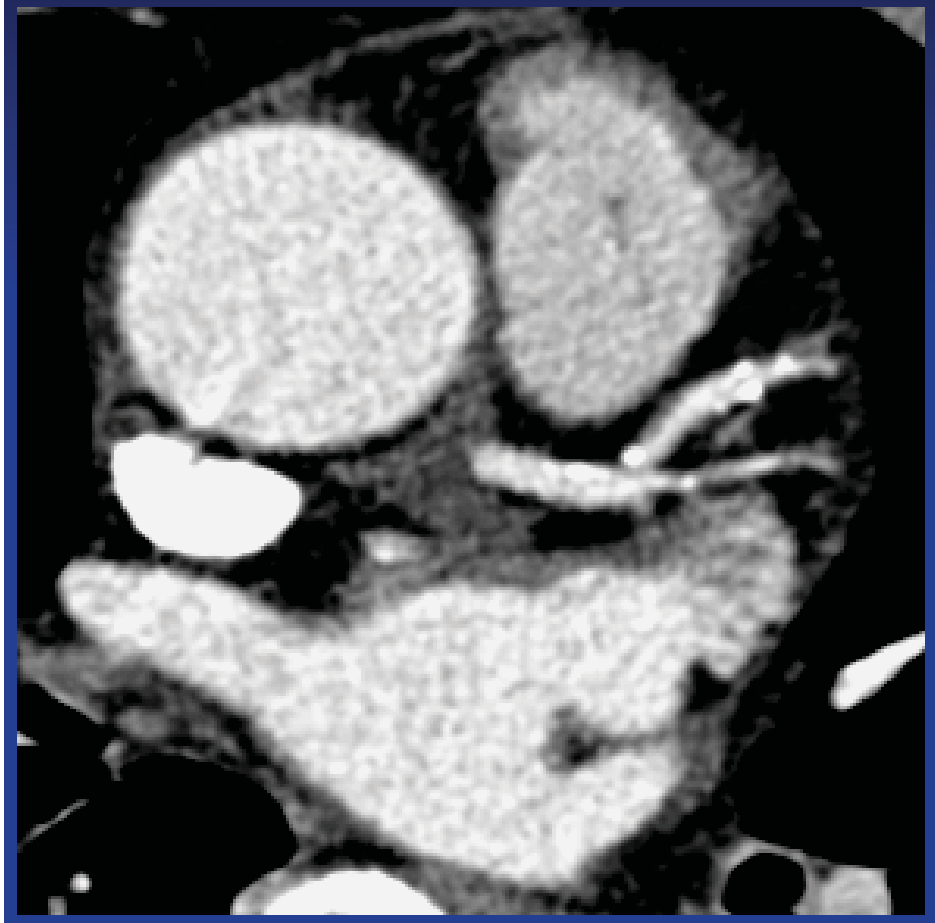
Coronary Angiography

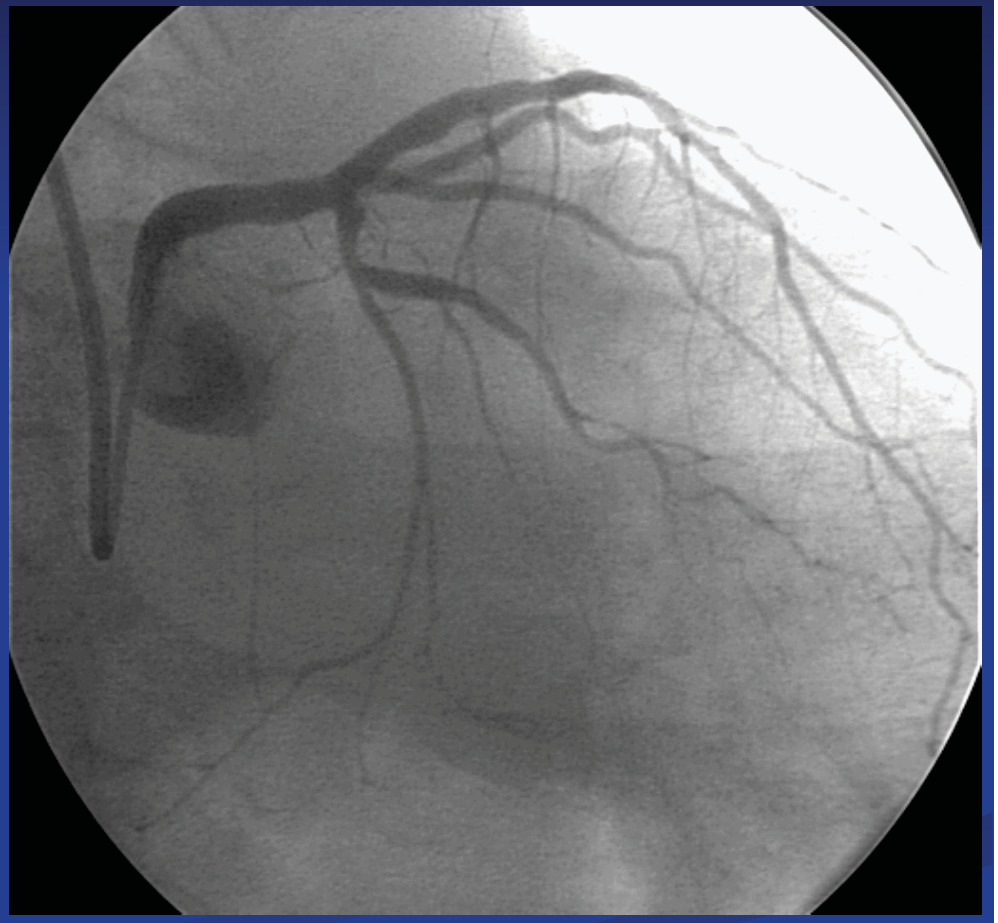
Atheroma





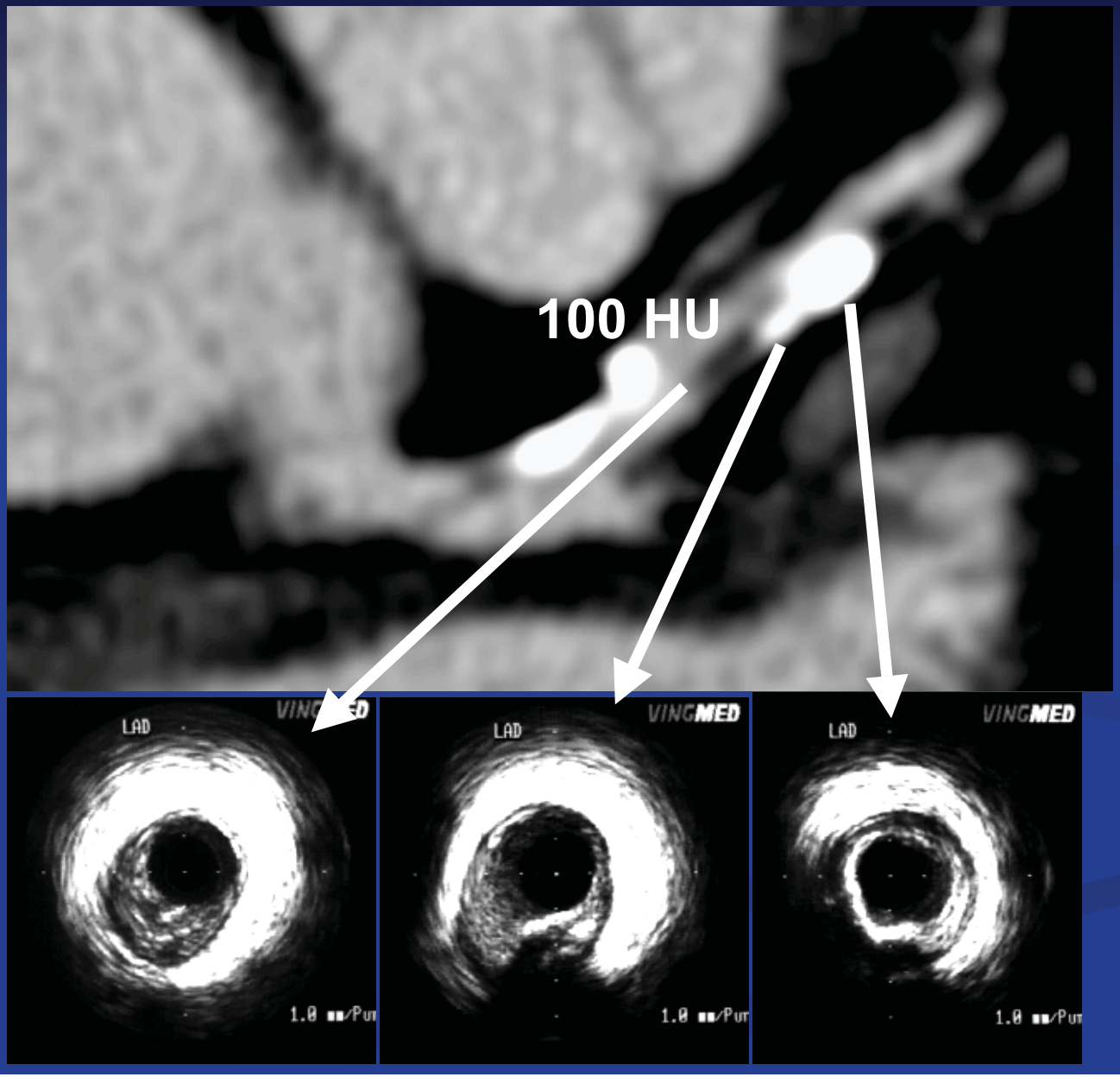
Calcified Nodule



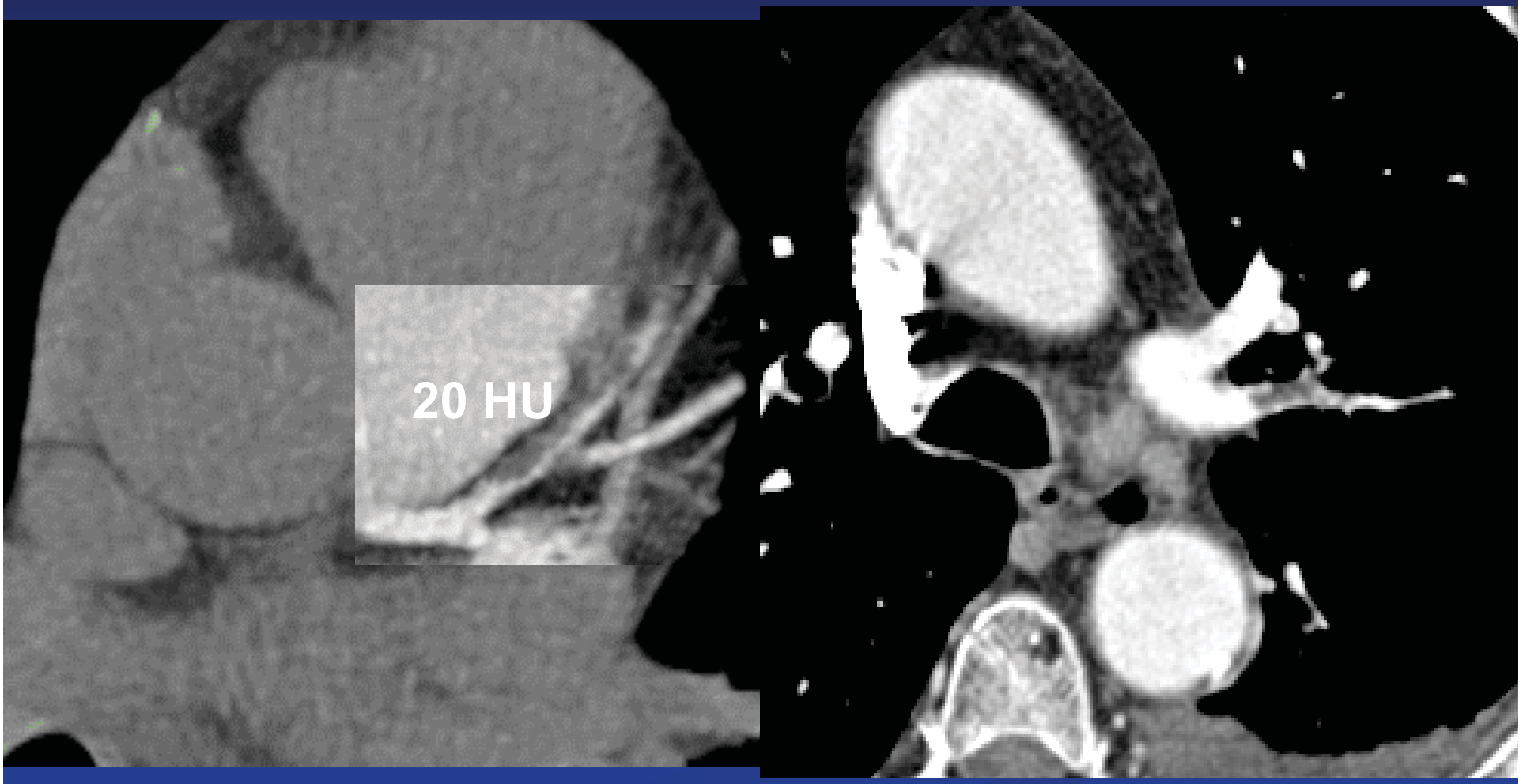


- 62 /M
- Suspicion of CAD

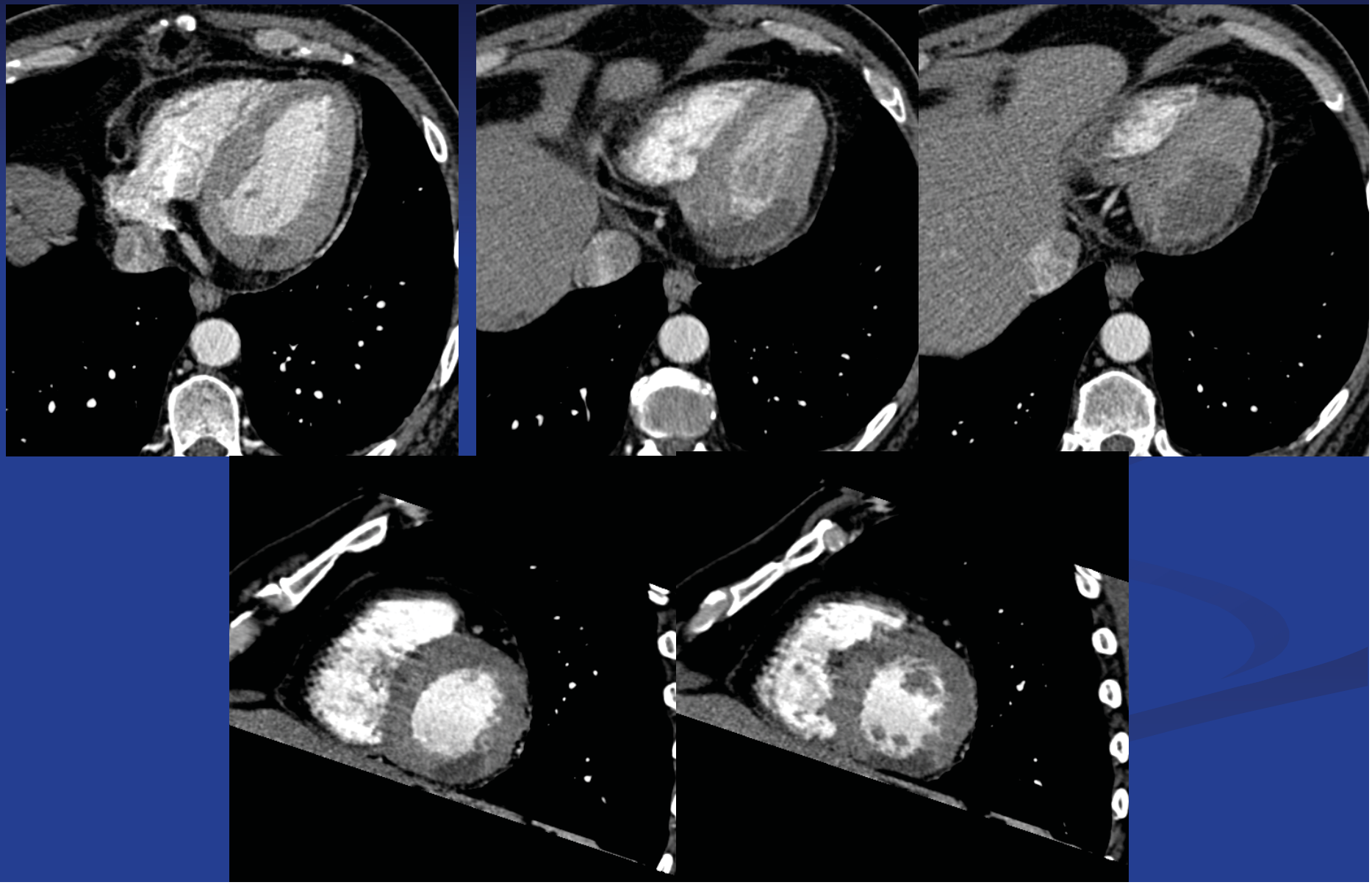
Fibrocalcified Plaque



Thrombus



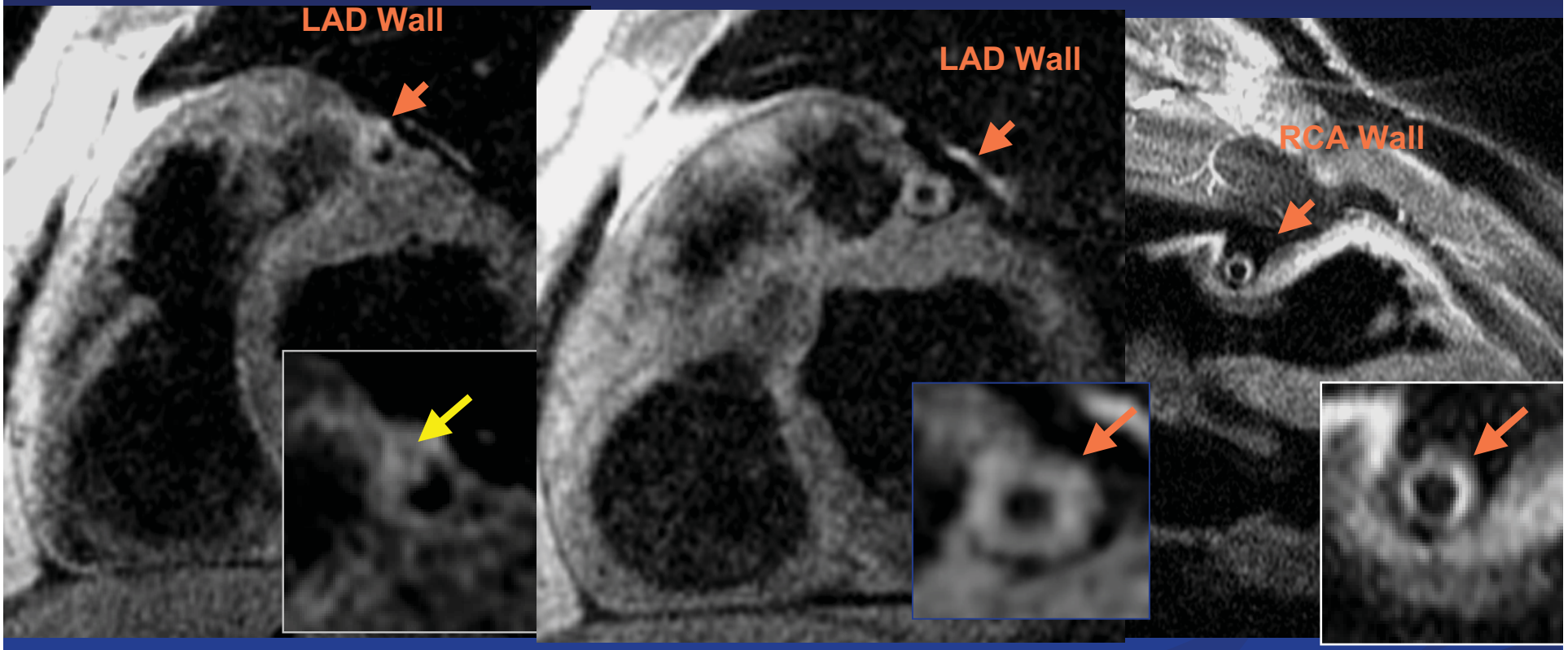
Acute Posterior Wall Infarction



Limitations of CT Angio

- **Artifacts**
  - Cardiac motion
  - Breathing
  - Blooming
- **Poor opacification**
- **Small vessel**

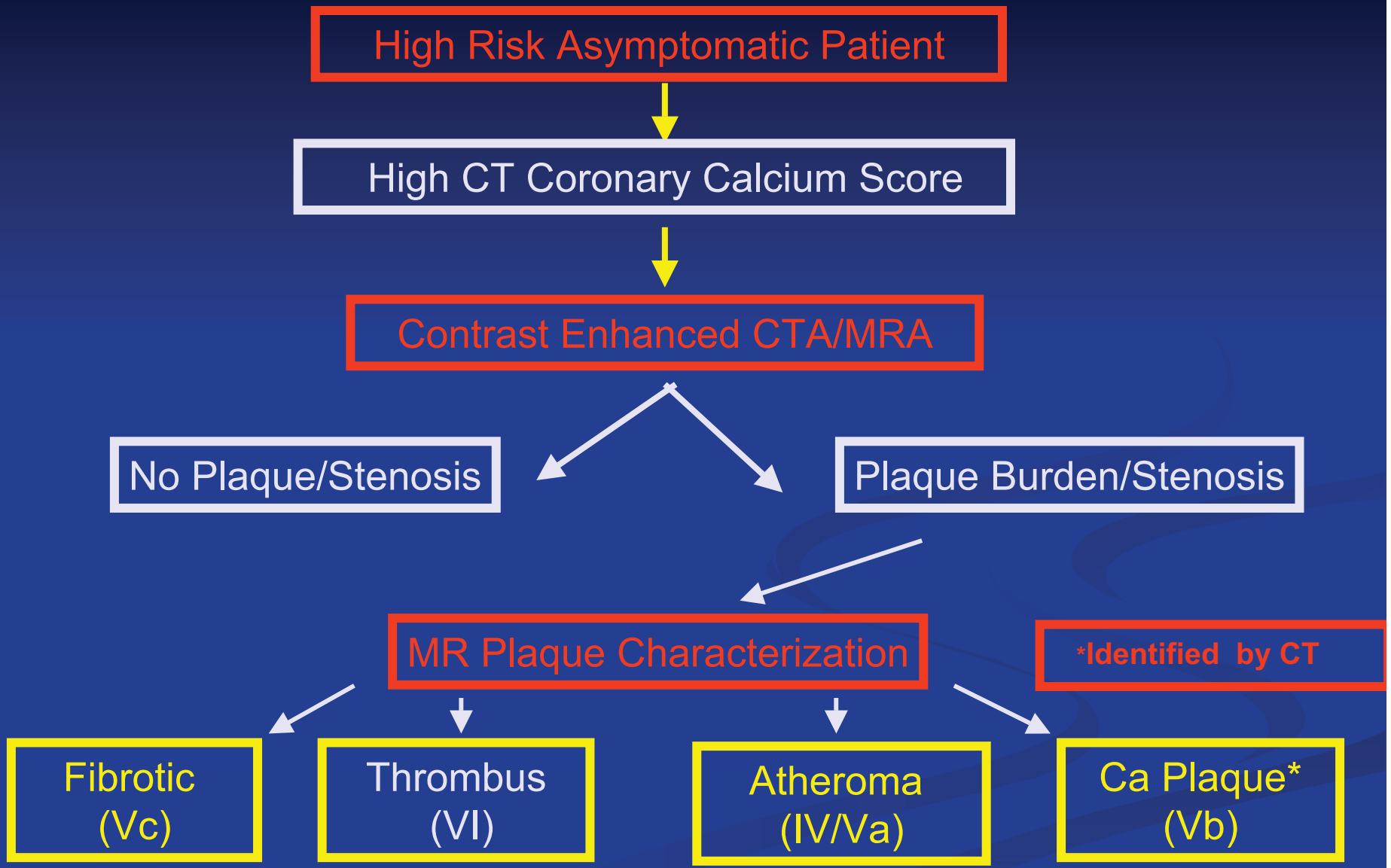
Black-Blood Coronary Plaque MR



Eccentric ("lipid-rich") *Concentric ("fibrotic")* *Ectatic ("remodeled")*

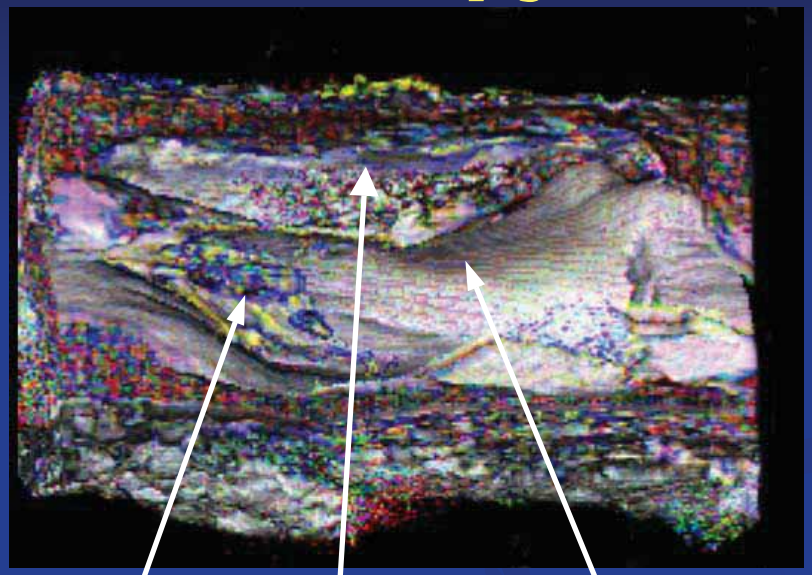
Fayad ZA, Fuster V et al. *Circulation. 2000;102;506-510*

Integration of CT and MRI



Fayad ZA, Fuster V, Nikolaou K, Becker C *Circulation*. 2002;106:2026

Characterization of Human Coronary Lesions by Magnetic Resonance Microscopy



3D images isotropic voxel 39 microns

Stabilization of Vulnerable Plaques

Short-Term Stabilization of Destabilized Plaques

Percutaneous intervention with stenting and GP IIb/IIIa inhibitors

Long-term antithrombotic+anticoagulant therapy

(ASA+Coumadin)

- APRICOT-2, ASPECT-2, WARIS-2

Long-term combined antithrombotic therapy

(ASA+Clopidogrel)

- CURE

High dose lipid lowering therapy

- MIRACL

Ambrose et al, Circulation 2002;105:2000

Long-Term Stabilization of Destabilized Plaques

Culprit lesion undergoing PCI:

Reducing restenosis

- Drug-eluting stents
- Brachytherapy
- Stents + GP IIb/IIIa inhibitors in diabetics

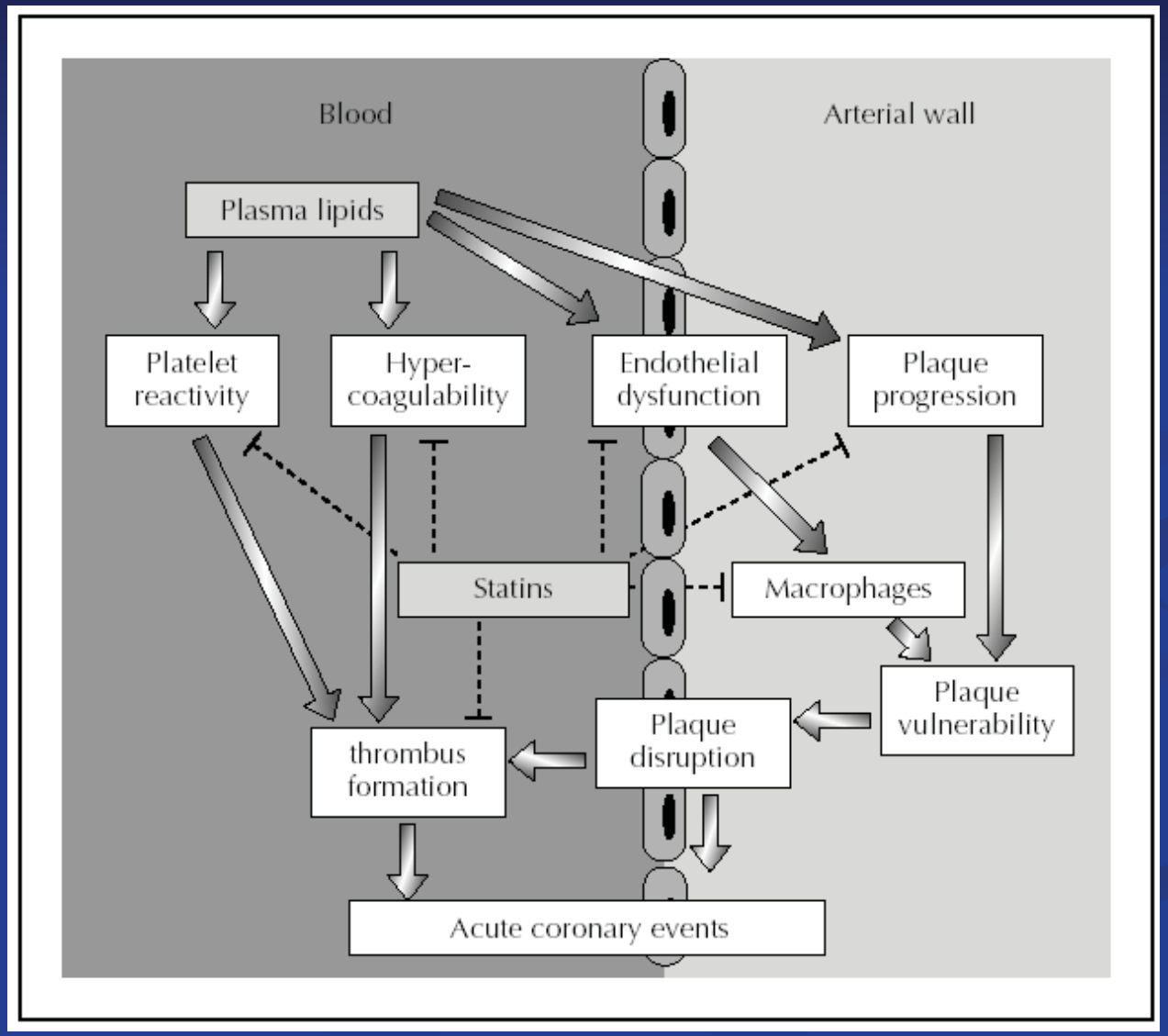
Non-PCI lesion

Reducing future acute events

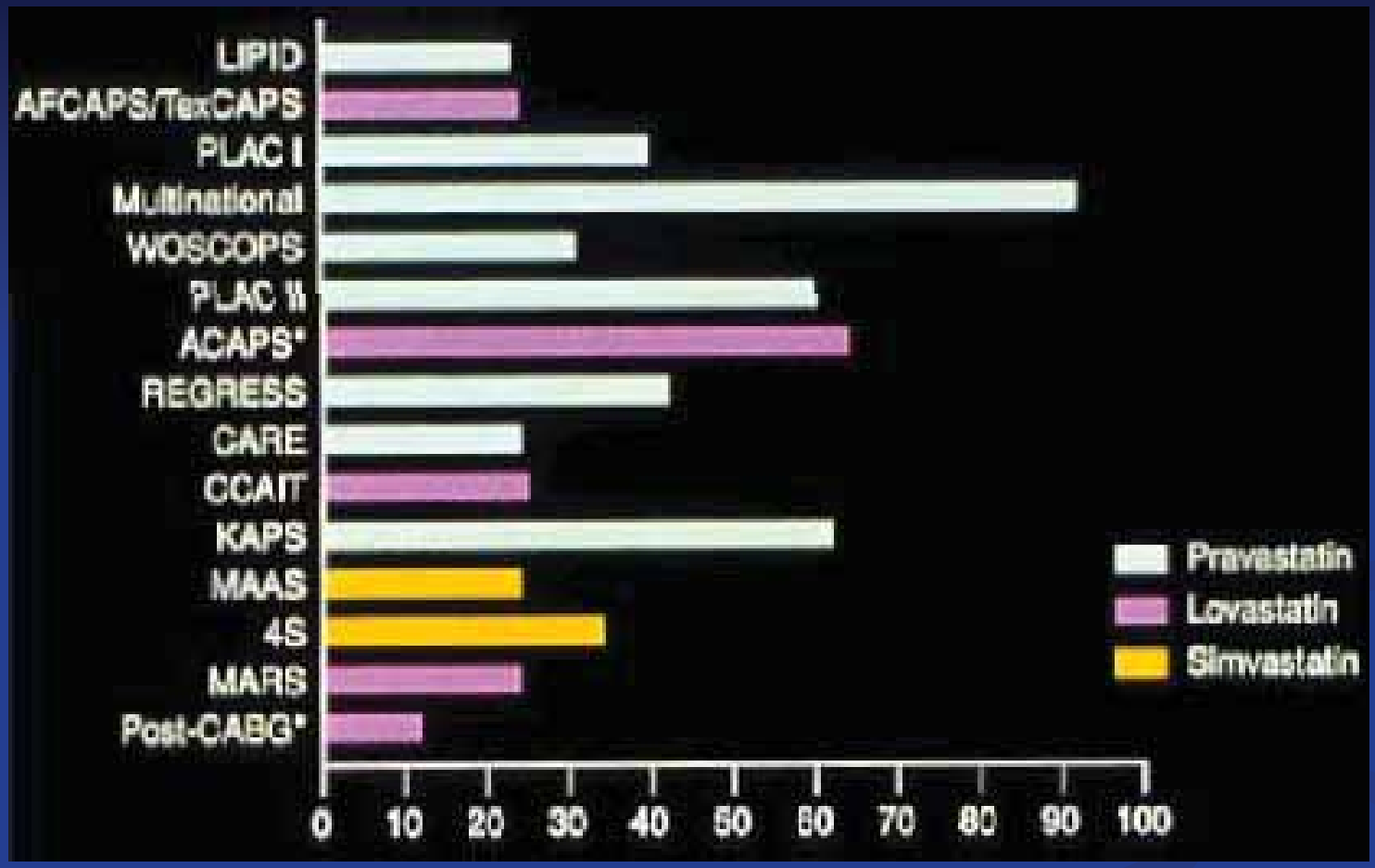
- Antithrombotics
- Lipid lowering agents
- ACE inhibitors
- β-blockers

Ambrose et al, Circulation 2002;105:2000

Potential Mechanisms of Action of Statin therapy



Effect of Statins on CHD Event Reduction



CHD event reduction (%)

Rosenson et al JAMA 1998;279:1643-50

Summary of the Results of the 15 Published Angiographic Lipid Lowering Trials

In control population

- <10% of patients showed lesion regression
- >50% of patients showed lesion progression
- Average estimates of disease severity per patient progressed by ~ 3%

In treated population

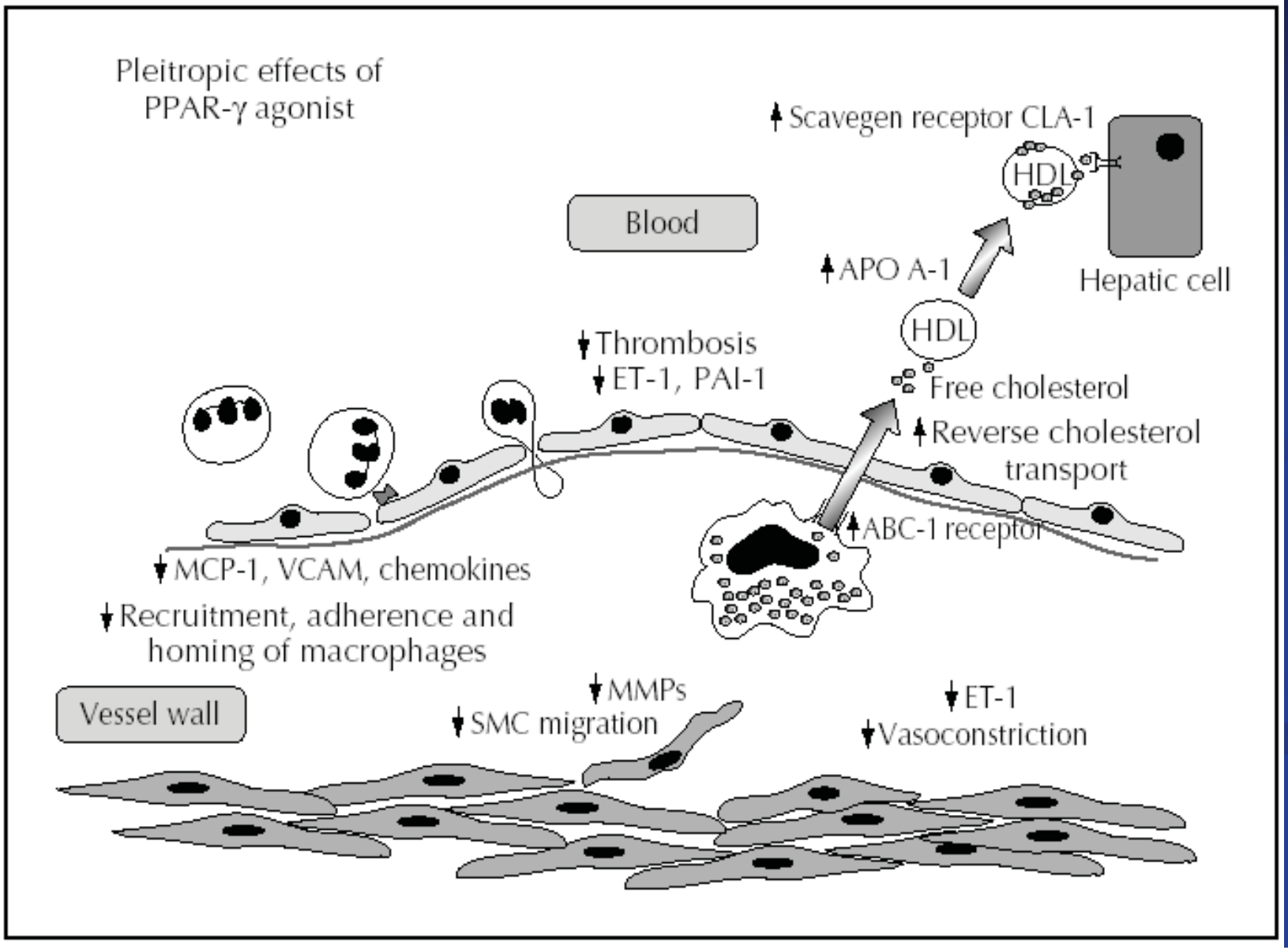
- ~25% of patients regressed
- ~25% of patients progressed
- Average estimates of disease severity per patient regressed by ~1%

Lipid Lowering Angiographic Trials-Reduction in CV Events

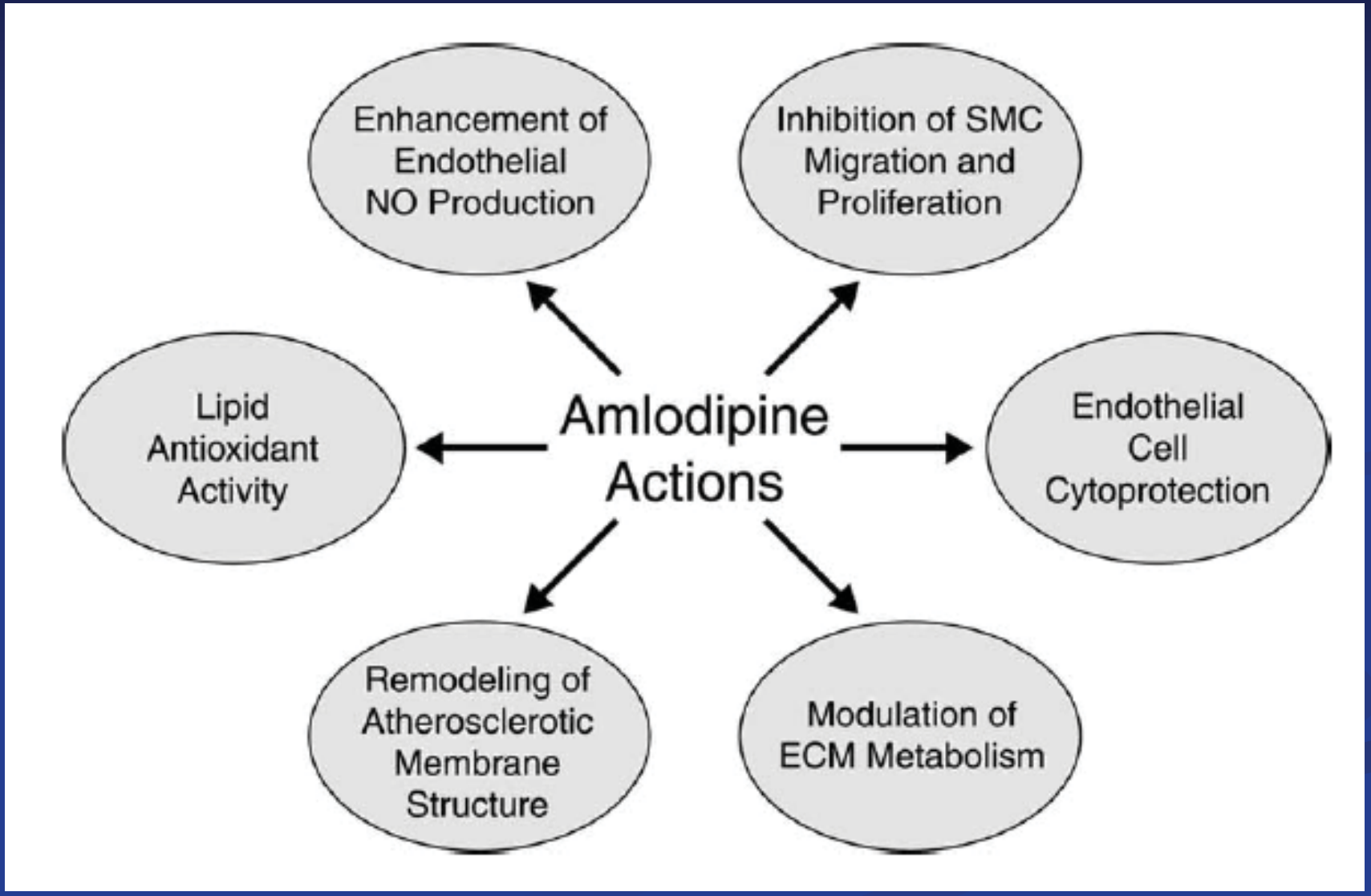
NHLBI, CLAS, POSCH, FATS, SCOR, STARS, SCRIP, HARP, MARS, CCAIT, MAAS, REGRESS, HEIDELBERG, PLACI

	Reference	Treated	Relative Risk	95% CI
All Cardiac Events	602/2106 (28.1%)	417/2173 (19.2%)	0.69	0.62-0.76
Cardiac Mort/Non-fatal MI	231/1982 (11.7%)	151/2049 (7.4%)	0.64	0.53-0.78

Peroxisomal Proliferator-Activated Receptors (PPARs) Agonists



Potential Antiatherosclerotic Mechanisms of Action for Amlodipine



Mason RP, et al Atherosclerosis 2002;165:191–199

Future Pharmacologic Stabilization of Vulnerable Plaque?

- Antioxidants
- Antibiotics
- Angiogenesis inhibitors
- MMP inhibitors
- Apo A1 Milano, HDL
- TF inhibitors
- Cytokines antagonists (selectins, ICAM, VCAM, NFkB, MCP-1, PDGF)
- Antibodies to CD40 ligand
- Cap strengthening (TGF-beta, antibody to IFN-gamma)
- Anti-inflammatory agents

Conclusion

(1) The concept of plaque stabilization should be expanded to include treatment for plaques that have already destabilized as well as preventing future destabilization in quiescent plaques.

(2) For the destabilized plaque, percutaneous intervention is an effective method of short-term stabilization in selected cases. As an alternative, new randomized trials with either long-term aspirin therapy in combination with coumadin, the combination of aspirin and clopidogrel, or high-dose lipid-lowering therapy will reduce subsequent coronary events potentially through plaque-stabilizing effects. Short-term powerful antithrombotic agents alone such as GP IIb/IIIa inhibitors in this setting do not appear effective in reducing events on follow-up.

Conclusion

(3) ACE inhibitors and ß-blockers in addition to lipid-lowering agents potentially possess plaque-stabilizing properties that contribute to their beneficial effects on reducing subsequent events. Aspirin reduces future events by its antiplatelet effects and possibly through an antiinflammatory mechanism.

The End