Invasive Diagnostic

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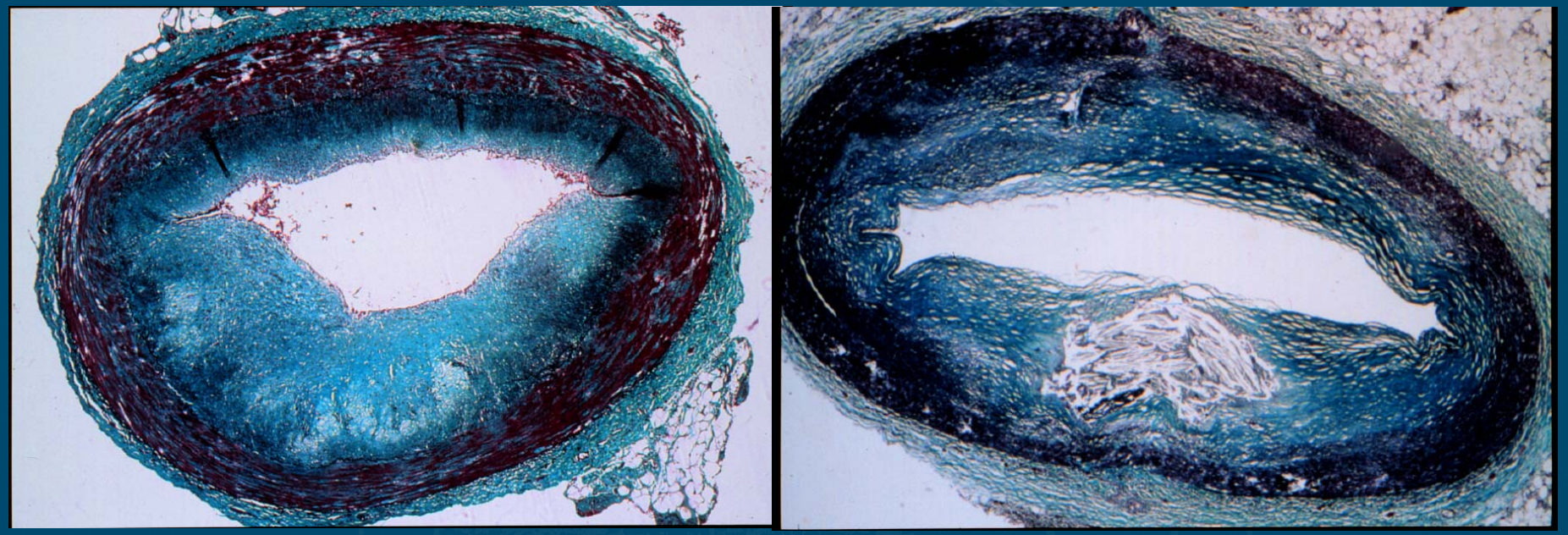
Angioplasty Summit 2008

Stable vs Vulnerable Plaque



Stable Plaque

- Low lipid conc.
- Thick fibrous cap
- Low mΦ density

Vulnerable Plaque

- High lipid conc.
- Thin fibrous cap
- High mΦ density

Current Technology for VP Identification

Non invasive

- CTA
- MR

Invasive

- Anatomic
- Physiologic

Intravascular Modalities

- IVUS
- Angioscopy
- IV MR
- OCT

Anatomic Information

- Thermography
- Spectroscopy

Biochemical Information

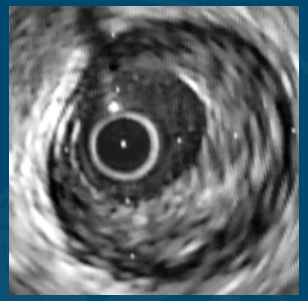
Intravascular Modalities

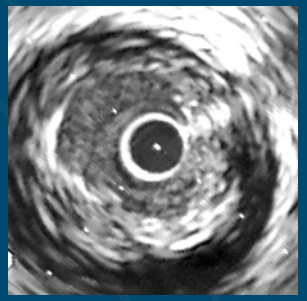
- IVUS
- Angioscopy
- IV MR
- OCT

- Thermography
- Spectroscopy

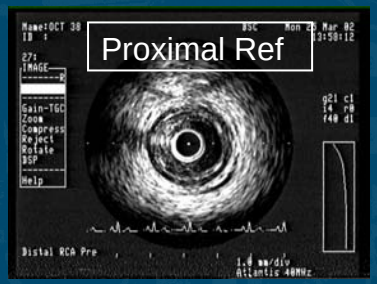
IVUS

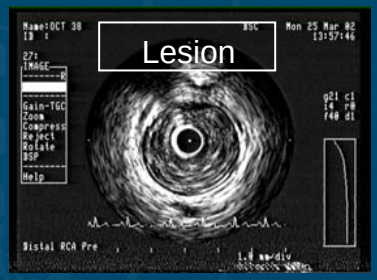
- Echolucency



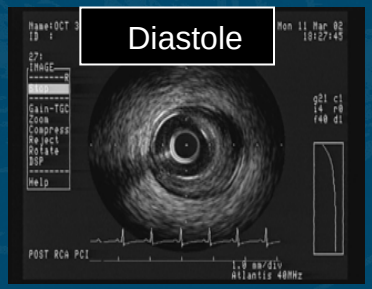


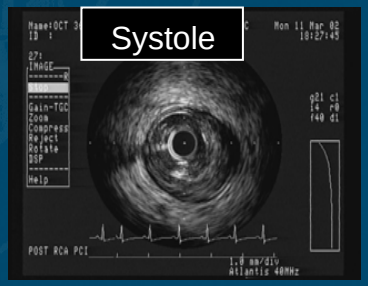
- Remodeling





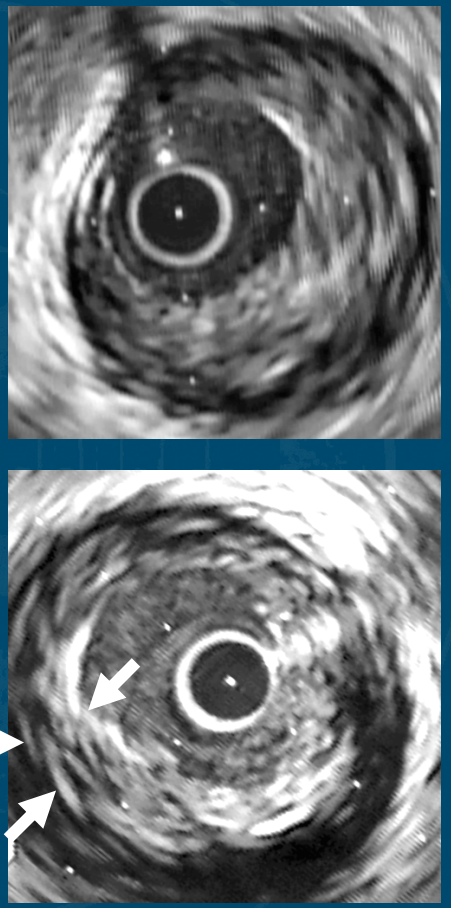
- Distensibility



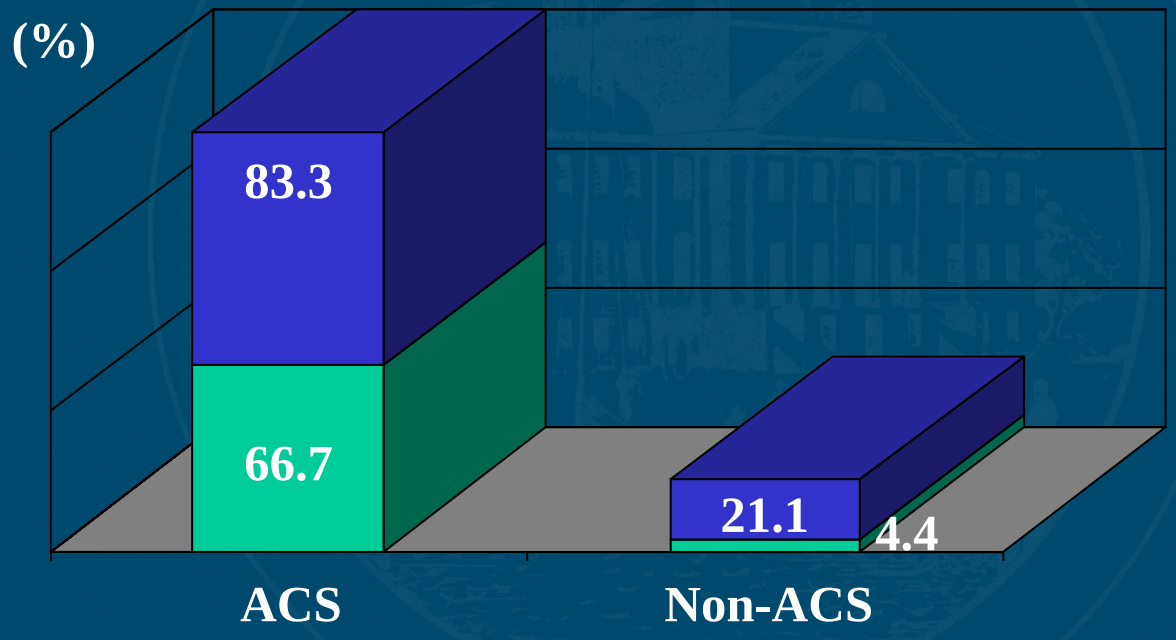


IVUS

- **Echolucency**
- **Remodeling**
- **Distensibility**

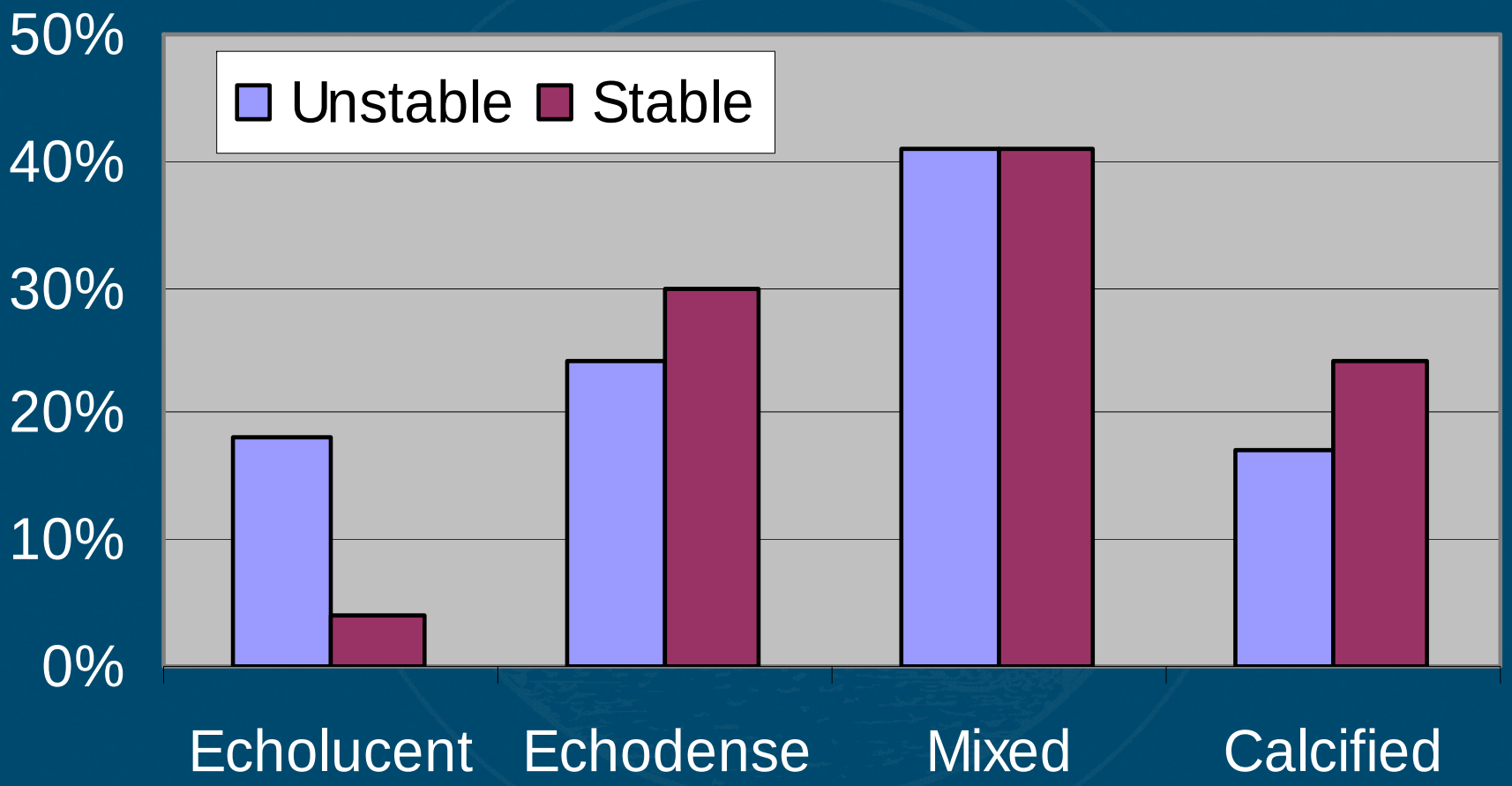


Prevalence of Echolucent Area on IVUS



Yamagishi et al. JACC 2000

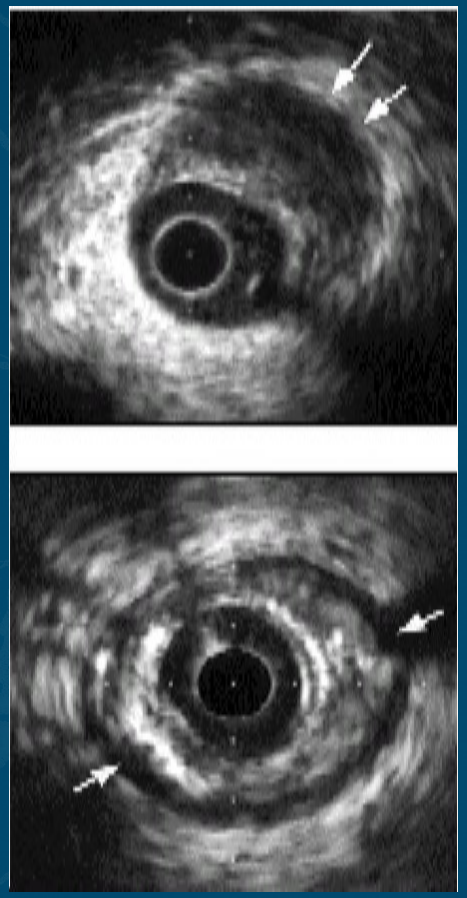
Echolucent Area: Unstable vs stable angina



Schoenhagen et al. Circulation 2000

Echolucency

- Previous histological studies have demonstrated that the discrimination of lipid is inconsistent using greyscale images alone.
  - Palmer *et al.* Eur Heart J., 1999
  - Peters *et al.* J Am Soc Echocardiogr., 1994
  - Peters *et al.* Circulation, 1994

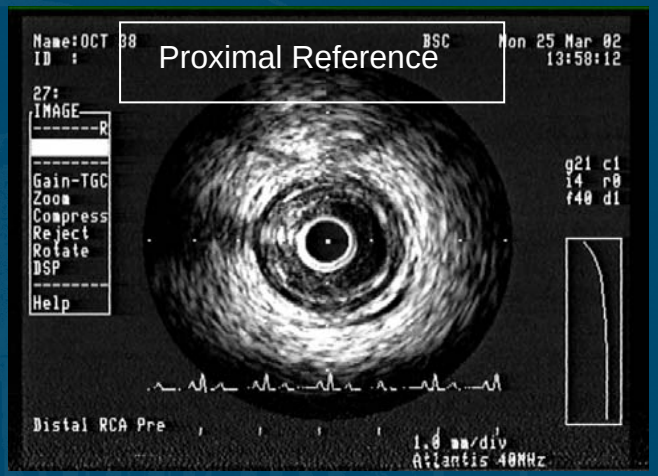


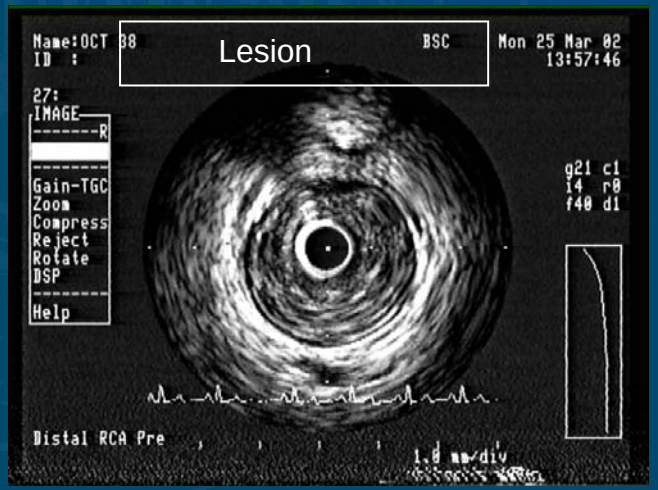
IVUS vs OCT (n = 145)

	Sensitivity (%)	Specificity (%)	PPV (%)
Deep lipid	17.9	97.0	95
Superficial lipid	6.3	97.0	88
1 quadrant lipid	22.7	93.9	93
2 quadrant lipid	1.8	100.0	100

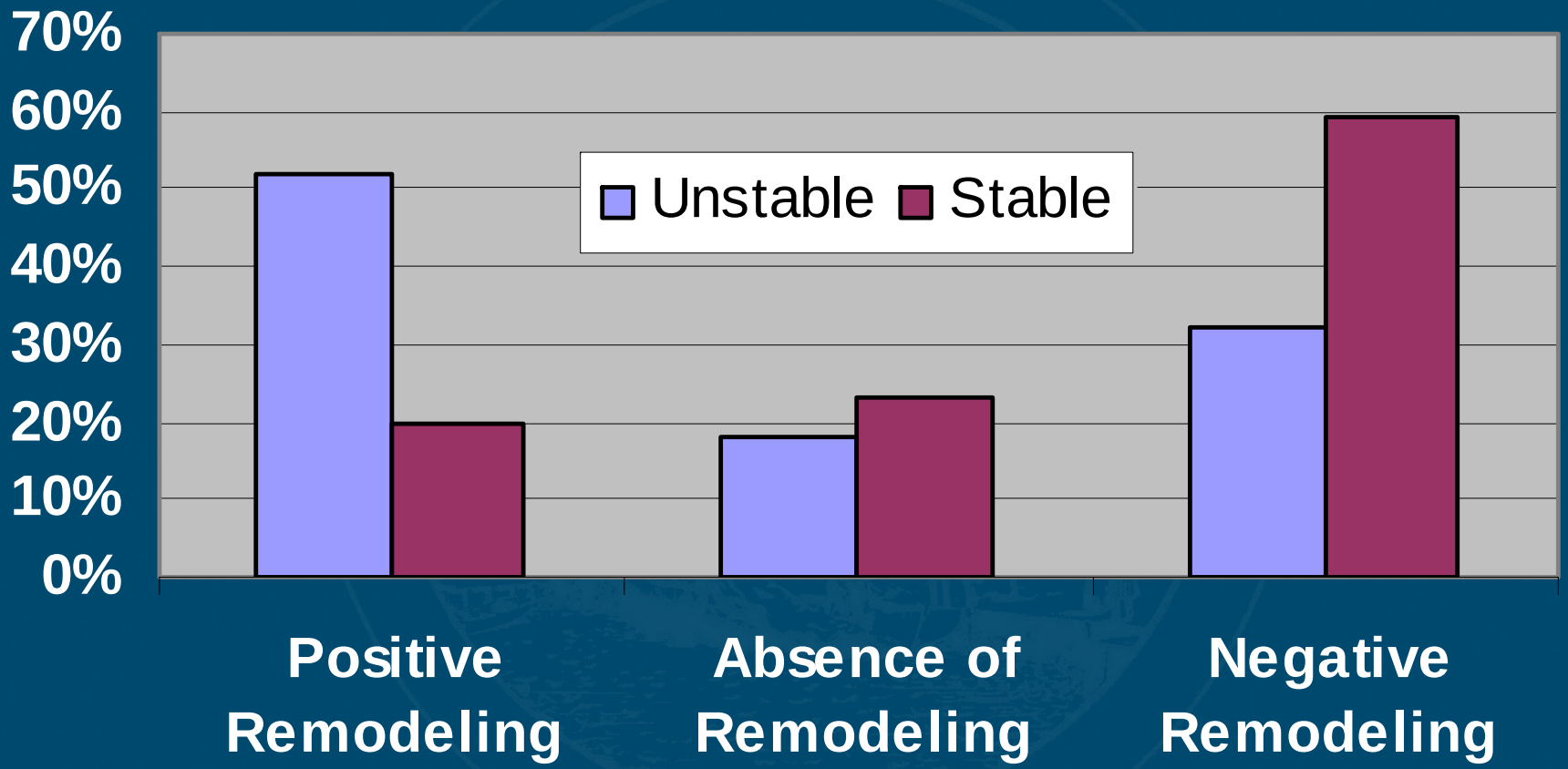
IVUS

- Echolucency
- Remodeling
- Distensibility





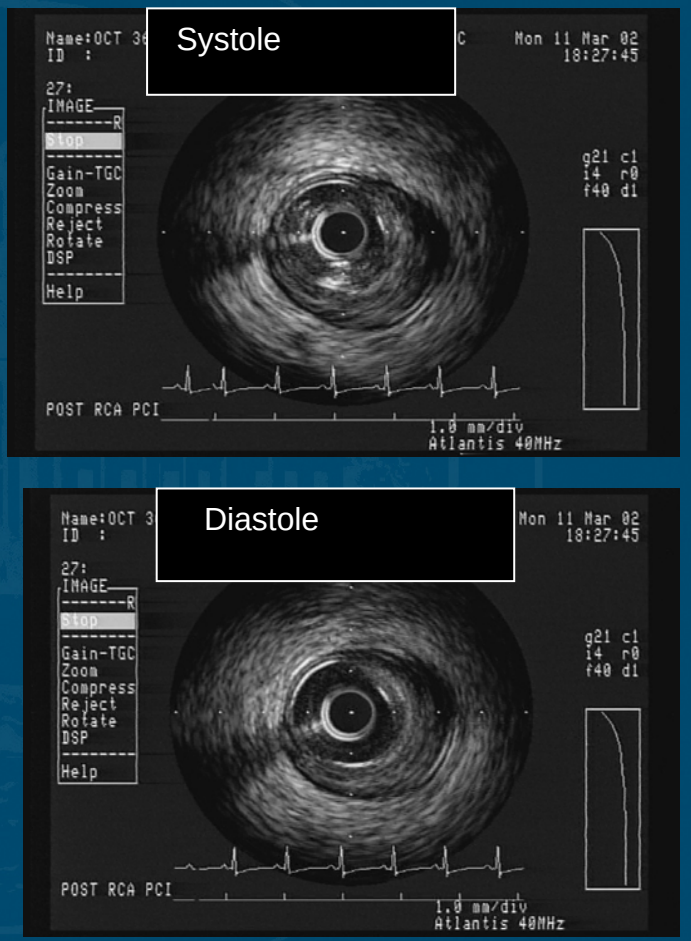
Vascular remodeling: Unstable vs stable angina



Schoenhagen et al. Circulation 2000

IVUS

- **Echolucency**
- **Remodeling**
- **Distensibility**

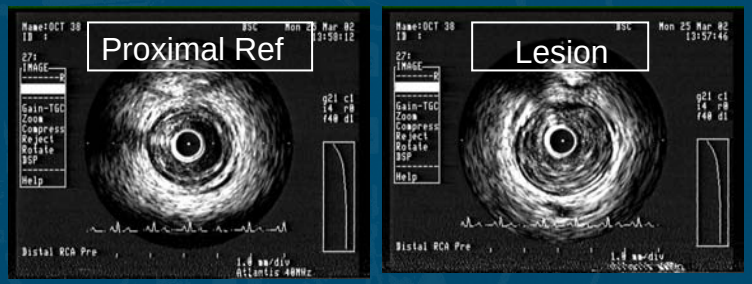


Arterial Distensibility Results

	Lipid Rich	Mixed	Fibrous	P
Number	7	6	16	
EEM CSA (mm^2)	16.1 ± 7.2	16.9 ± 4.6	17.1 ± 0.4	NS
Lumen CSA (mm^2)	7.2 ± 1.4	8.5 ± 3.6	8.5 ± 0.4	NS
Plaque Volume (mm^2)	8.9 ± 5.2	8.4 ± 3.5	8.6 ± 2.9	NS
Distensibility Index ($mmHg^{-1}$)	2.8 ± 1.8	1.7 ± 0.9	1.0 ± 0.8	0.004

IVUS

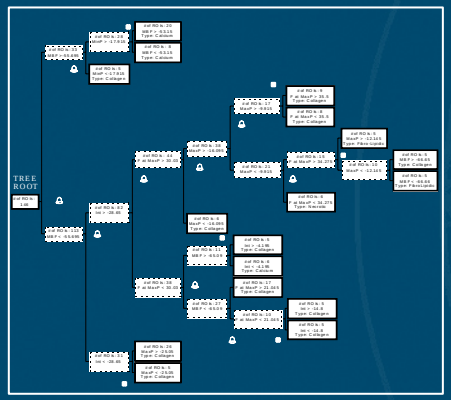
- **Echolucency** → **Virtual Histology**
- **Remodeling (Plaque volume)**



- **Distensibility** → **Palpography**

Virtual Histology™ IVUS

Classification Tree



VH Legend

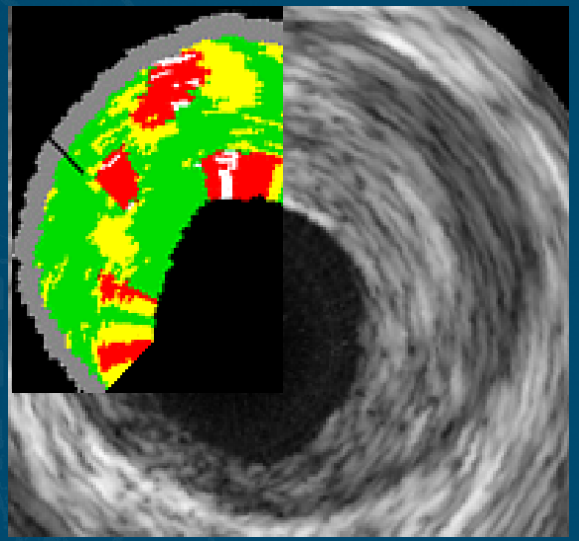
MEDIA

FIBROUS

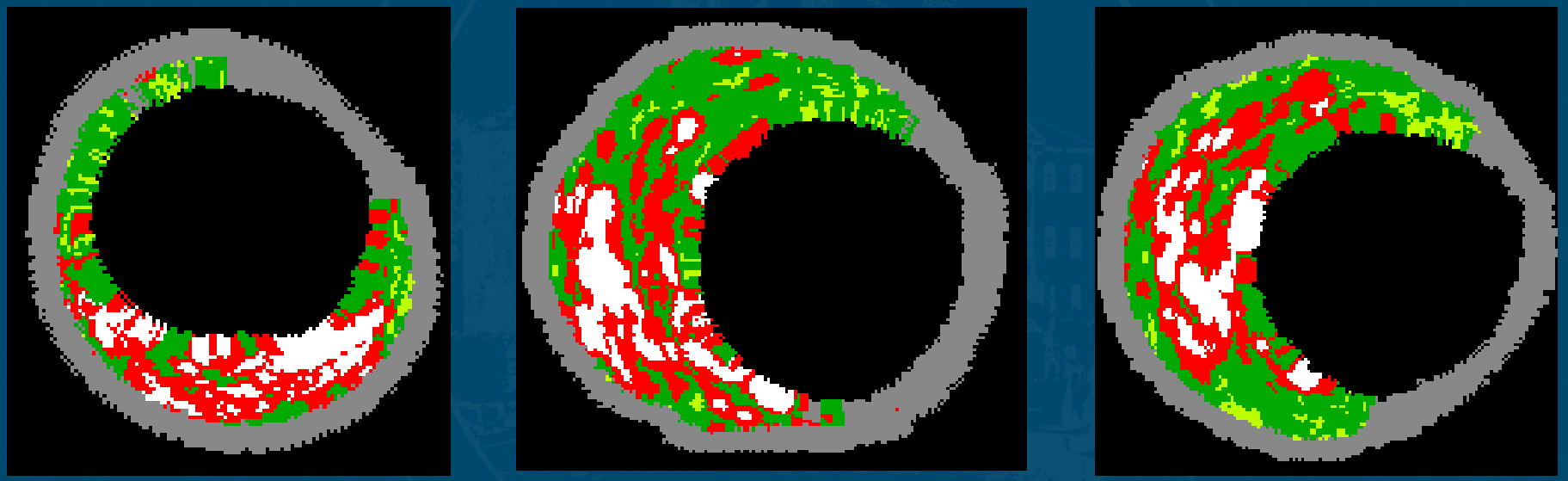
FIBROLIPIDIC

CALCIUM

LIPID CORE

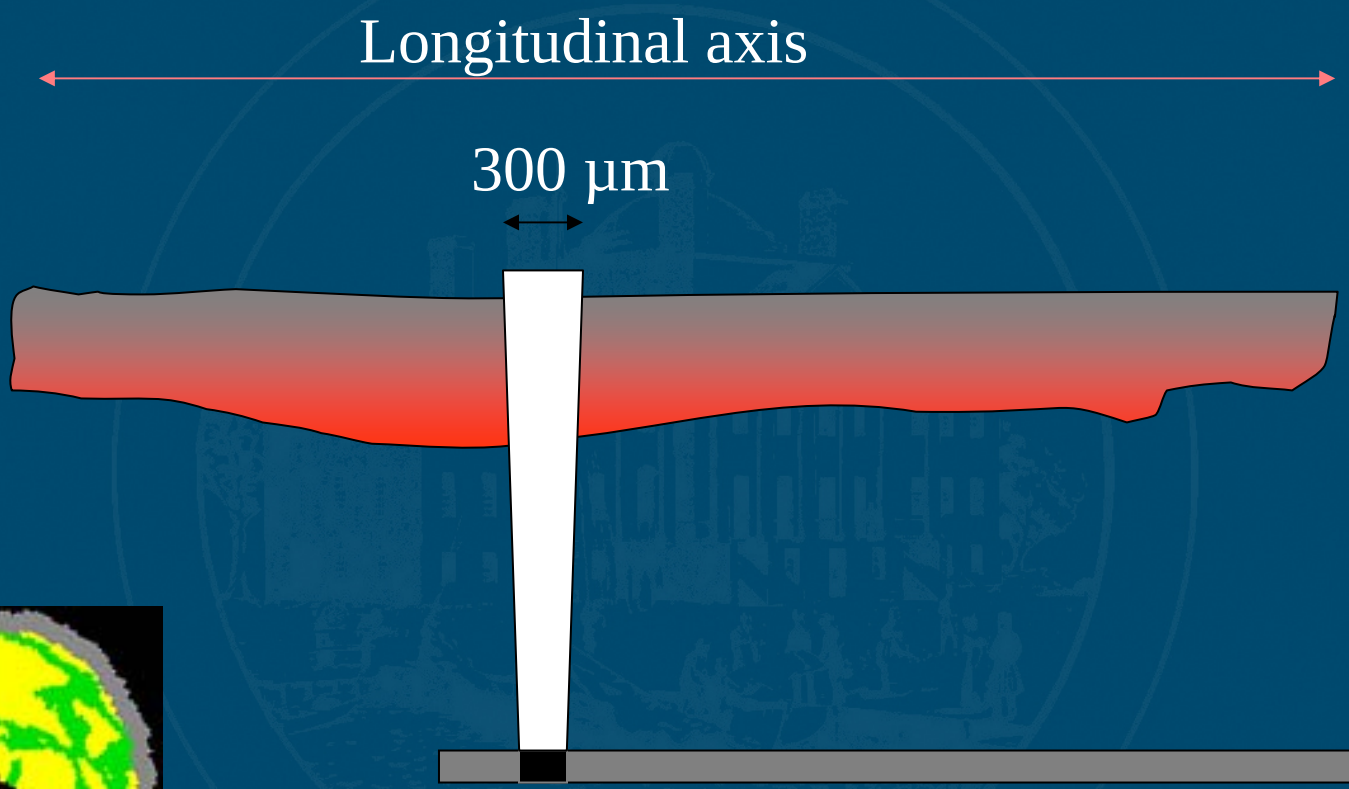


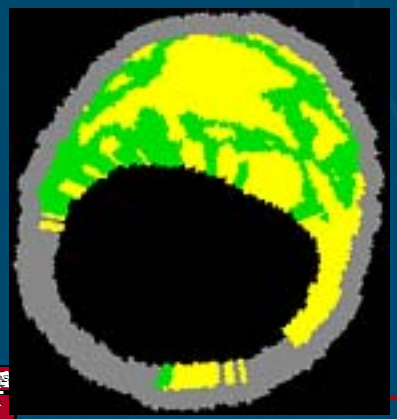
THIS IS THE PROBLEM !



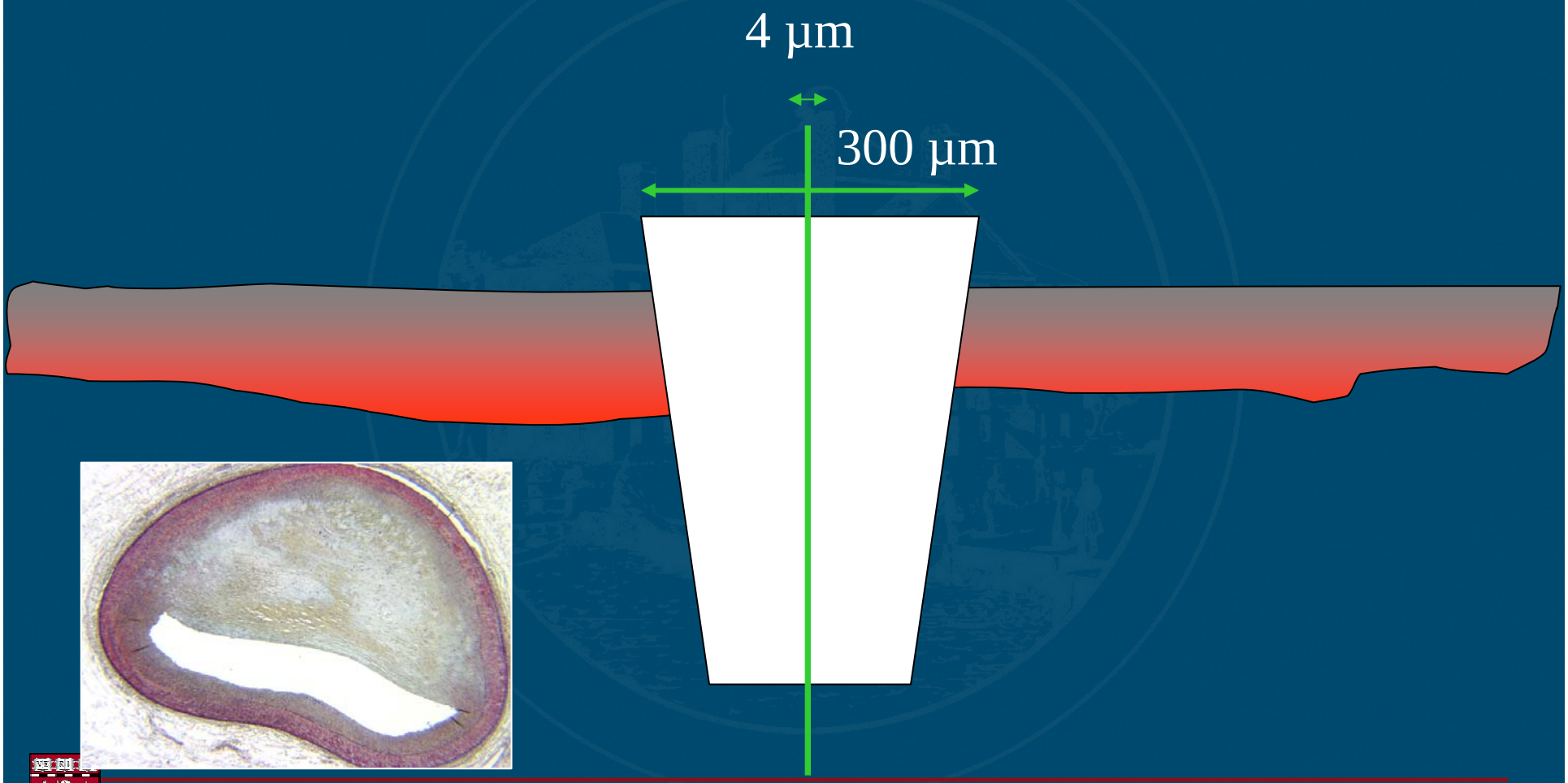
ID (IVUS Defined) TCFAs

What is VH IVUS: VH slice thickness

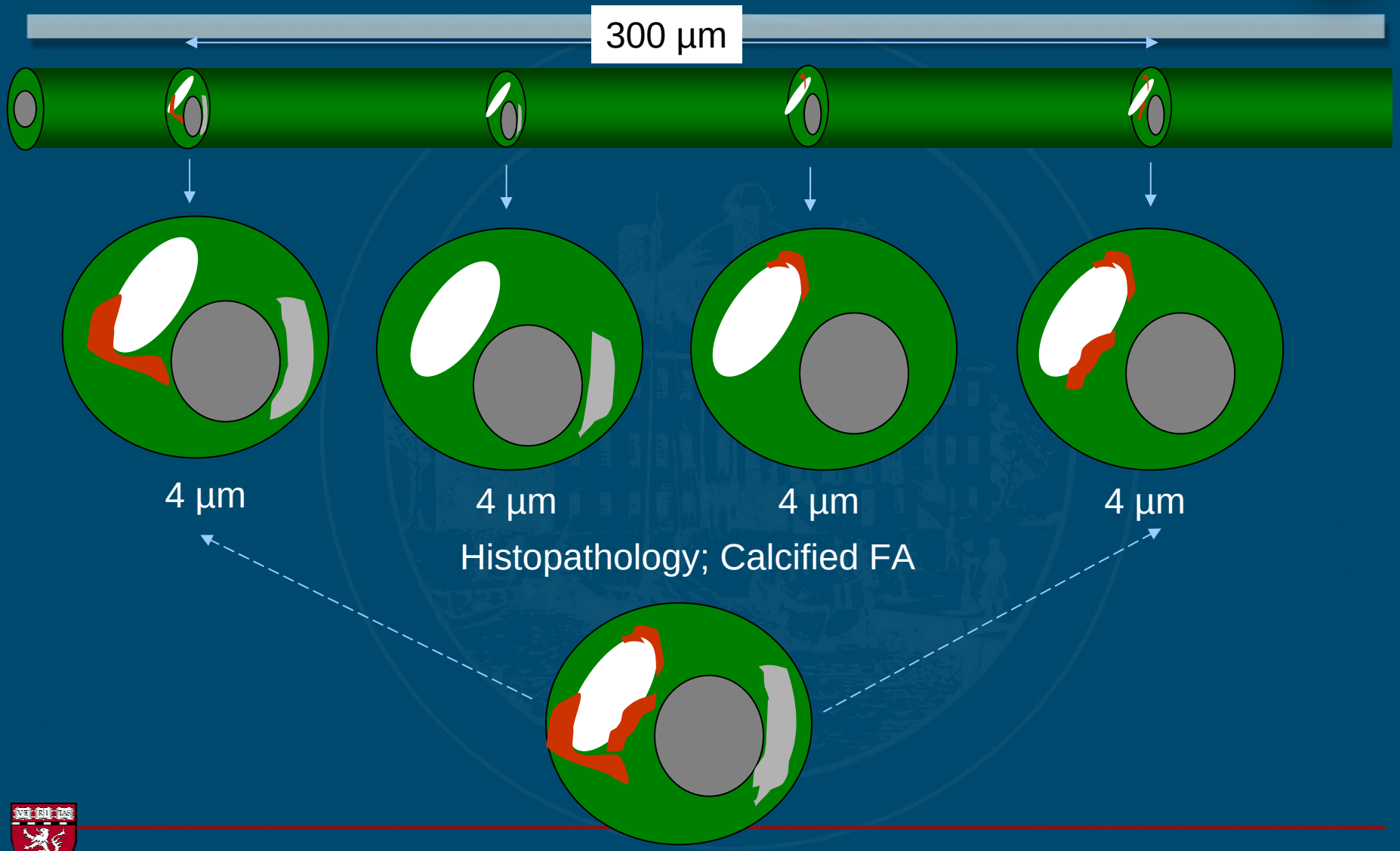




Histology slice thickness

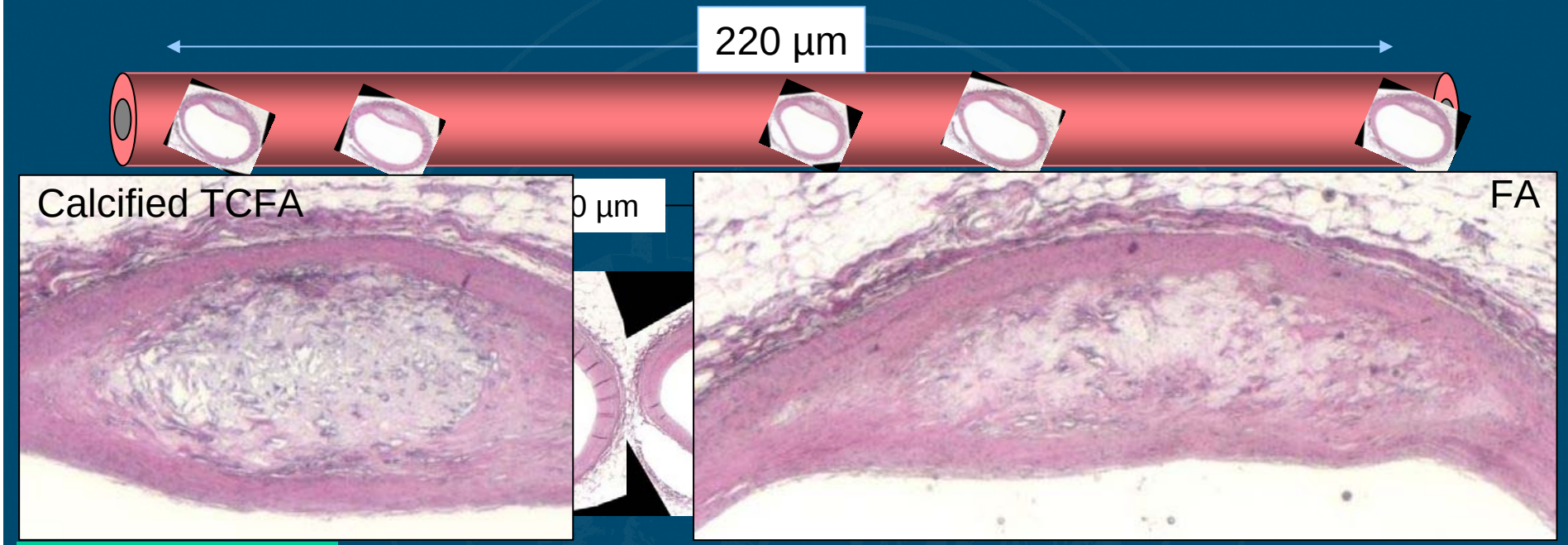


The Effect of Slice Thickness on VH Plaque Composition



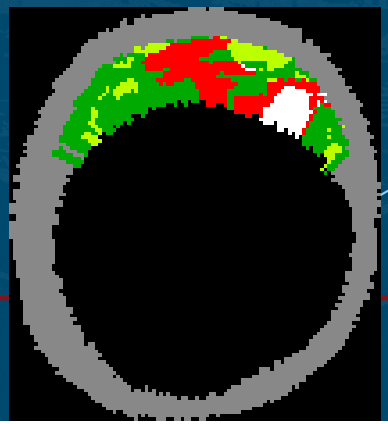
Effect of Lesion Thickness on VH Plaque Composition

Lesion Analysis by Histopathology: Calcified TCFA



Histopathology: Calcified TCFA on left

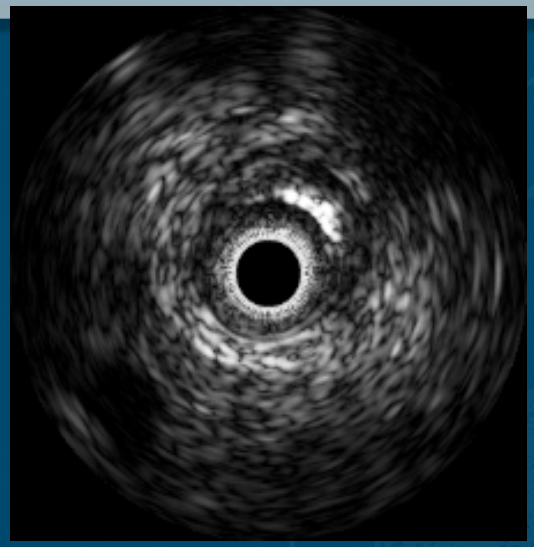
Histopathology: FA on right

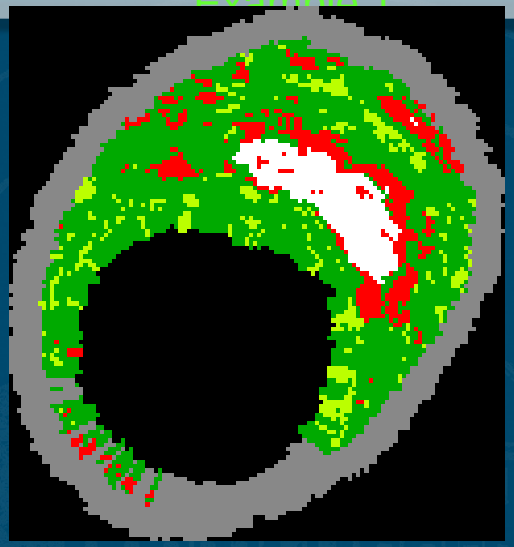


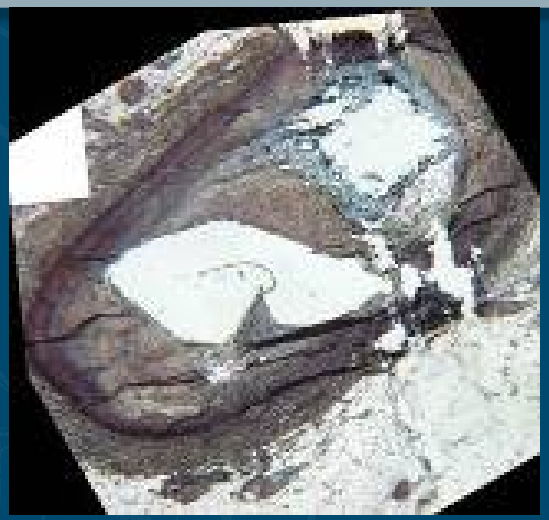
VH IVUS: Calcified TCFA

What is the “Gold Standard” for *In-Vivo* “histology”?
Histopathology or Pathologists?

Example 1



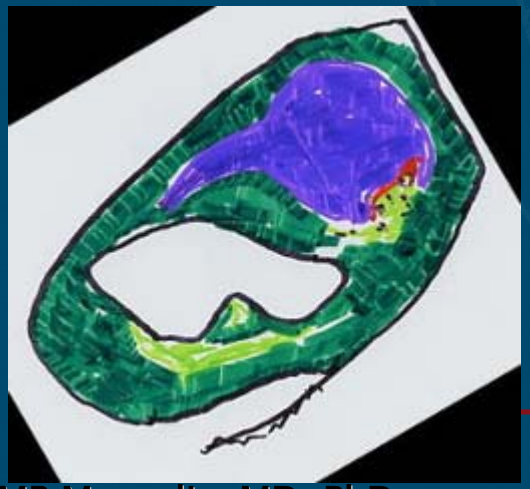




Pathologists 1(March 2006)

Pathologists 2 (Aug 2006)

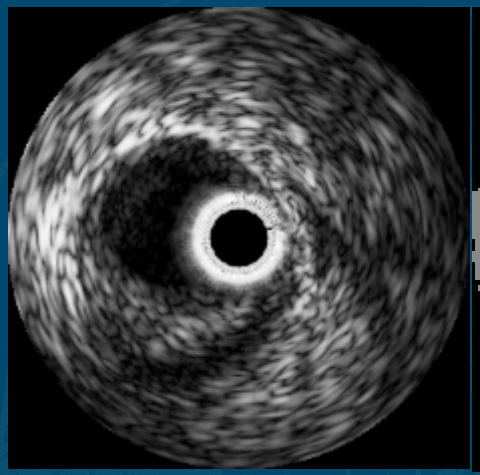
Pathologists 3 (Sept 2006)

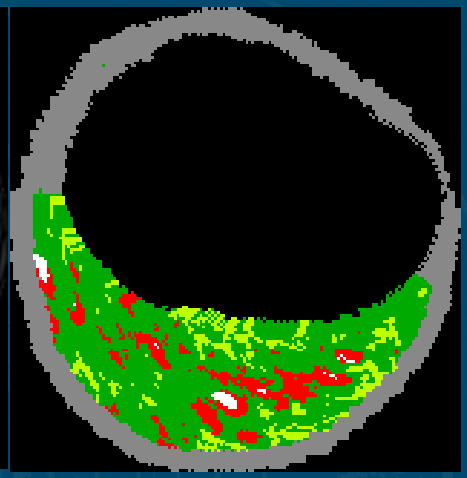


MP Margolis, MD, PhD

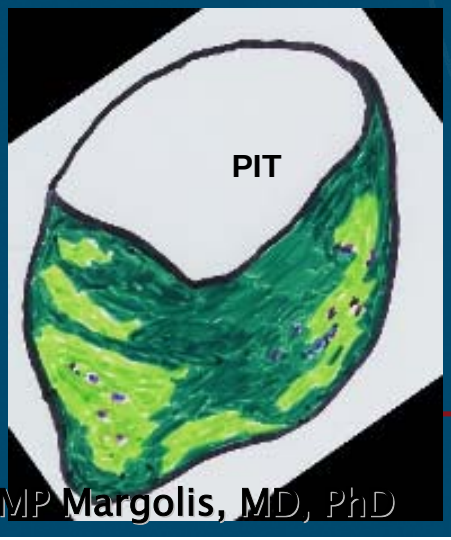
Single Lesion

19) CCF 05104 B2





Pathologists 1(March 2006)



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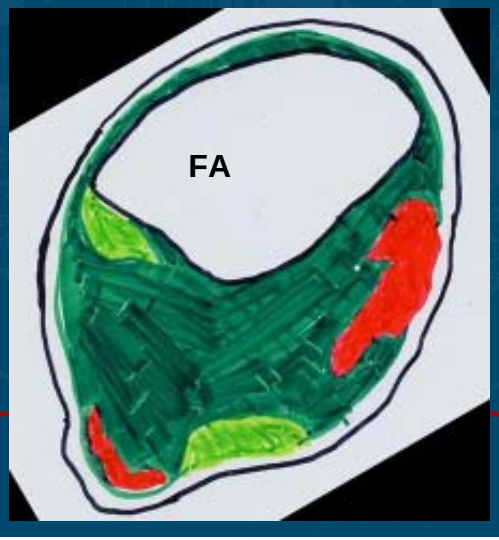
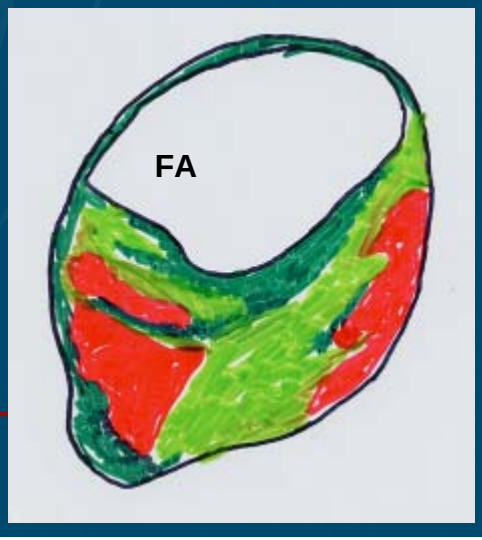


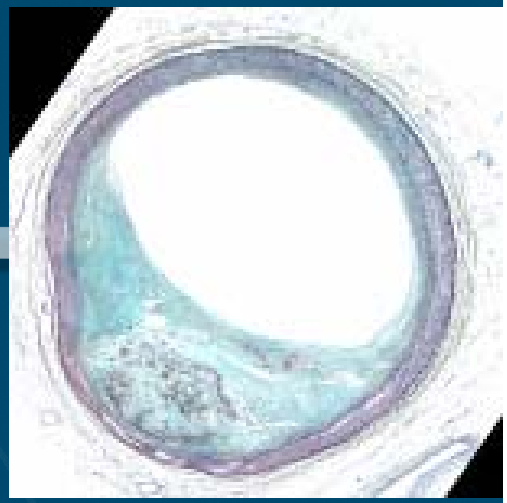
Pathologists 3 (Sept 2006)

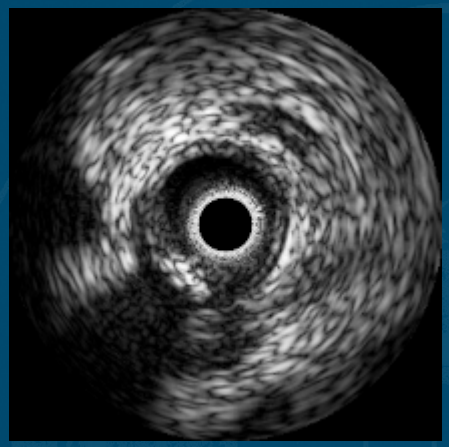


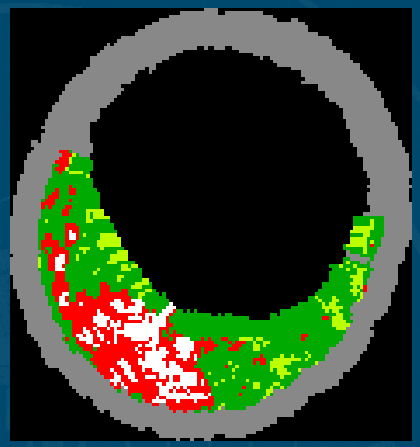
MP Margolis, MD, PhD

Single Lesion

7) CCF 05065 B2







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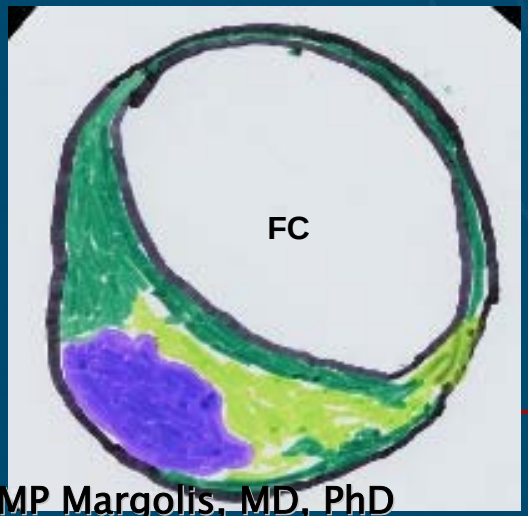
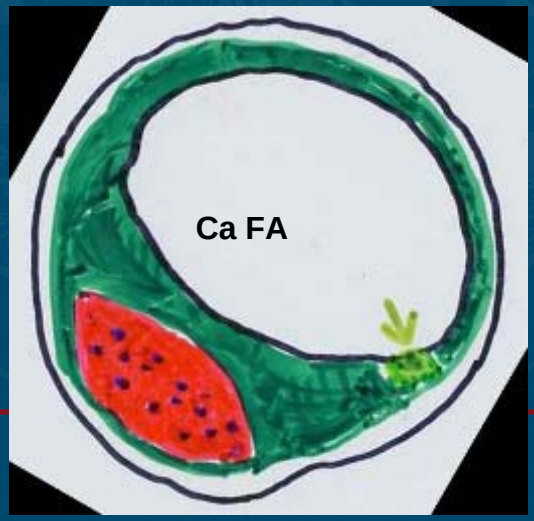


Pathologists 2 (Aug 2006)



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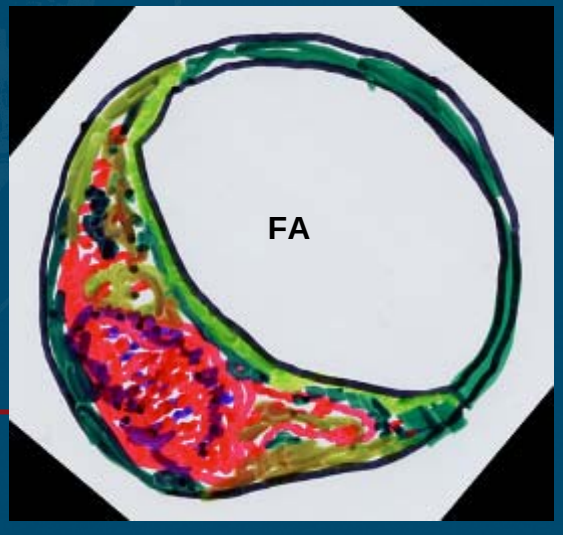
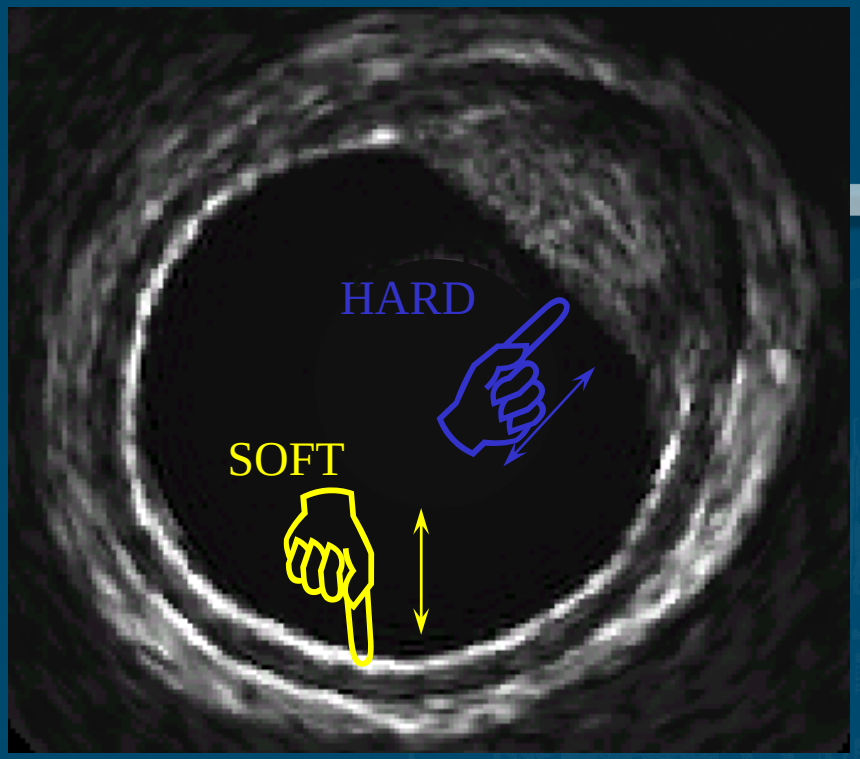
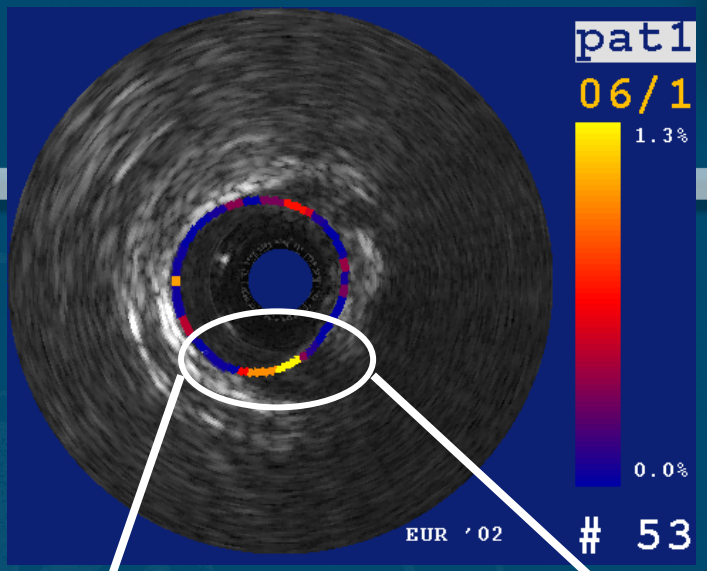


MP Margolis, MD, PhD


HARD
SOFT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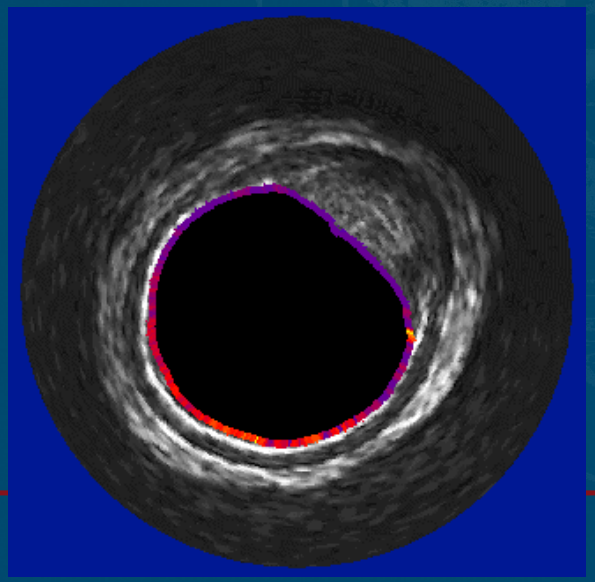
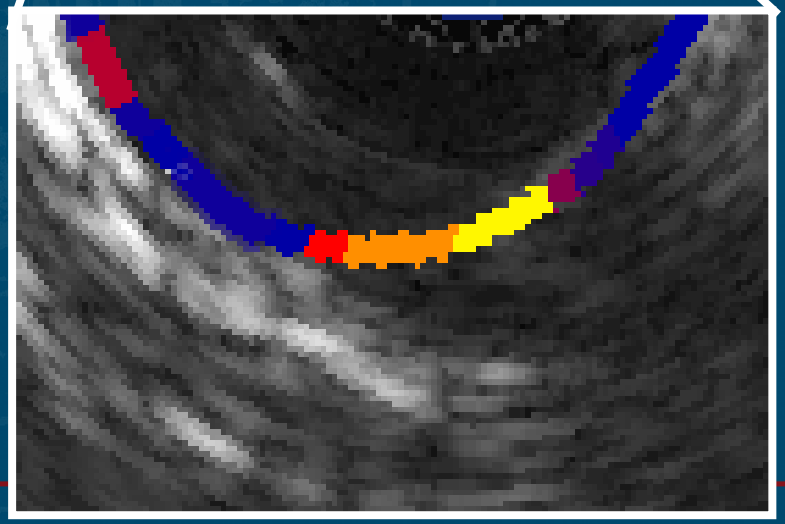




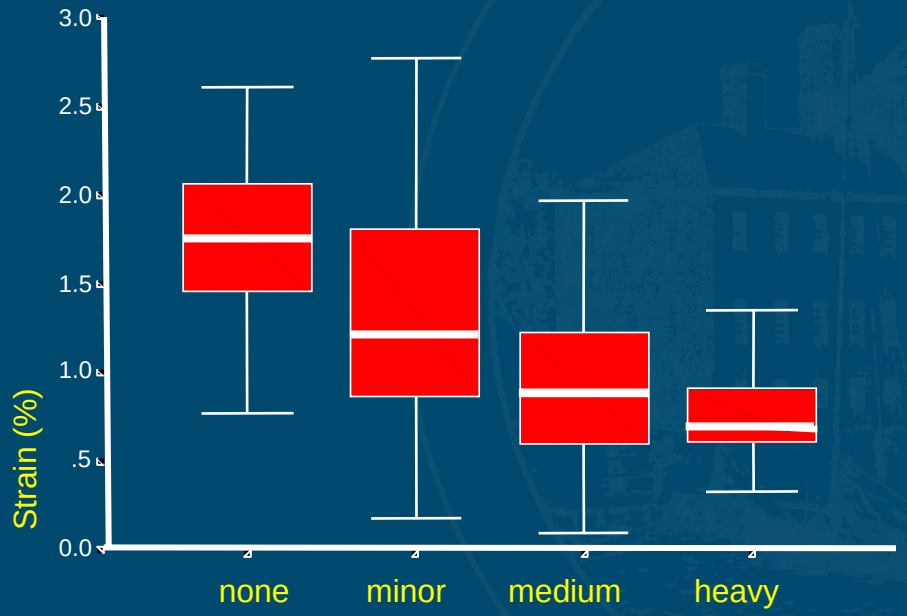
Sensitivity and Specificity: in vitro

	Elastogram positive	Elastogram negative	
Histology positive	20	3	23
Histology negative	4	27	31
	24	30	54

$\Rightarrow$ Sensitivity = 88%
Specificity = 89%

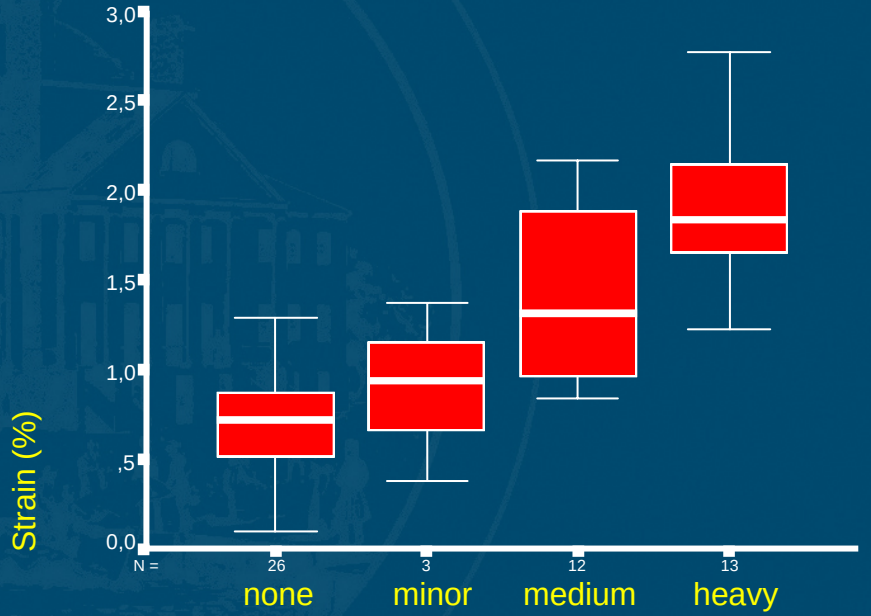
Schaar JA, et al. Circulation 2003

Strain and tissue components



Smooth muscle cells

$p < 0.0001$



Macrophages

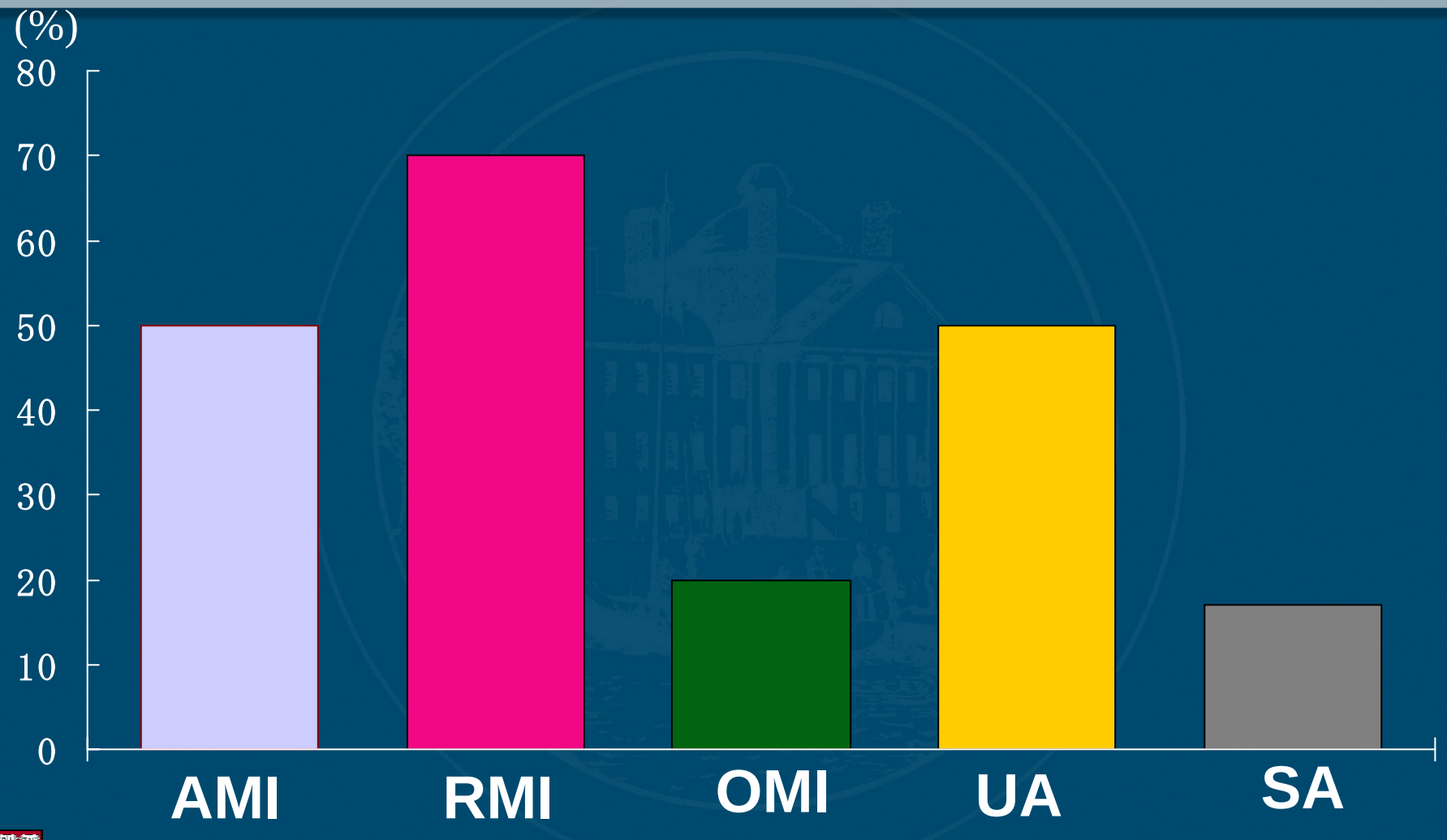
$p < 0.006$

Invasive Imaging Modalities

- IVUS
- **Angioscopy**
- IV MR
- OCT

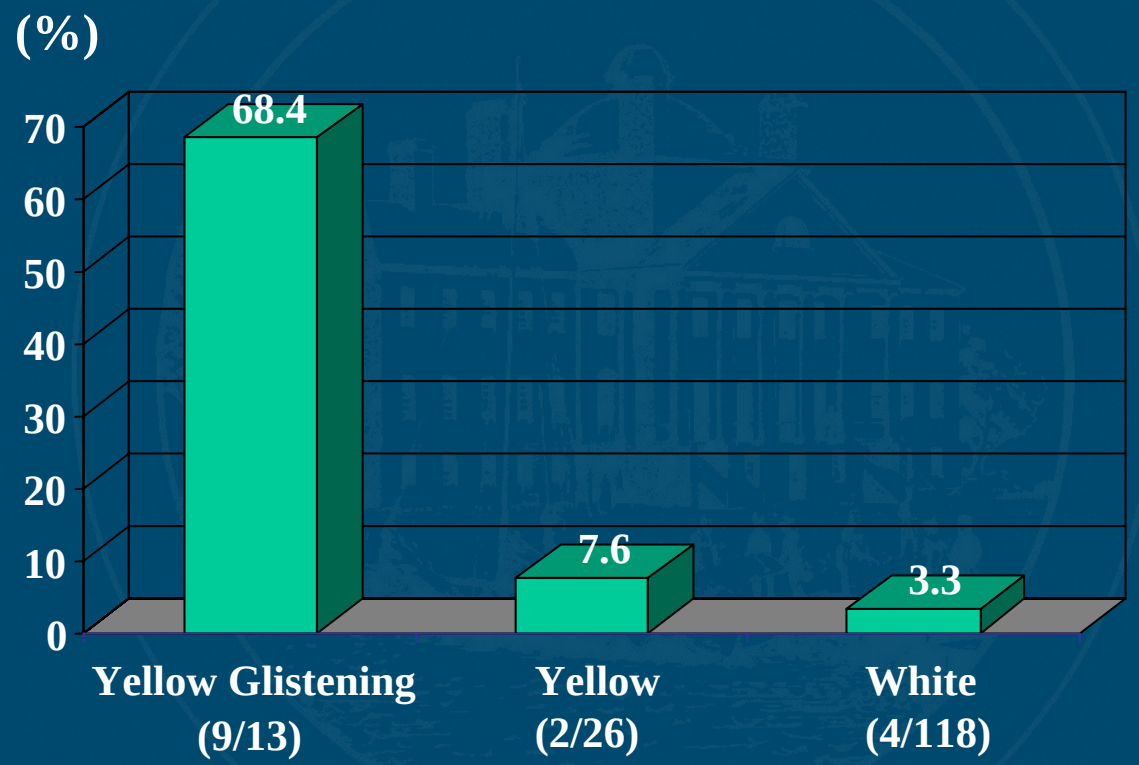
- Thermography
- Spectroscopy

The frequency of yellow plaque



Mizuno et al. Lancet 1991

Incidence of ACS: Angioscopic Finding



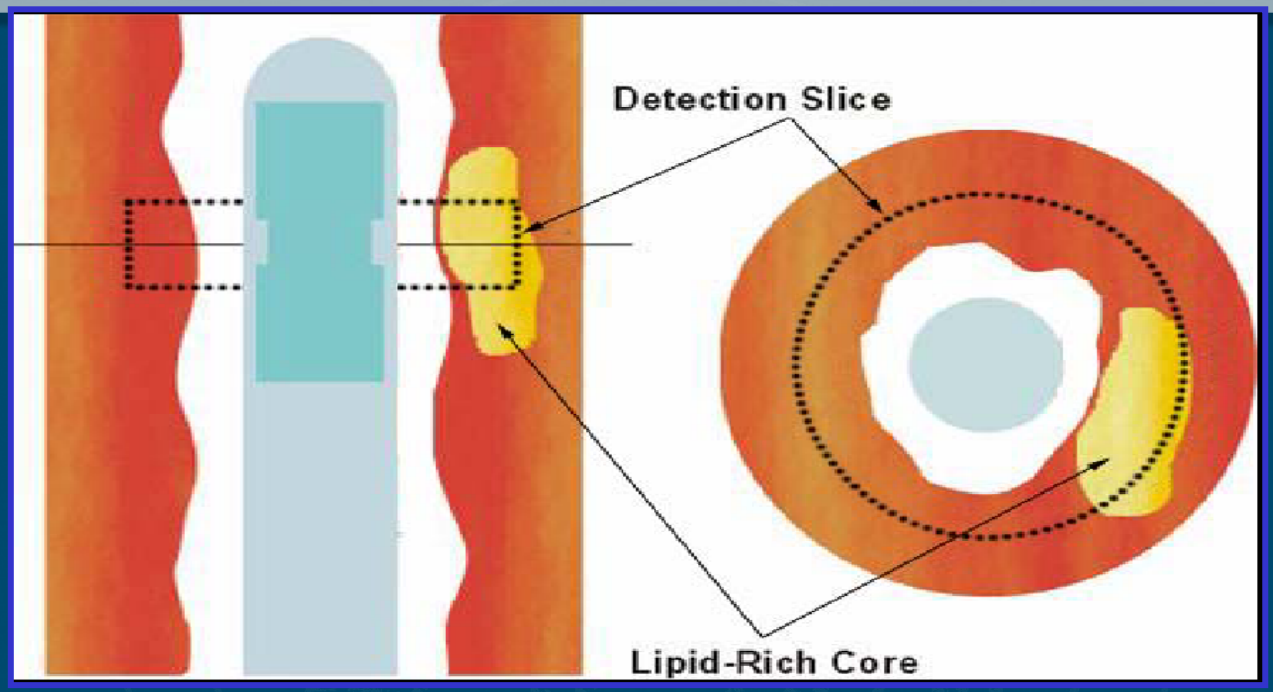
Uchida et al. Am Heart J 1995

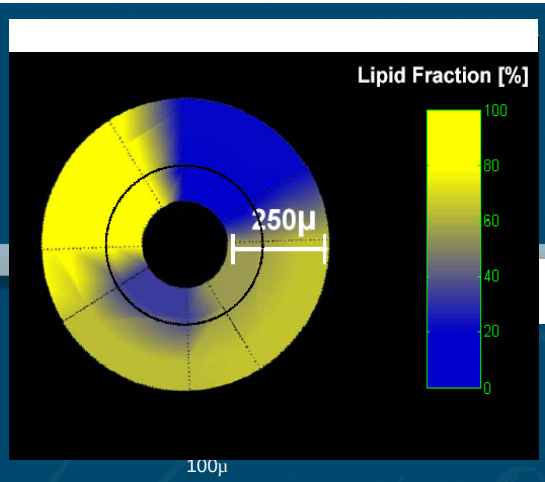
Invasive Imaging Modalities

- IVUS
- Angioscopy
- **IV MR**
- OCT

- Thermography
- Spectroscopy

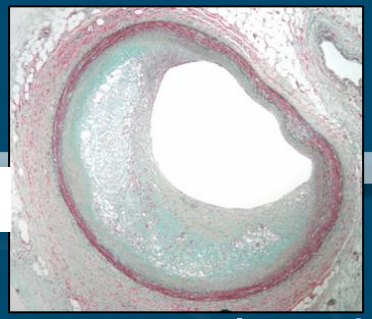
Top-spin® intracoronary MR catheter

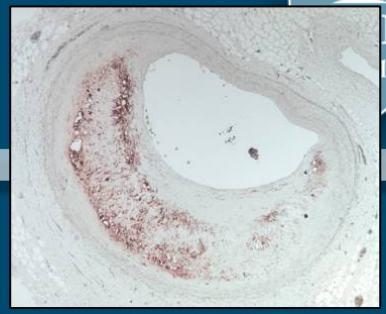




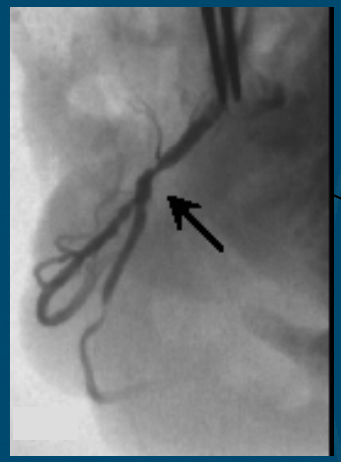
Movat's

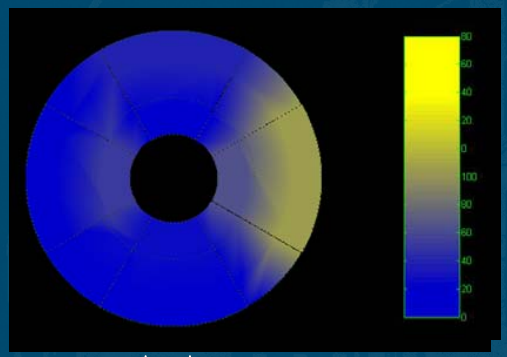
CD68

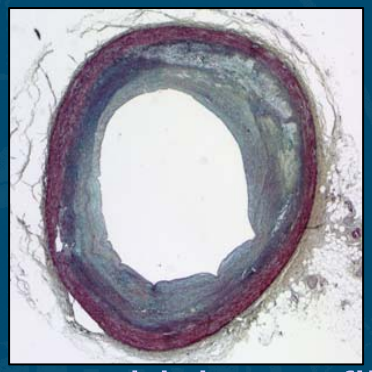


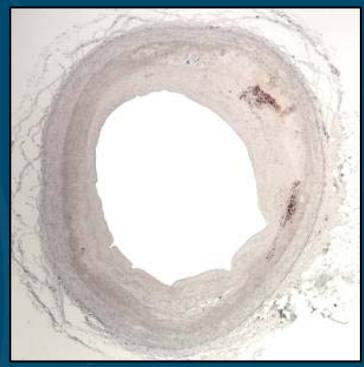


Vulnerable plaque

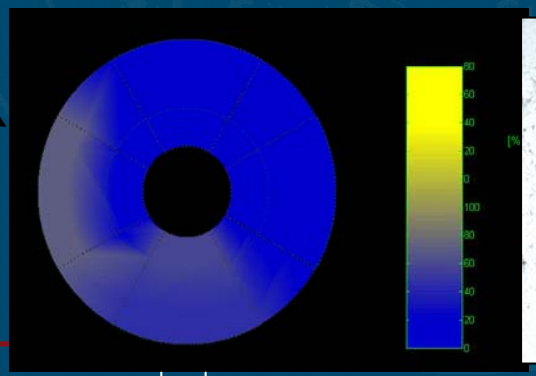


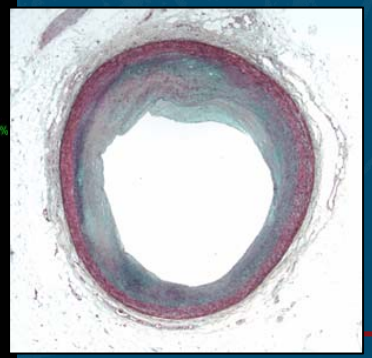






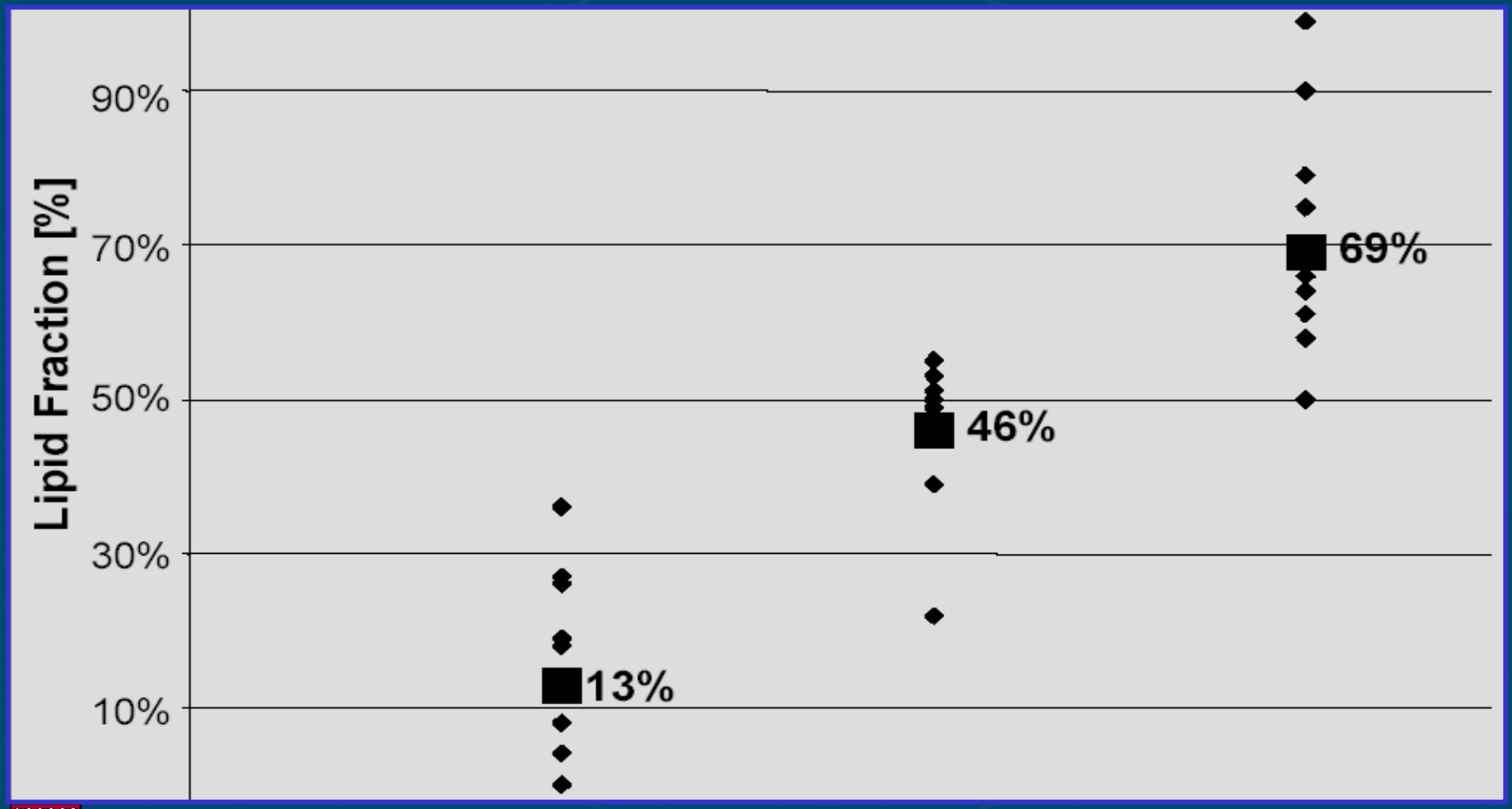
Thick cap fibroatheroma





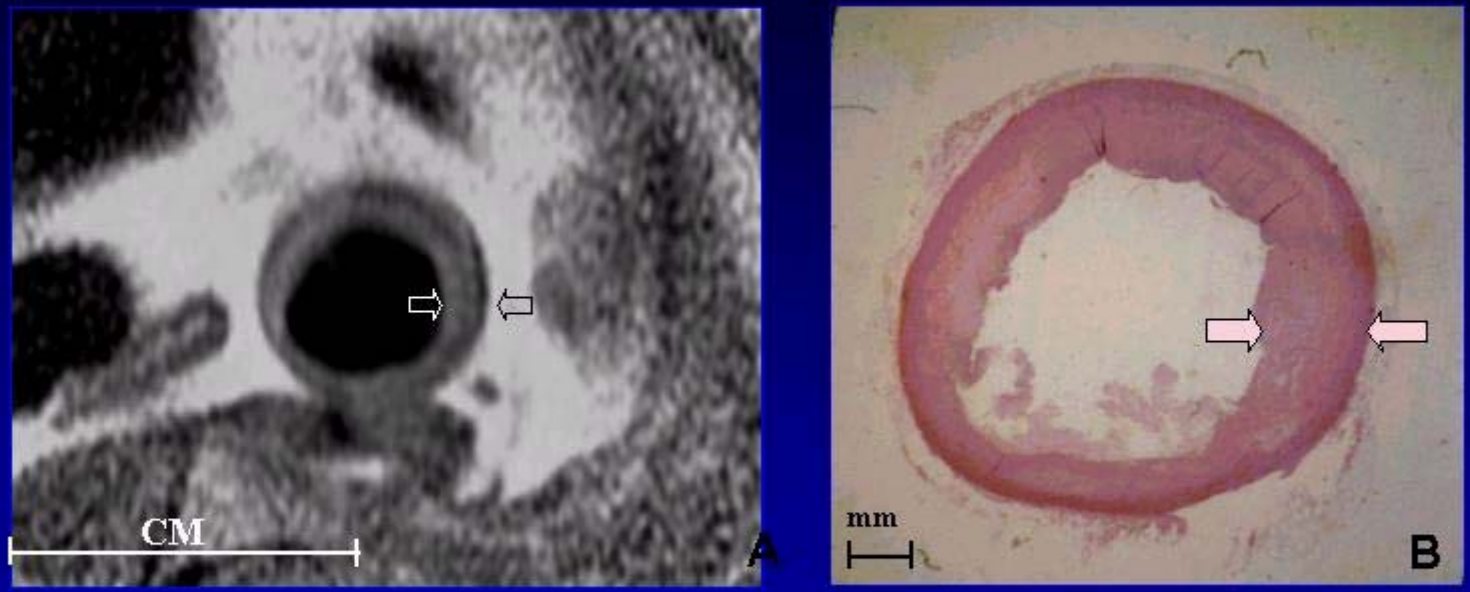
Stable plaque

Correlation of lipid fraction determined by ic MR and histology



Intravascular MRI of Watanabe Rabbits

Watanabe rabbit with a 0.032" MRI-Guidewire



FSE, 1200/13-msec TR/TE, Double IR blood suppression, 16 ETL, 4-cm FOV, 32 NEX, 256x256 matrix

- **Resolution: 150 µm**

Serfaty et al.

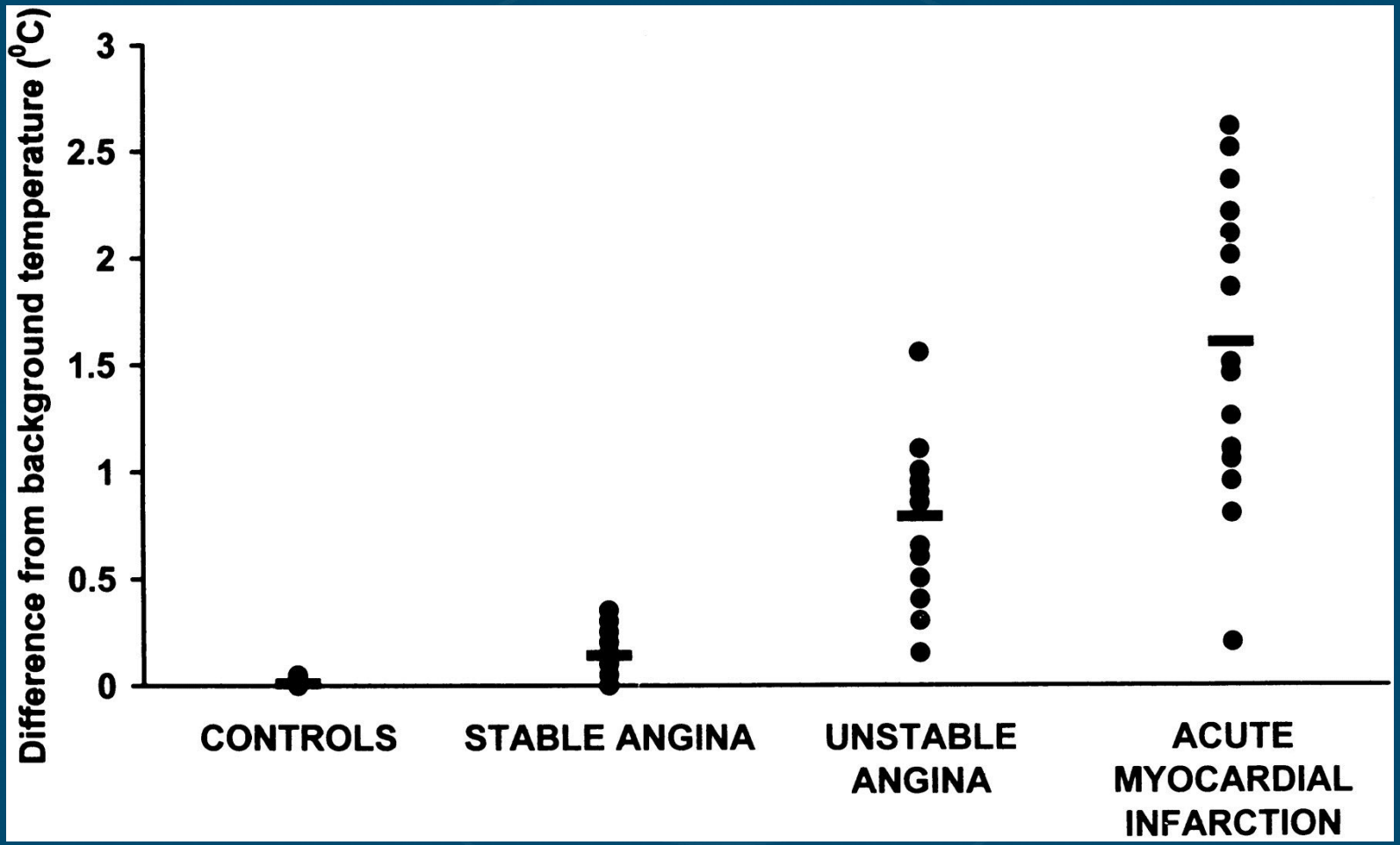
Stanford

Invasive Imaging Modalities

- IVUS
- Angioscopy
- IV MR
- OCT

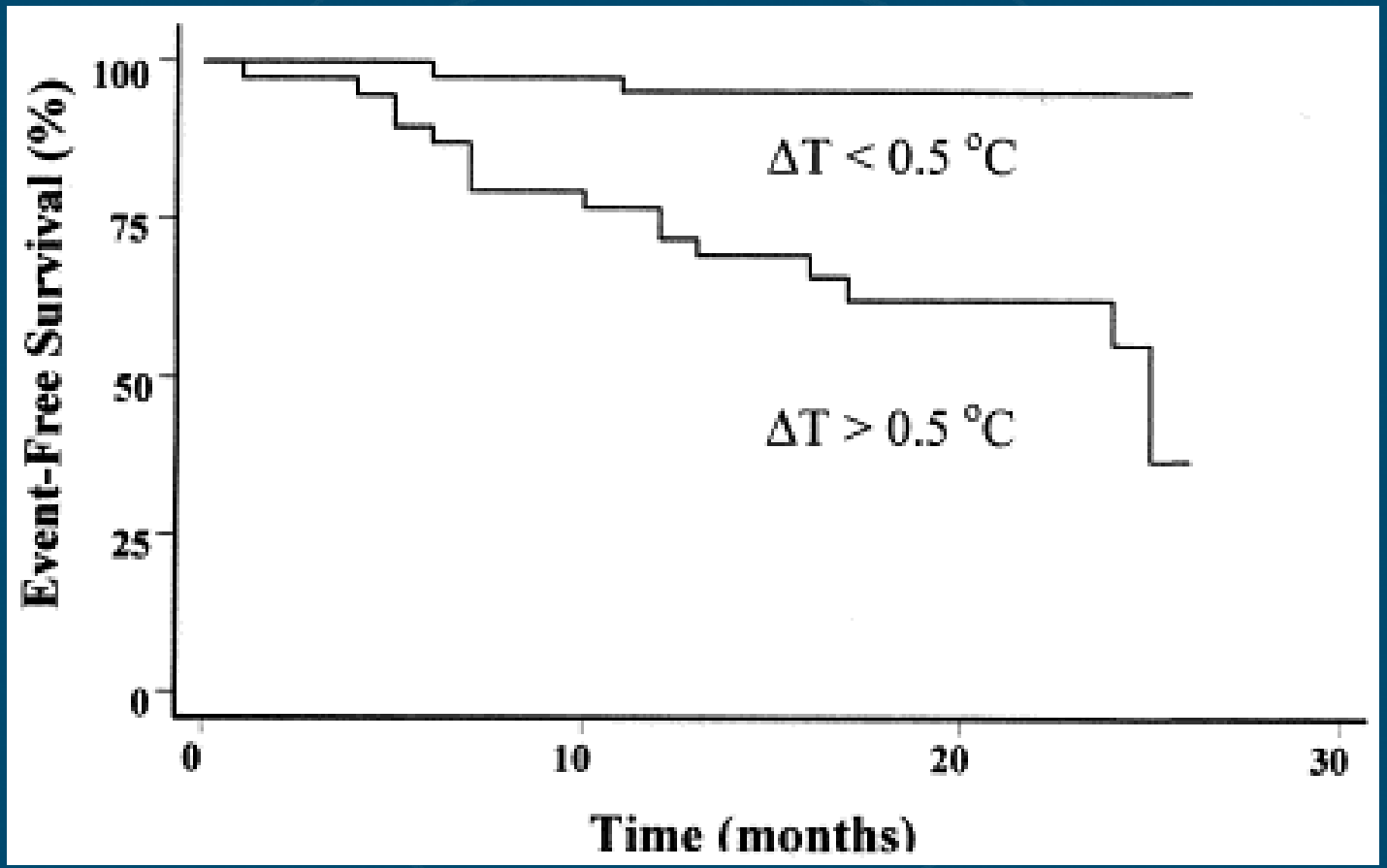
- **Thermography**
- Spectroscopy

In vivo thermal heterogeneity within human atherosclerotic coronary arteries



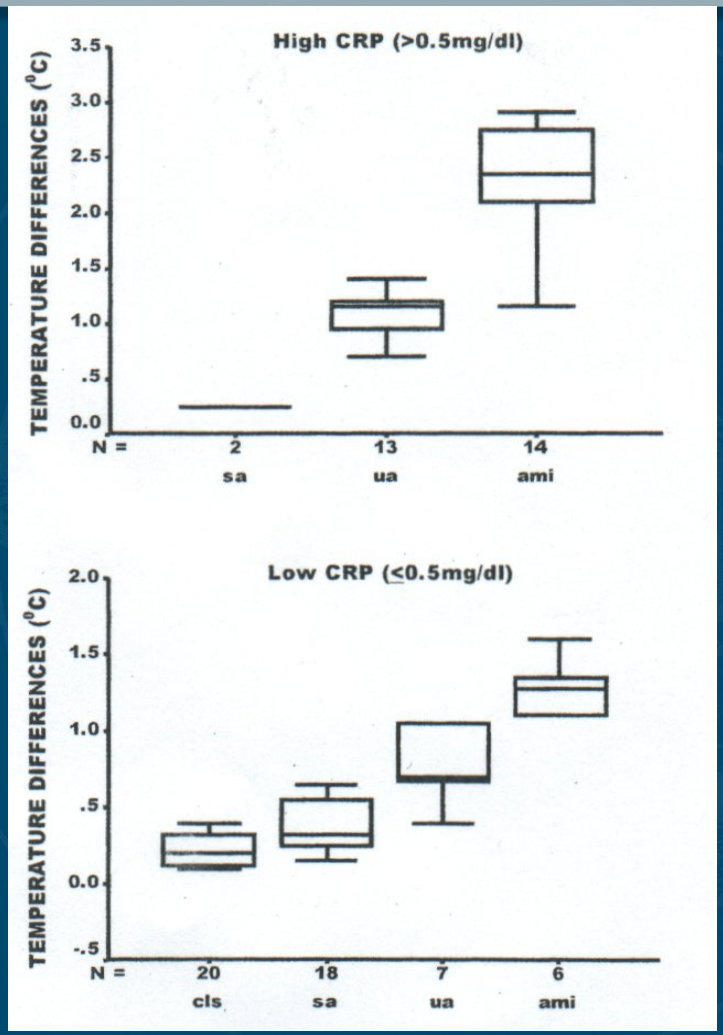
Stefanadis et al. Circulation 1999

Risk of Adverse Cardiac Events



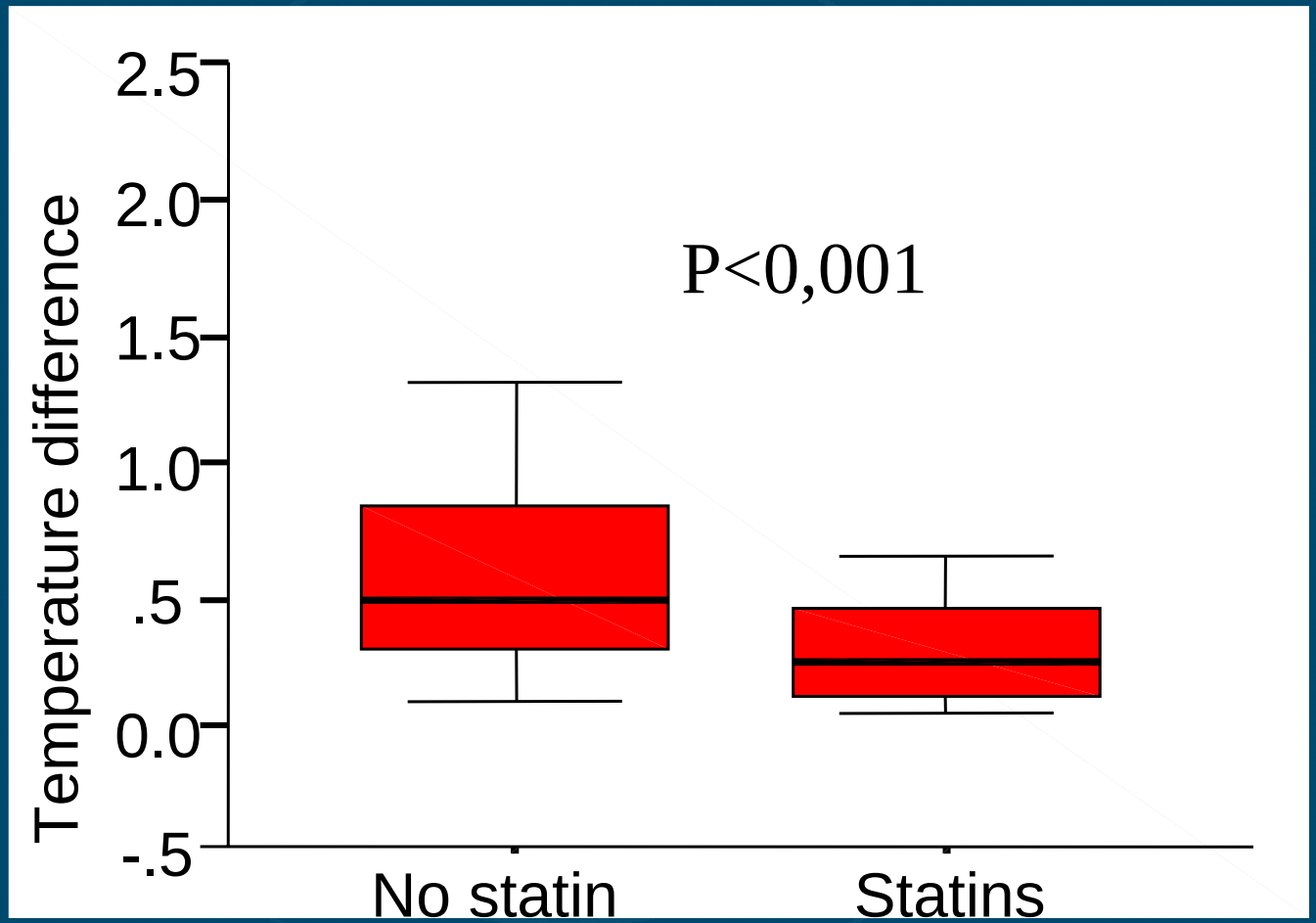
Stefanadis et al. JACC. 2001

Clinical Presentation and the Temperature Difference: hsCRP



Stefanadis et al. J Mol Cell Cardiol. 2000

Atorvastatin and Plaque Temperature



Stefanadis et al. Eur Heart J

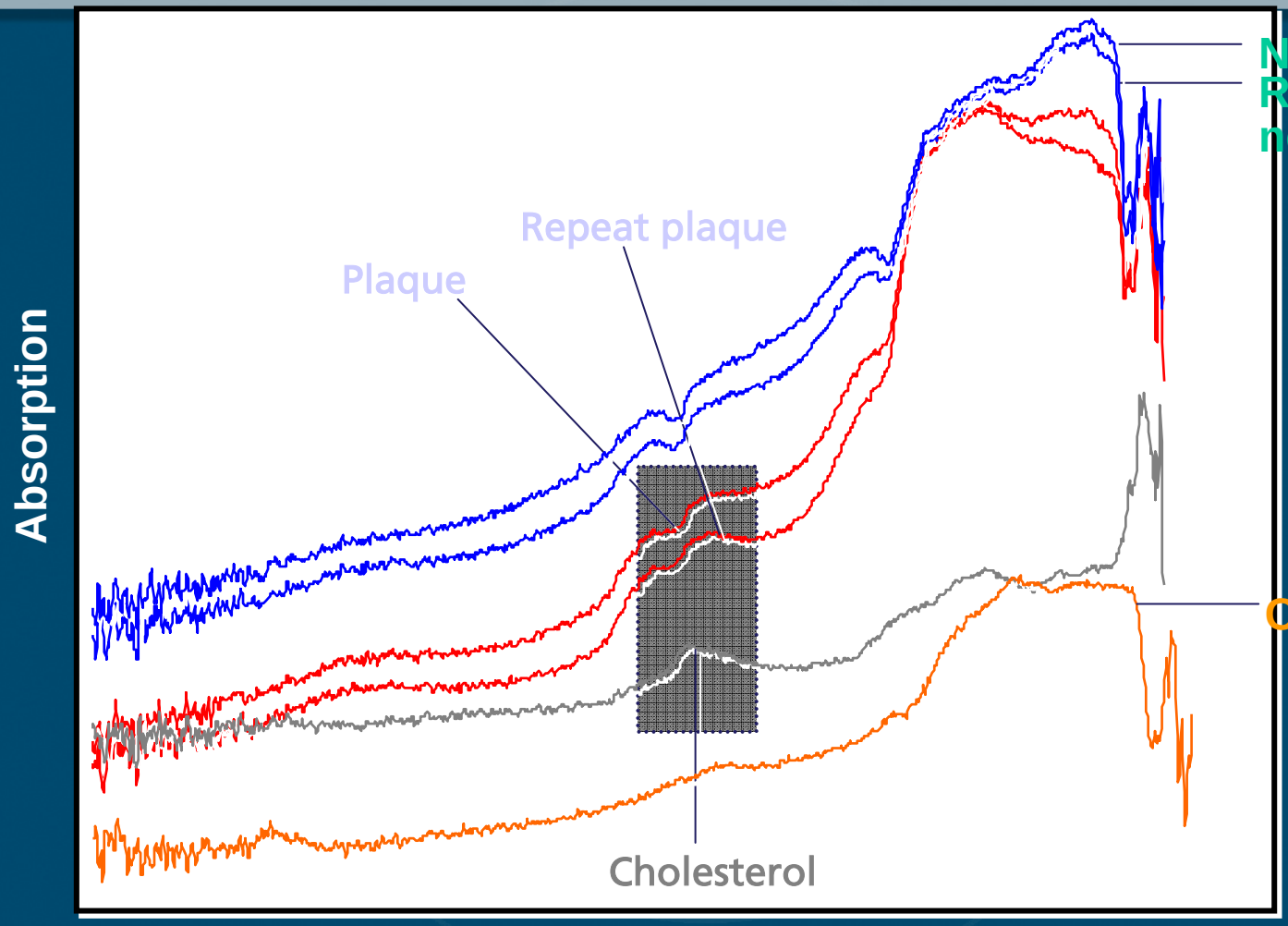
- Toutouzas et al reported correlation between temperature and expansive remodeling and MMP-9 concentration.
- Verheye et al showed that temperature heterogeneity was reduced after change from high to low-cholesterol diet in rabbits.

Invasive Imaging Modalities

- IVUS
- Angioscopy
- OCT
- IV MR

- Thermography
- **Spectroscopy**

Near-IR Spectra of Human Aortic Samples



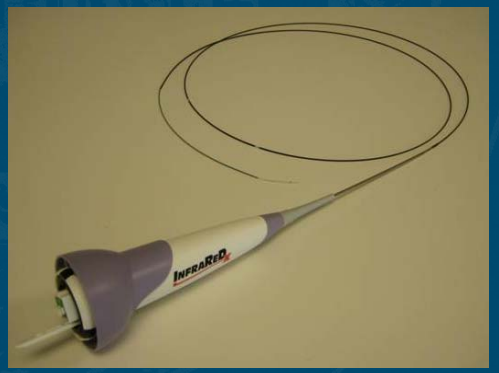
Characterization of plaque histology by NIR spectroscopy (*ex vivo, no blood, no motion)*

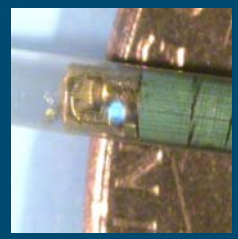
All values in %.			
Sensitivity			
Specificity			
Positive predictive value			
Negative predictive value			

Moreno P et al. Circulation 2002

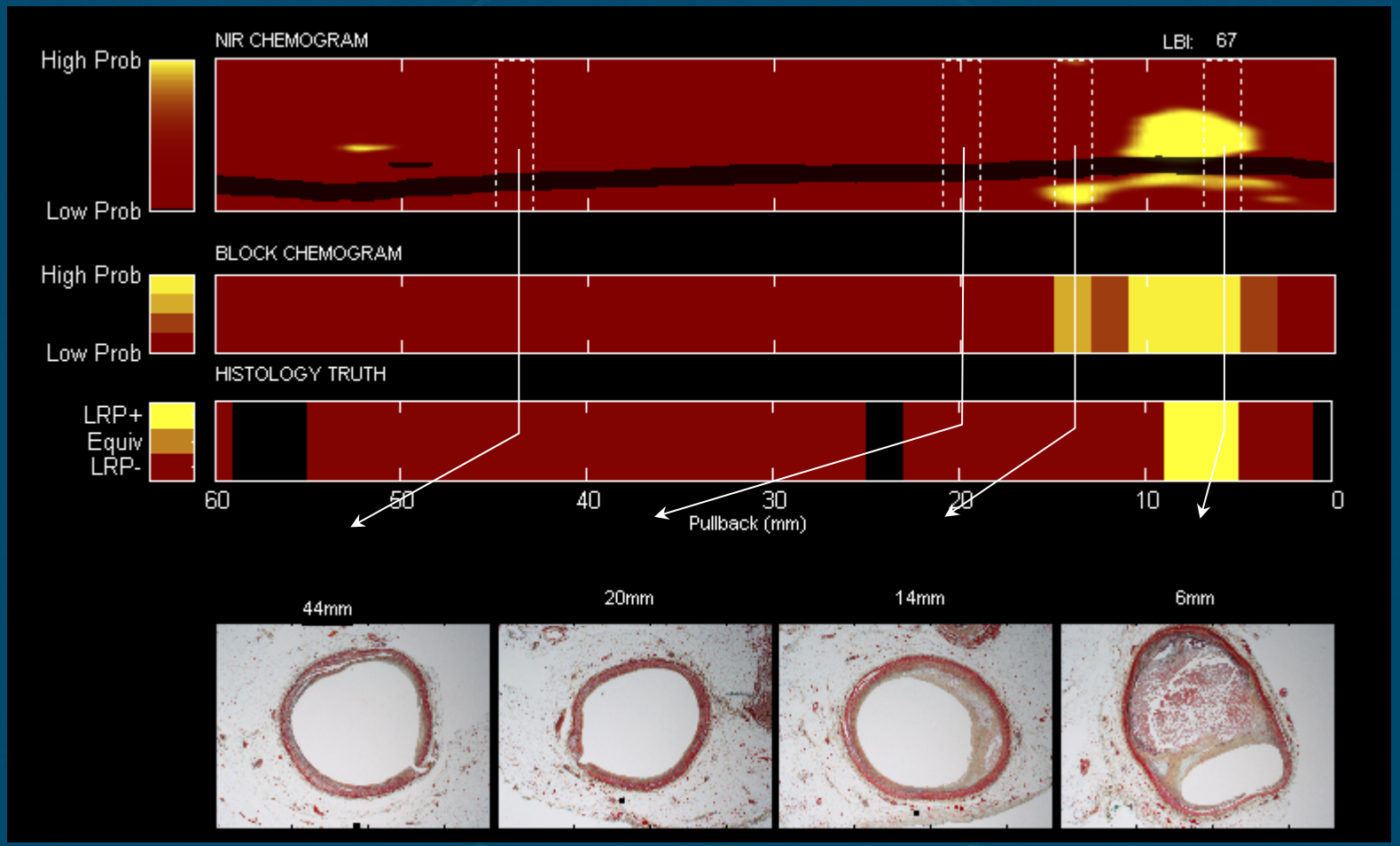
InfraReDx Spectroscopy System

- Three components: console, PBR, catheter (3.2 Fr, monorail, 0.014” compatible)
- Automatically scans artery
- Spectra processed by algorithm and displayed to user as a chemical image of lipid rich plaque probability (“Chemogram”)



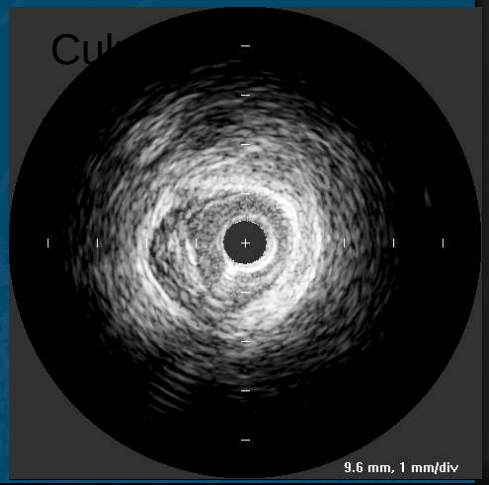


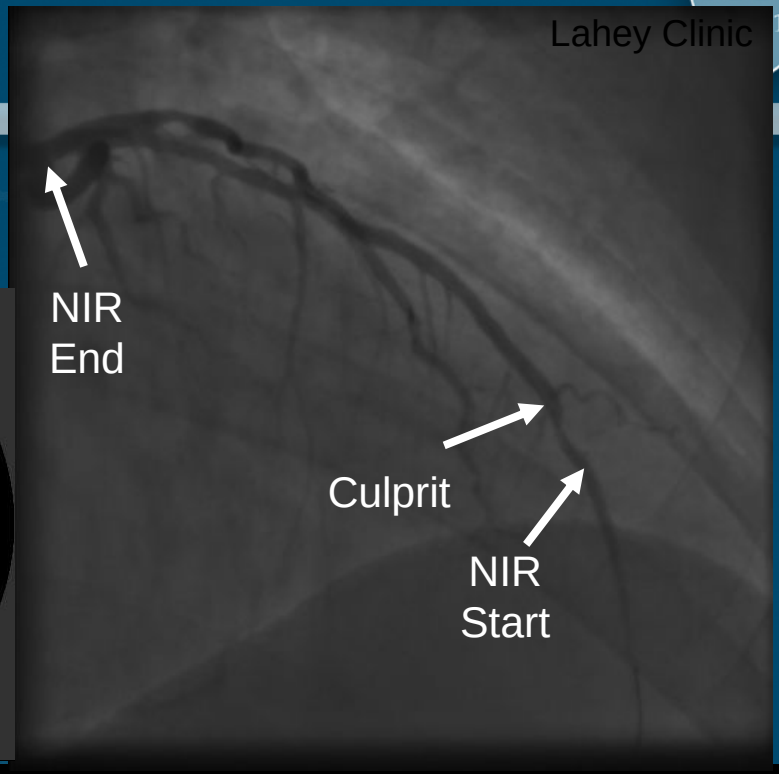
Comparison of Chemogram with Histology

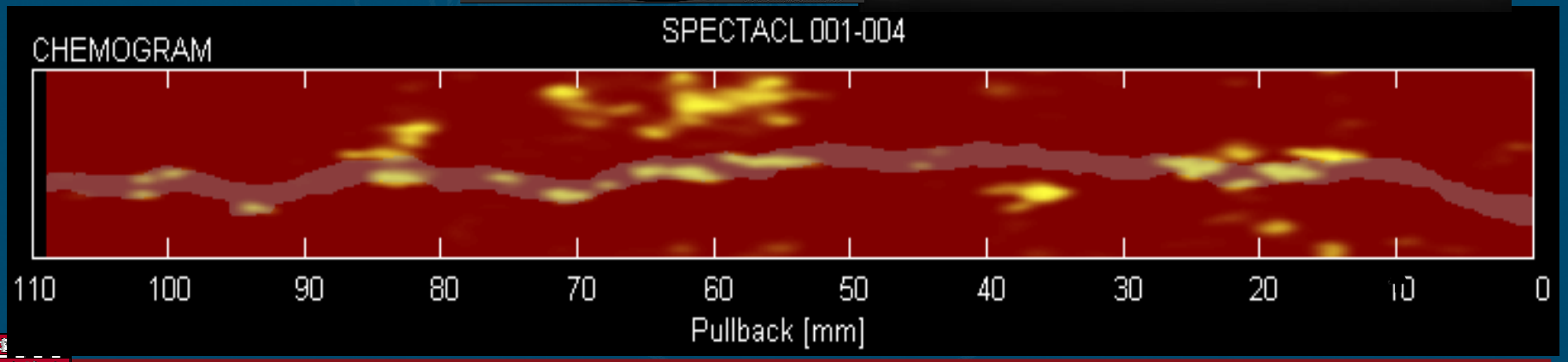


SPECTACL: No Lipid Signal at Culprit

- 55y, M
- BMI 32.4 kg/m²
- Prog Angina
- •+DM, HTN, Chol

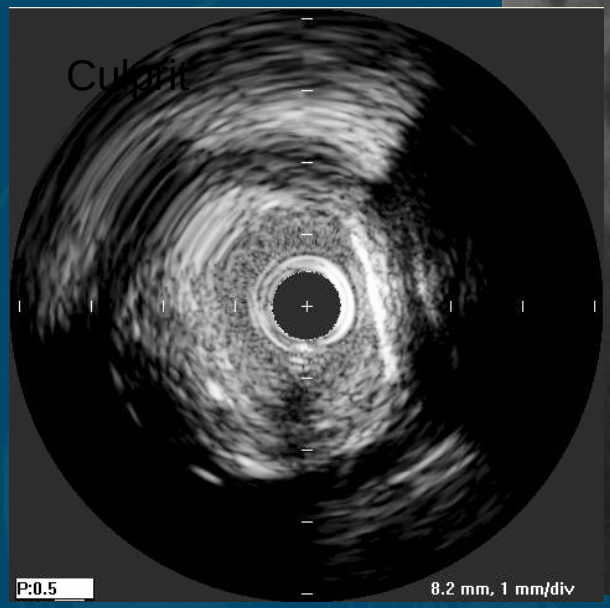


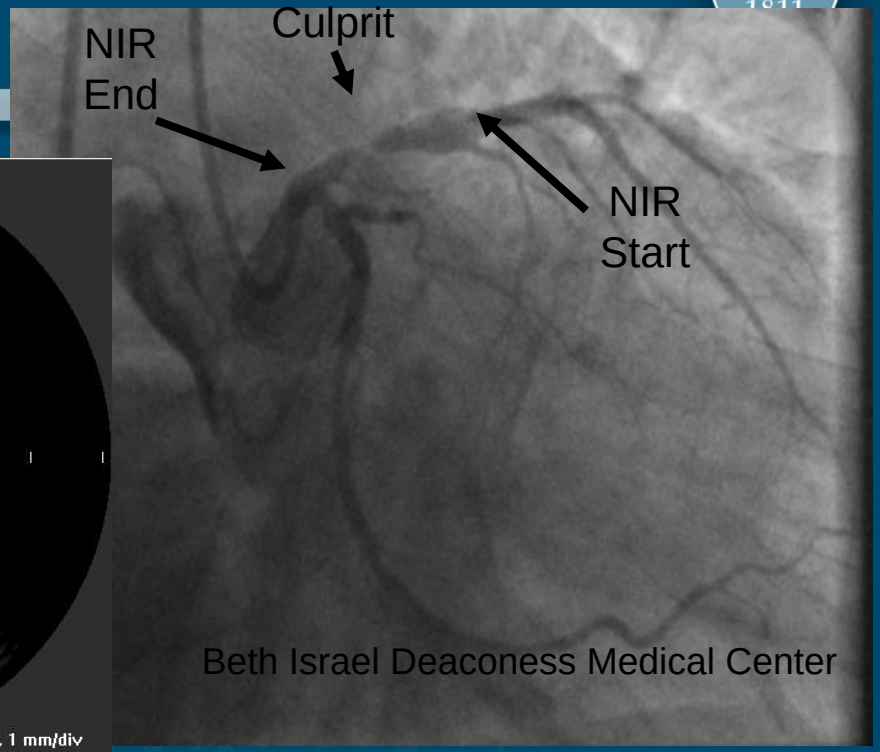


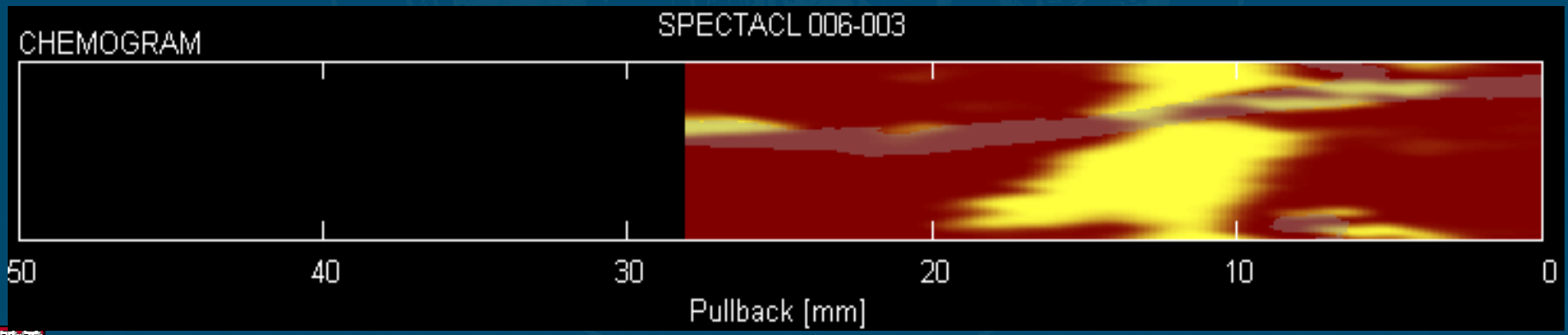


SPECTACL: Lipid Signal at Culprit

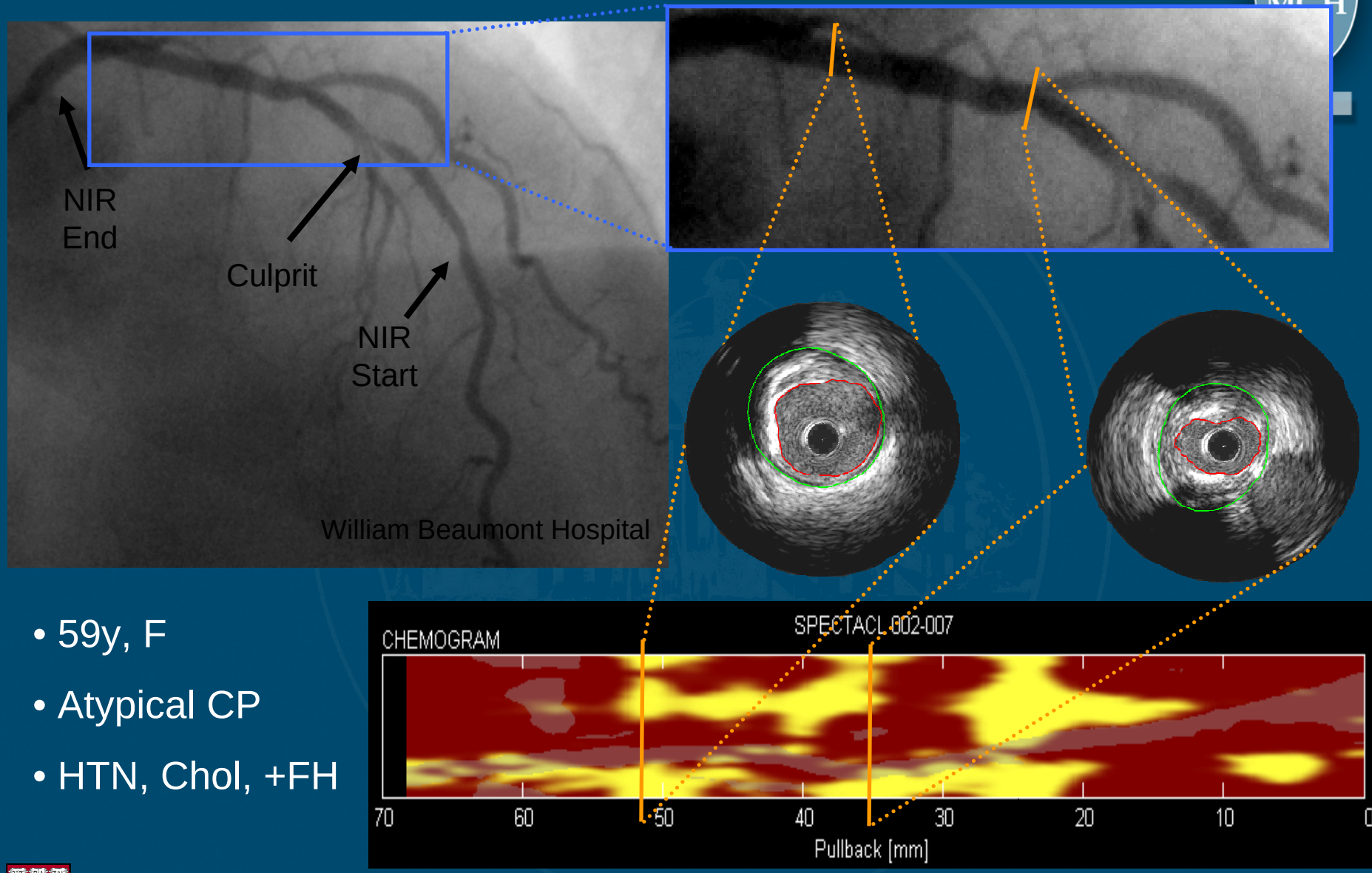
- 71y, M
- BMI 28.3 kg/m^2
- MI (<72 hrs)
- HTN





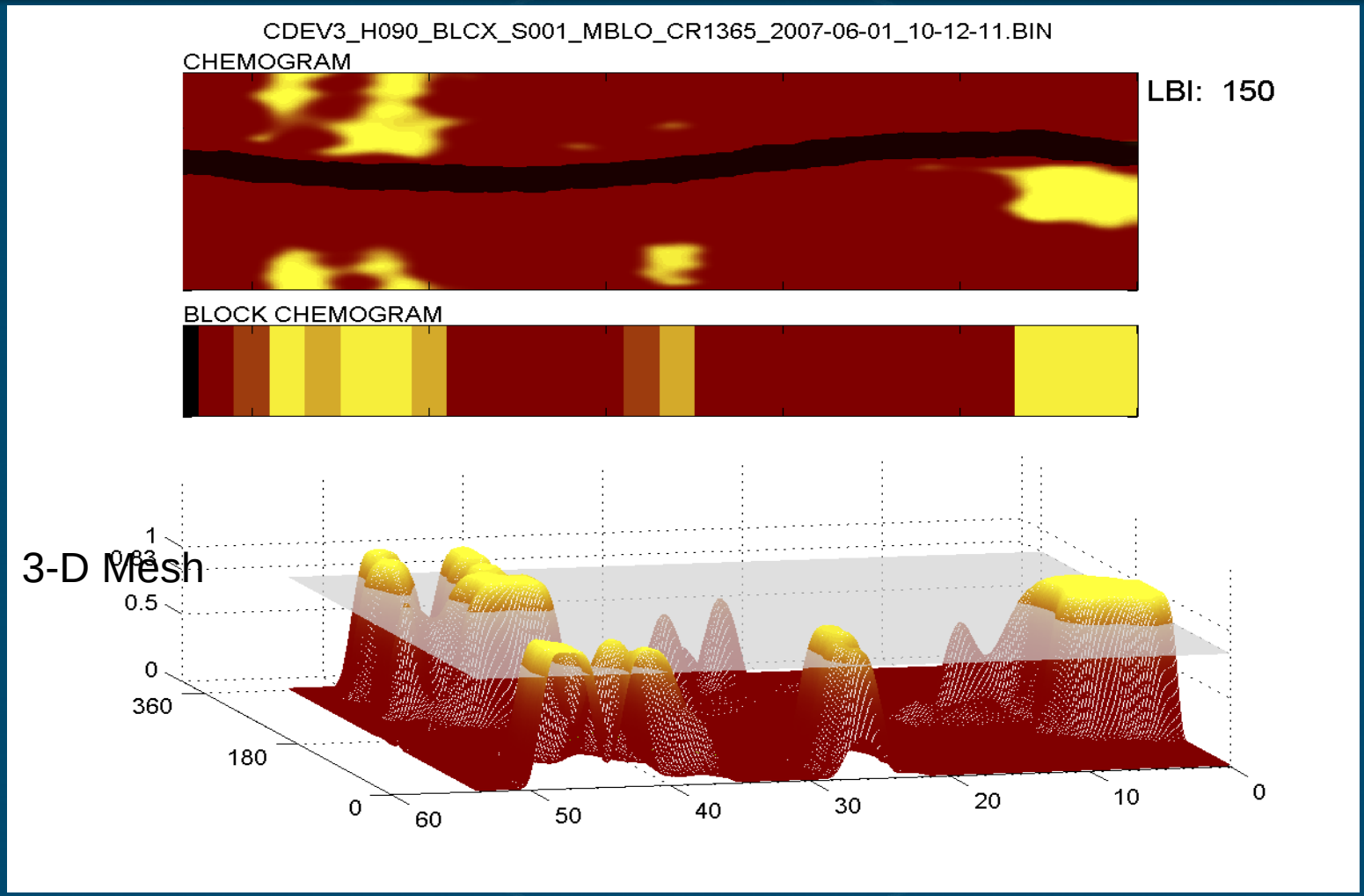


SPECTACL: Other Areas of Interest

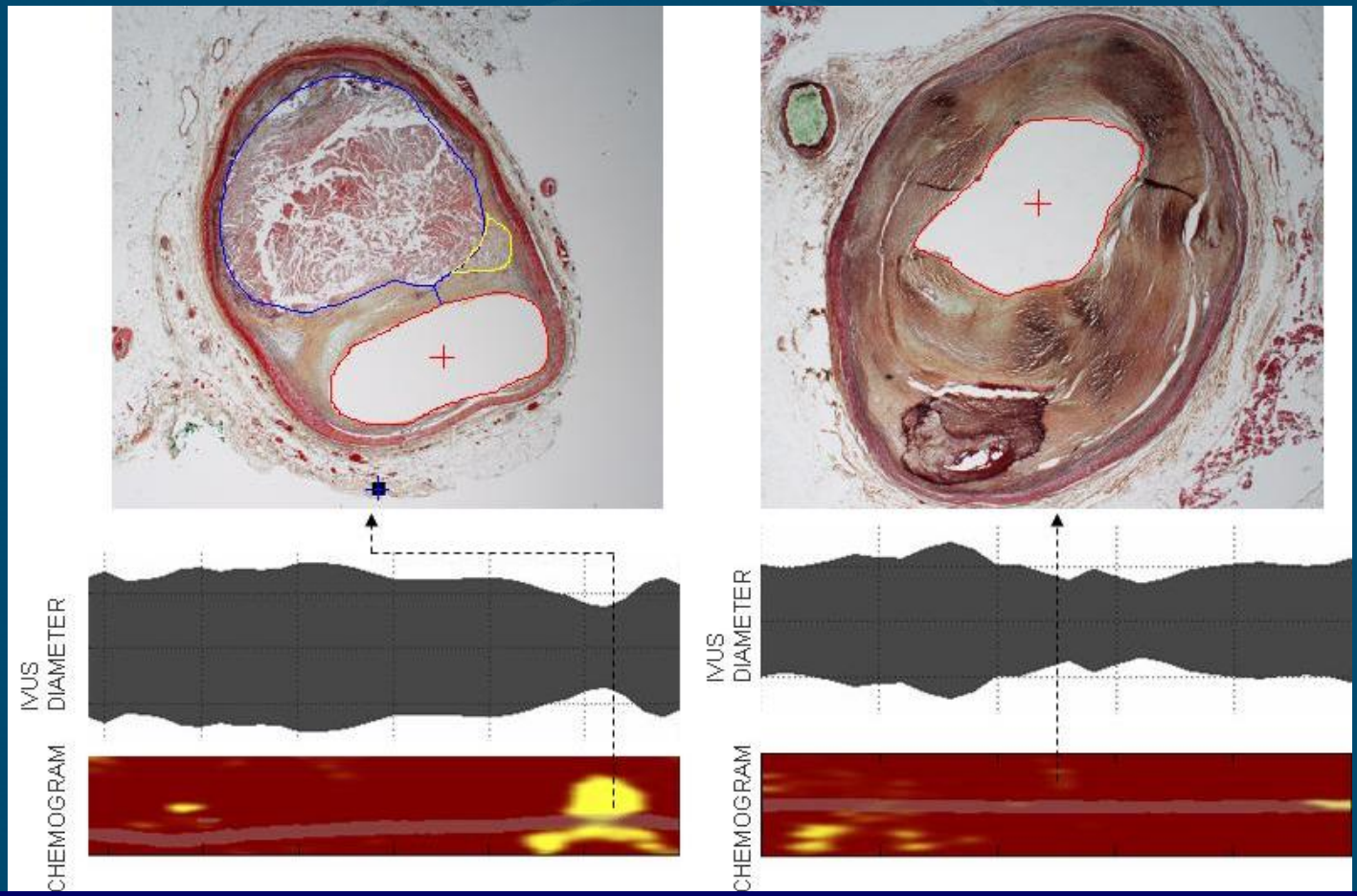


- 59y, F
- Atypical CP
- HTN, Chol, +FH

Multiple views of lipid-rich plaque probability

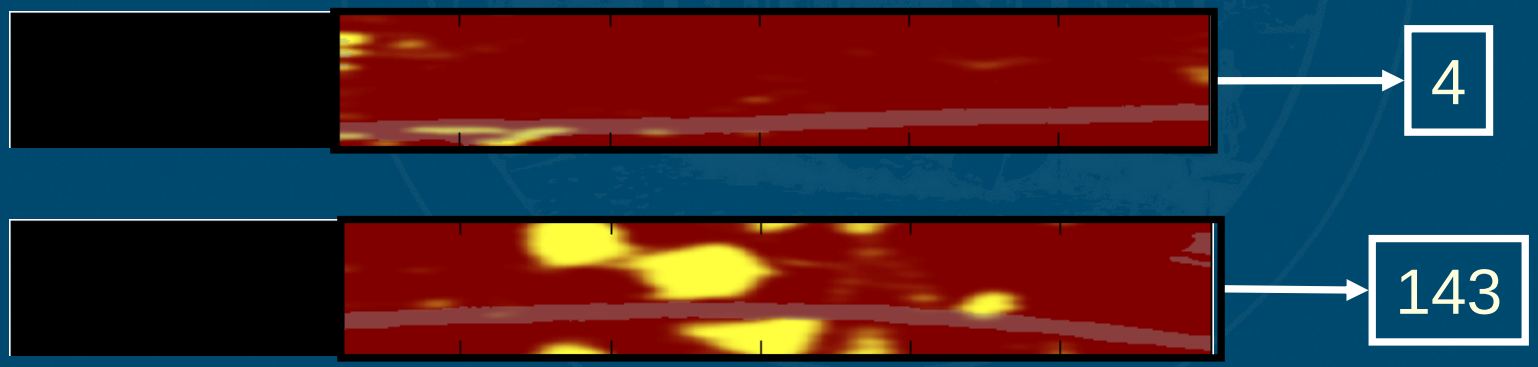


Intermediate Stenoses Caused by Lipid-rich vs Fibrotic Plaques: Detection by NIR Spectroscopy

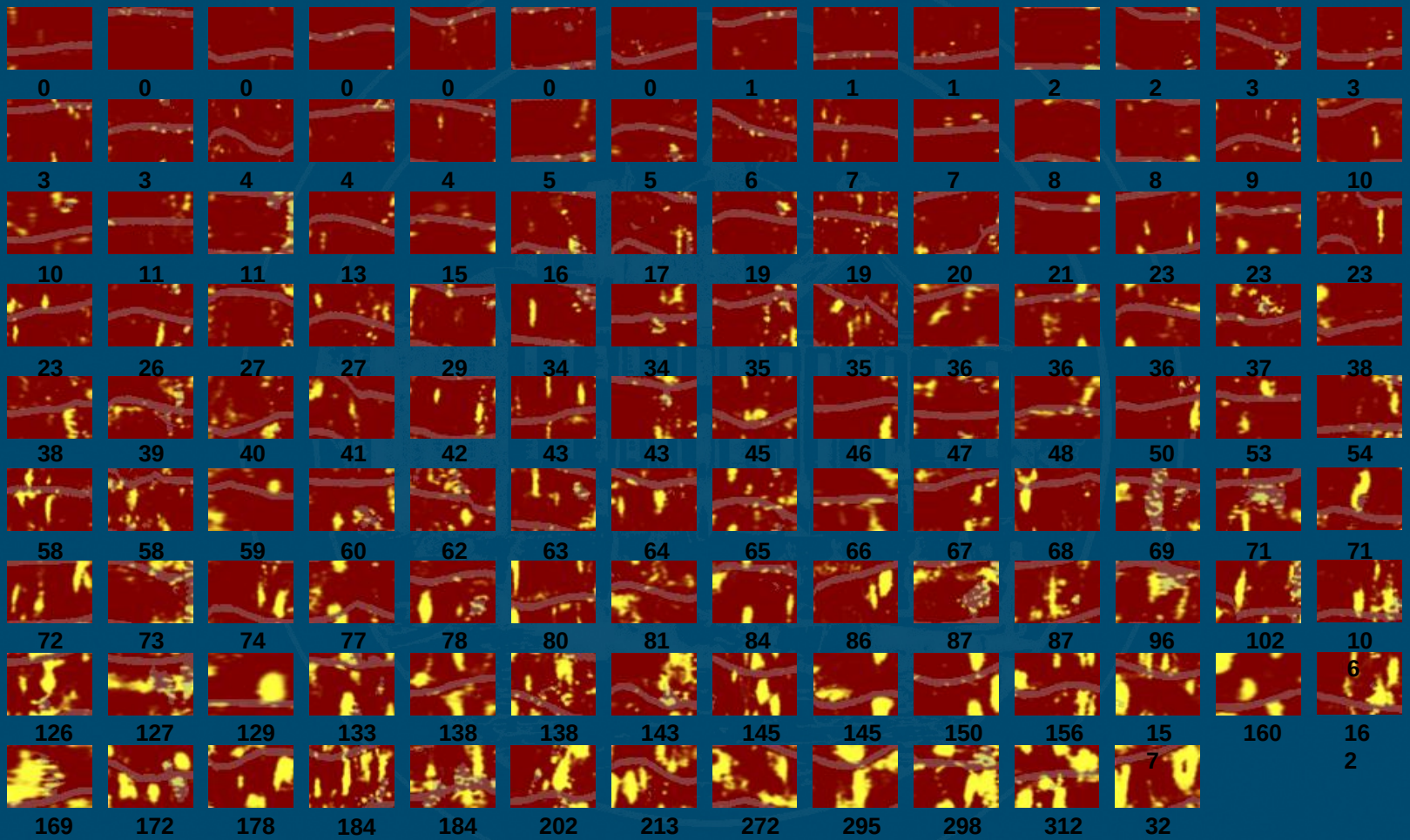


“Lipid Burden Index”

- Measure of overall Plaque Burden
  - Potentially useful as measure of risk or of pharmacologic treatment efficacy
- Fraction of Chemogram image pixels above probability of 0.6
  - Scaled from 0 to 1000
- 0.85 AUC vs. fibroatheroma presence (0.79 – 0.91)



LRP Burden Index Mosaic



Invasive Imaging Modalities

- IVUS
- Angioscopy
- IV MR
- **OCT**

- Thermography
- Spectroscopy

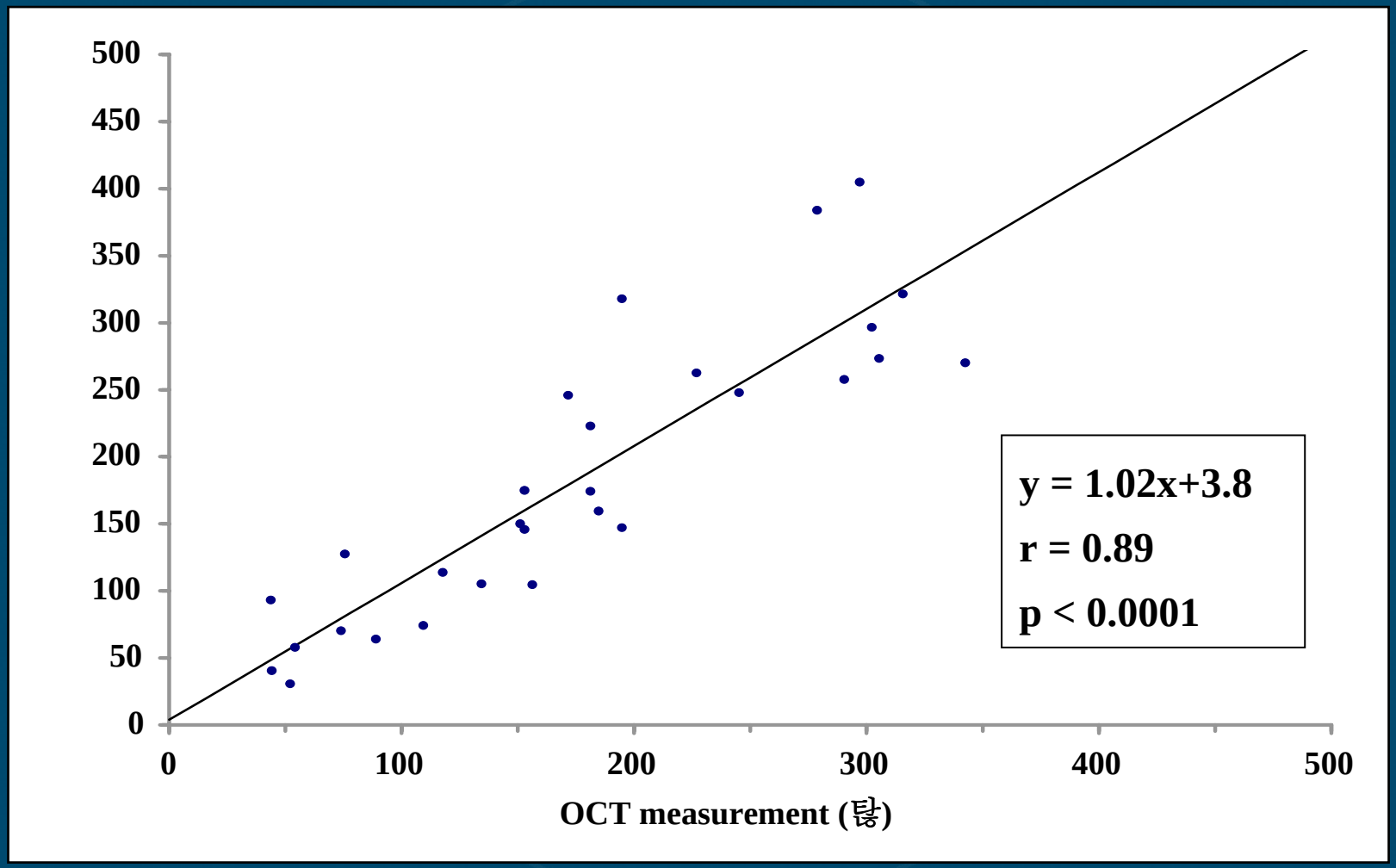
Ex Vivo Study Results

Fibrous	SENS	.87	PPV	.88
	SPEC	.97	NPV	.96
Calcific	SENS	.95	PPV	1.0
	SPEC	1.0	NPV	.95
Lipid pool	SENS	.92	PPV	.81
	SPEC	.94	NPV	.97

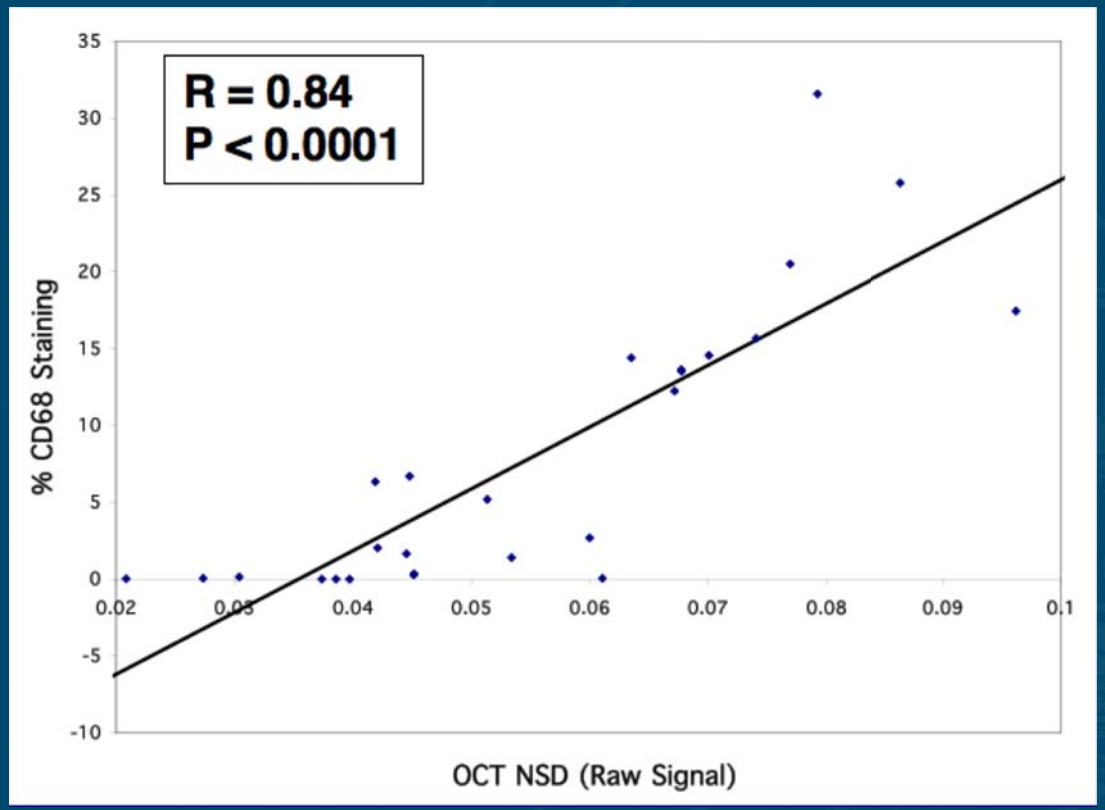
Interobserver k **= 0.88,** Intraobserver k **= 0.91**

Yabushita, .. Jang, Bouma, Tearney. Circulation 2002

Correlation between OCT and histology



Linear NSD vs. CD68



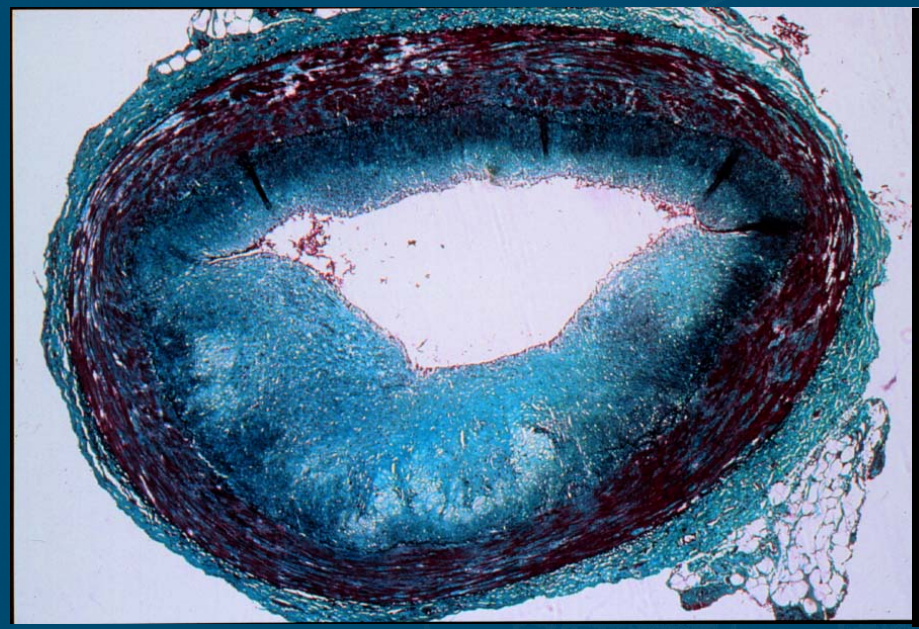
CD68 % area > 10 % - NSD cutoff 6.2%

SENS 100% (70-100%)

SPEC 100% (60 -100%)

Tearney, .. Jang, Bouma. Circulation 2003

Stable vs Vulnerable Plaque



Stable Plaque

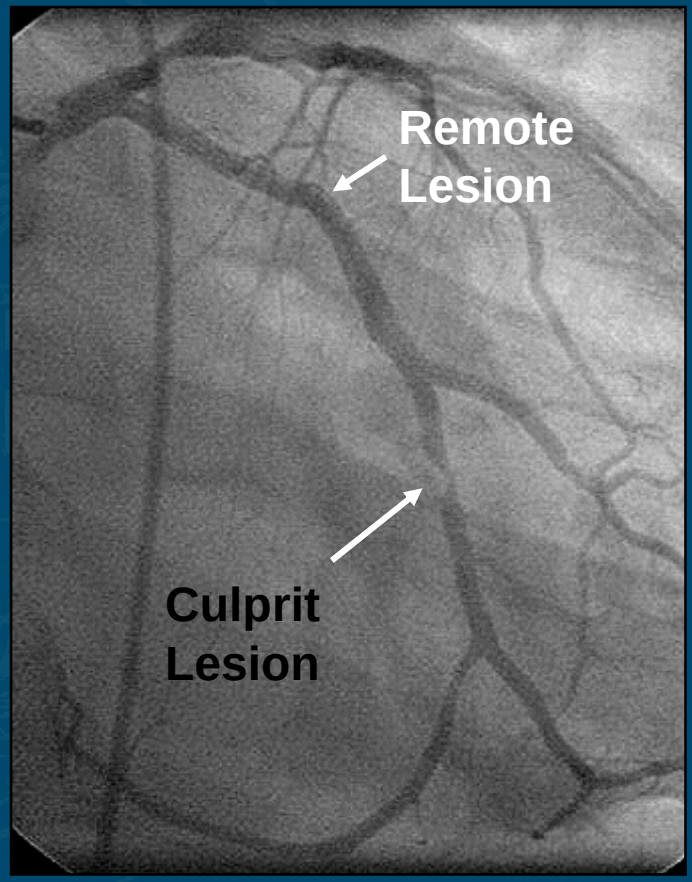
- Low lipid conc.
- Thick fibrous cap
- Low m Φ density

Vulnerable Plaque

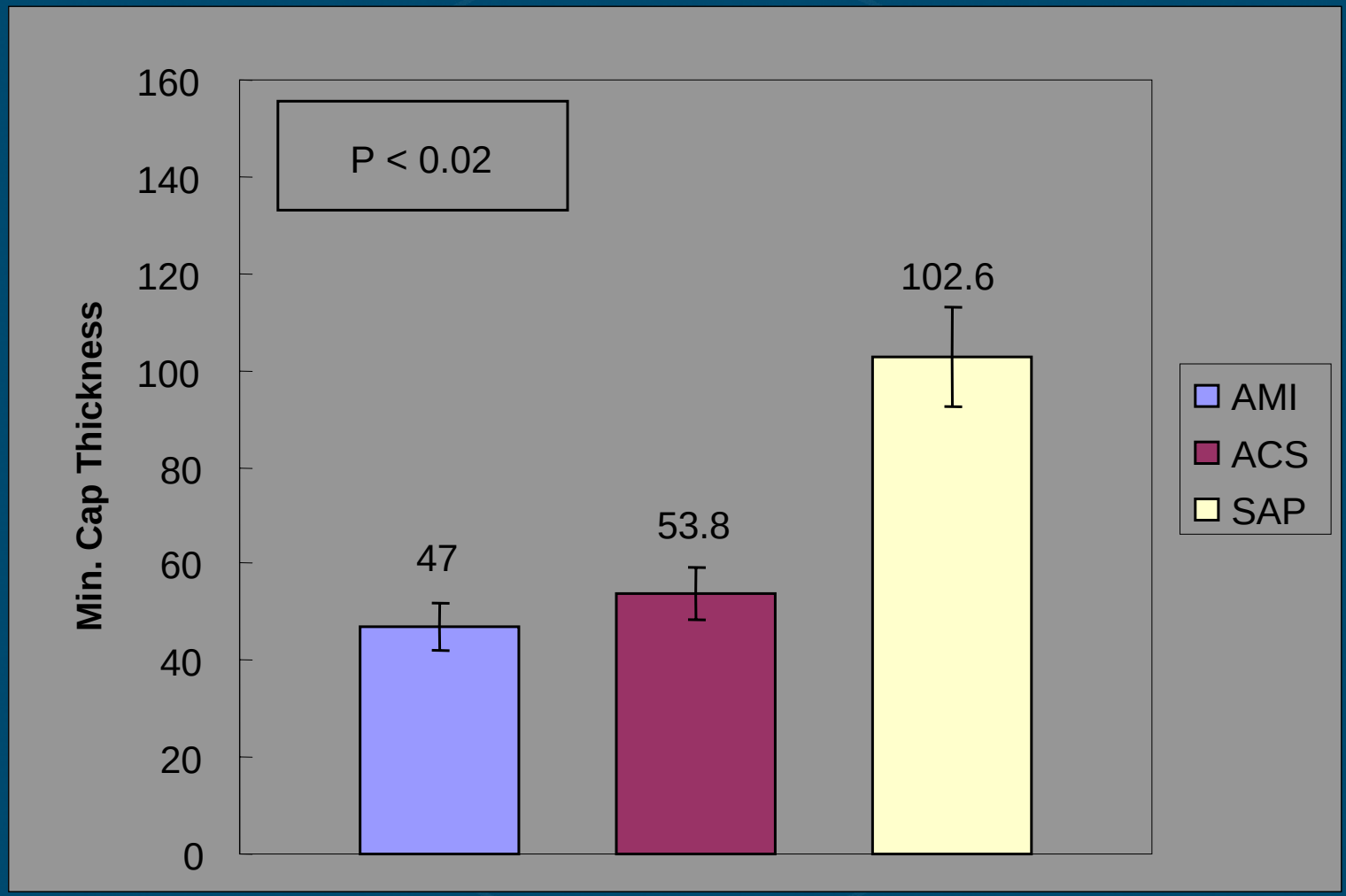
- High lipid conc.
- Thin fibrous cap
- High mΦ density

Plaque Characterization

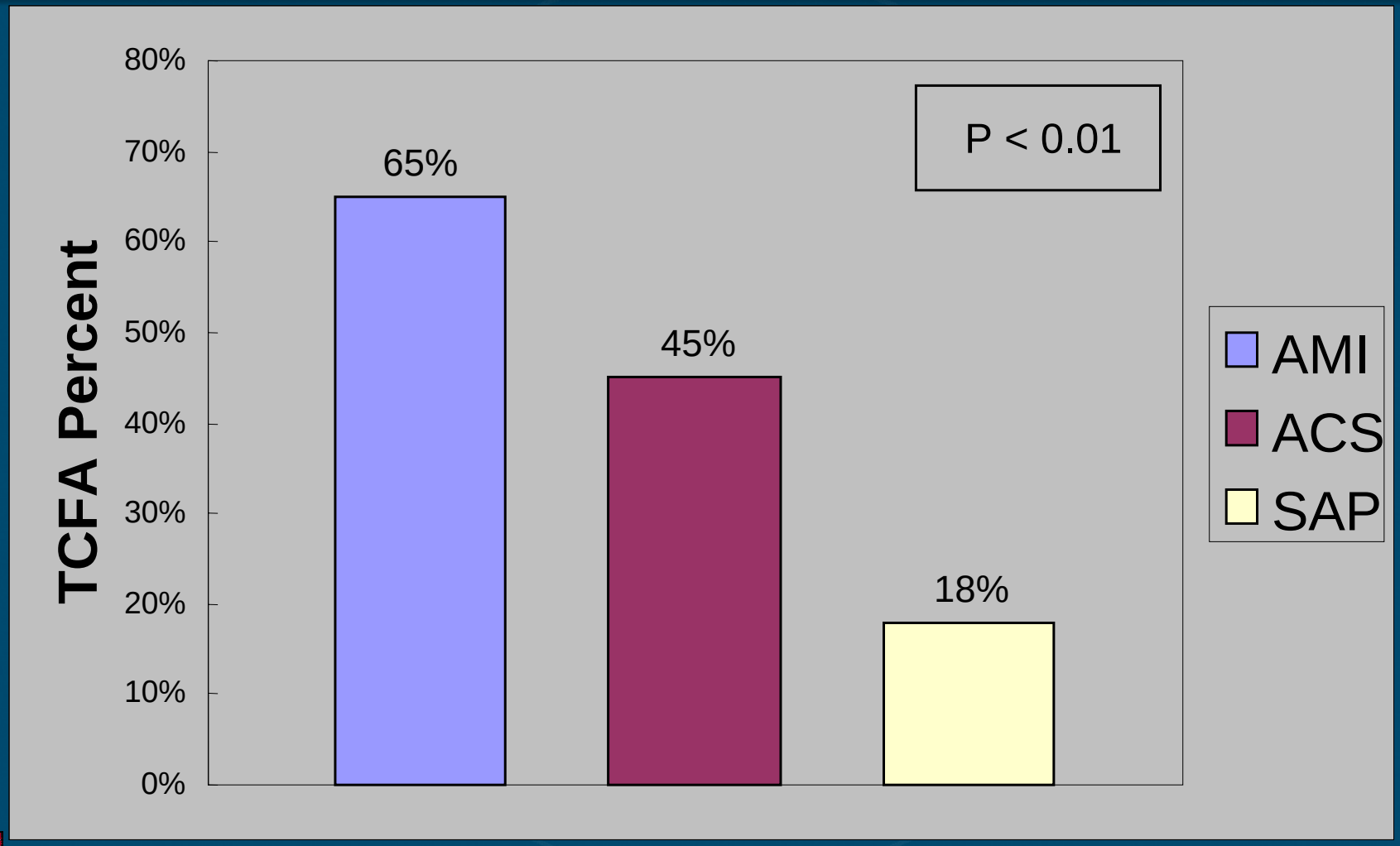
- Goal: Determine plaque characteristics in various presentations of CAD
- Methods
  - Patients with CAD; N=57
  - OCT imaging culprit/remote lesions
  - OCT: 3.0 F catheter 8 cc saline purge
- Analysis
  - Clinical presentation:
    - AMI (20)
    - ACS (20)
    - SAP (17)
  - Two OCT readers ⇨ consensus
  - Cap thickness
  - Macrophage density (~NSD)



Cap Thickness

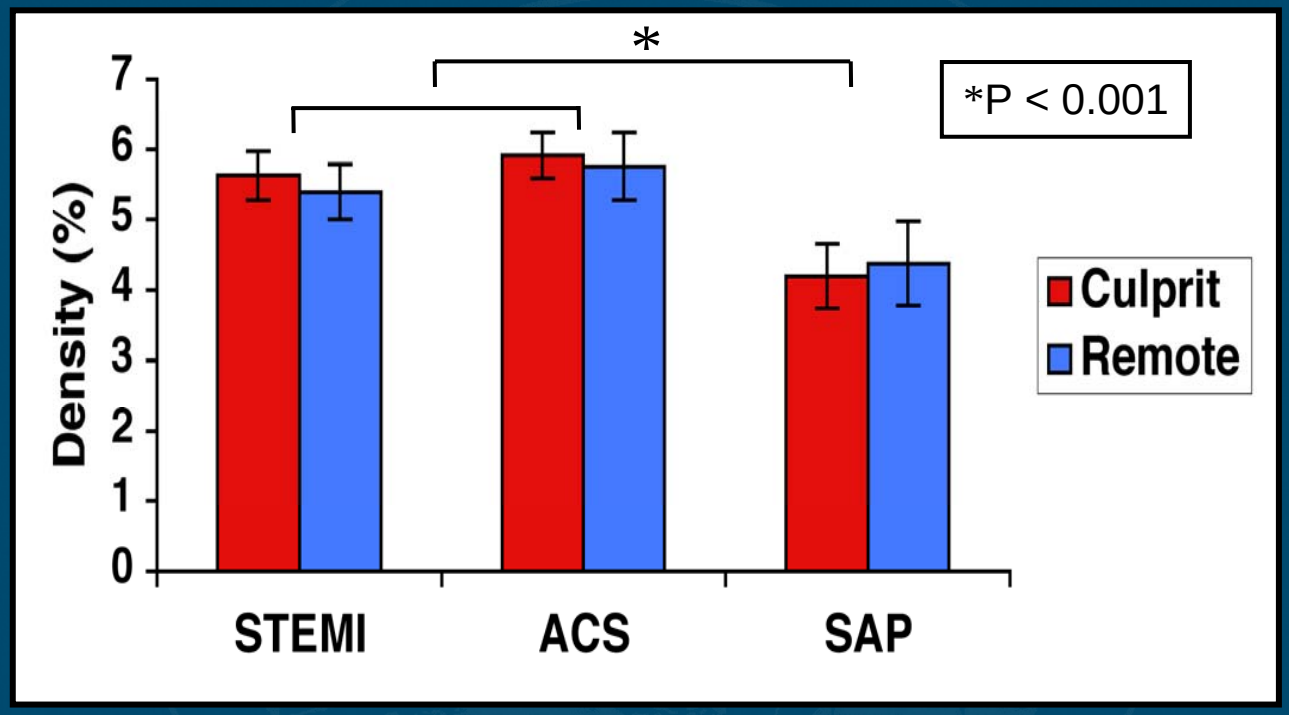


Prevalence of TCFA



Jang et al. Circulation 2005

Macrophage Density for Acute and Stable Clinical Syndromes



- Cap macrophage density is higher in acute clinical syndromes in both culprit and remote sites

Limitations of OCT

1. Need to create blood free zone
2. No scanning capability
3. Shallow penetration depth
4. No functional information

Intravascular Diagnostics for VP

Modality	Resolution	Penetration	Cap	Lipid	Inflam	Use
IVUS	100 um	good	+	++	-	+++
Angioscopy	-	poor	+	++	-	+
IV MR	160 um	poor	+	++	++	+
OCT	10 um	poor	+++	+++	++	+
Thermography	-	poor	-	-	+++	++
Spectroscopy	-	poor	+	++	++	+

Modified from MacNeill and Jang. ATVB 2003

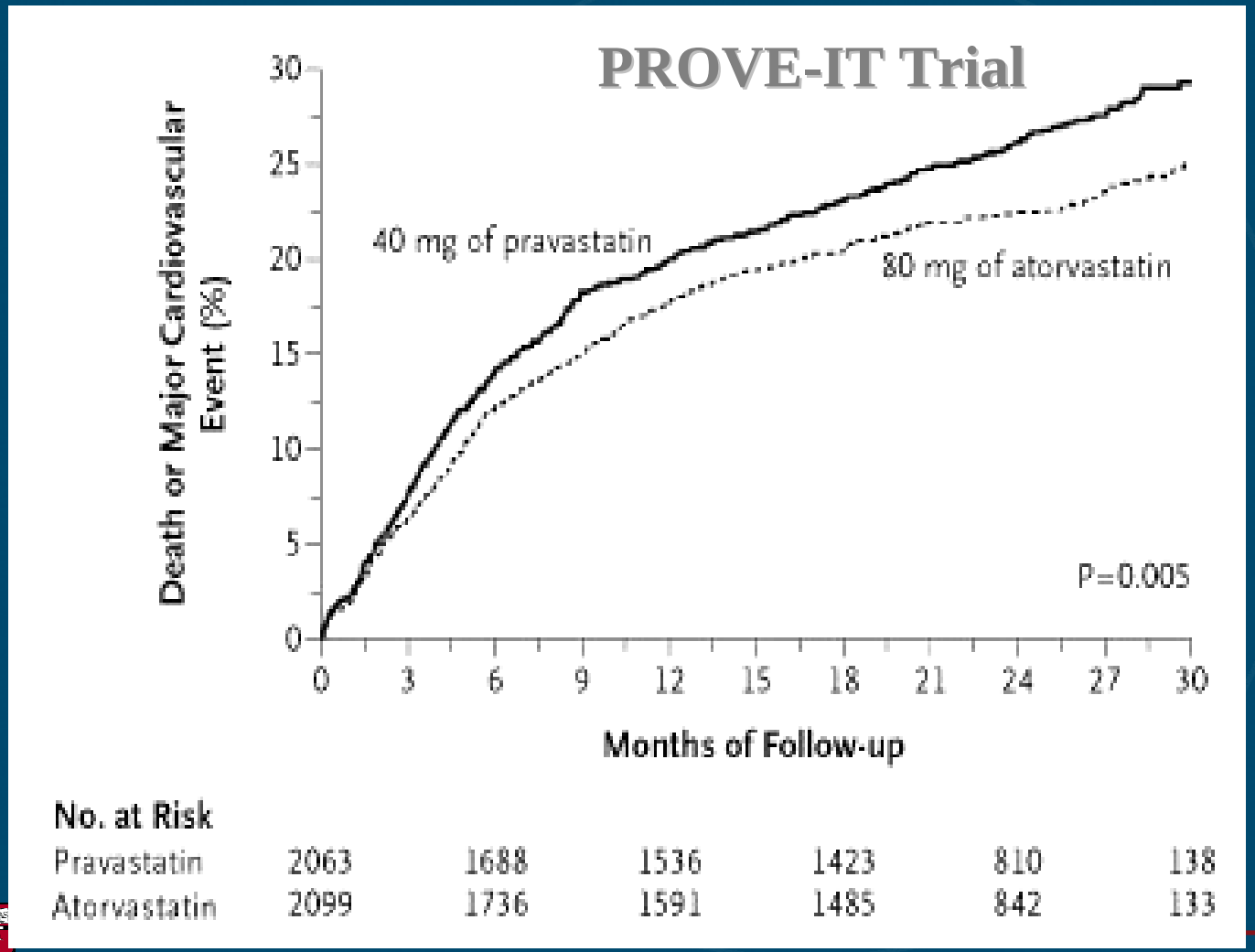
Ideal Invasive Diagnostics for VP

- Combination of imaging and physiologic test
  - OCT + thermography
  - OCT + spectroscopy
  - IV MR + thermography

Invasive Diagnostics for VP

- **Questions**
  1. Can one justify the invasive diagnostic tests?
     - invasive
     - high cost
     - pt acceptability as a screening tool
  2. Which patients?
  3. When to perform the tests?
  4. When to treat the lesions??

Optimal Medical Prevention



26.3%
vs.
22.4%
at 2y

Cannon et al. *NEJM* 2004; 350: 1495–1504.

Invasive Diagnostics for VP

- **Inherent limitations**
  1. Local information (systemic disease)
  2. Superficial information
  3. Difficulty in sampling the same site
  4. Gold standard (??) – validation problem
  5. Only when a local therapy is viable!!

Acknowledgements

Cardiology Division

OC Raffel
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