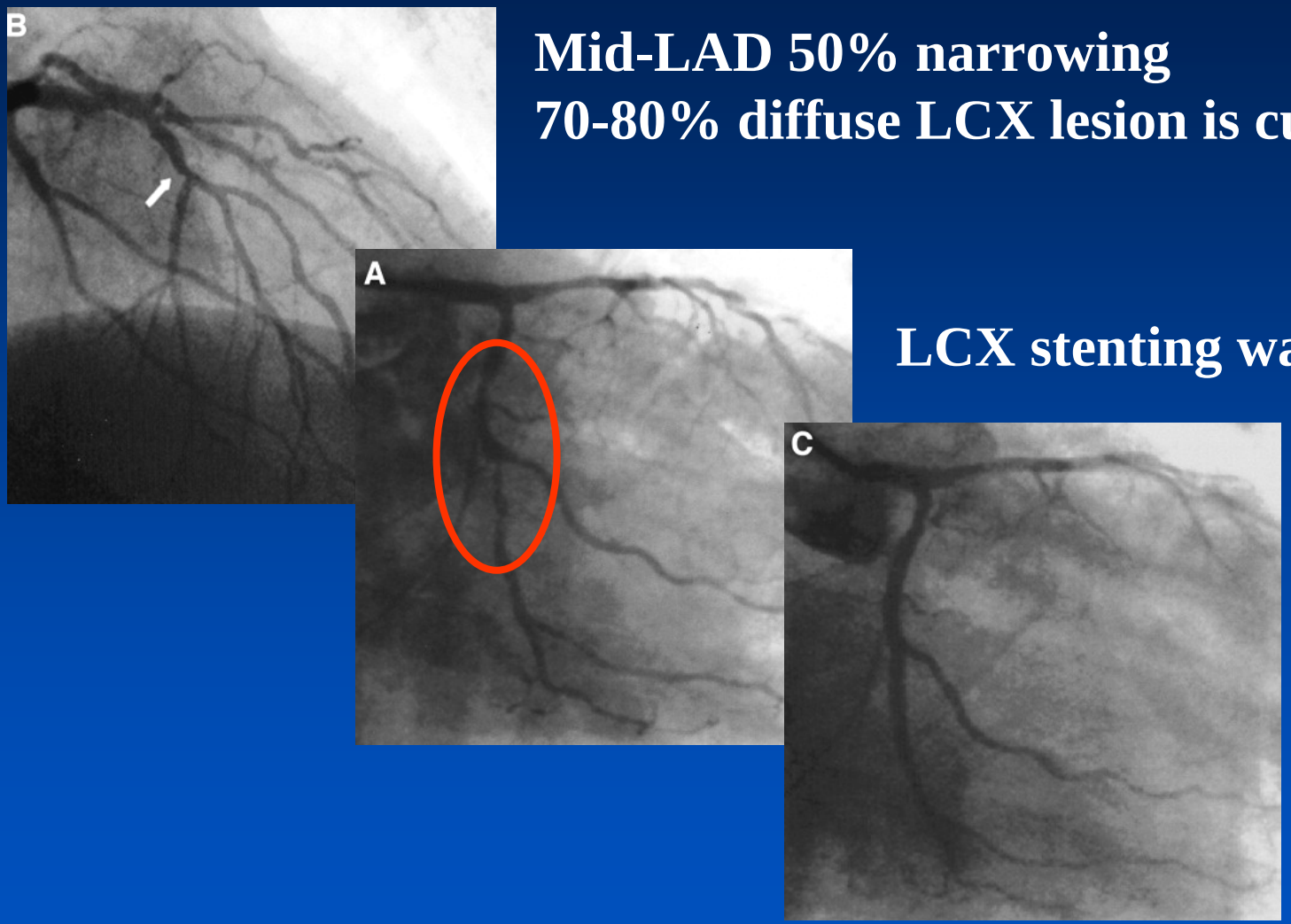
VH-IVUS
Matched and Mismatched
with Clinical Manifestation

Seung-Jung Park, MD, PhD

Professor of Internal Medicine
Asan Medical Center, *Seoul, Korea*

58/M, Recent infero-lateral MI

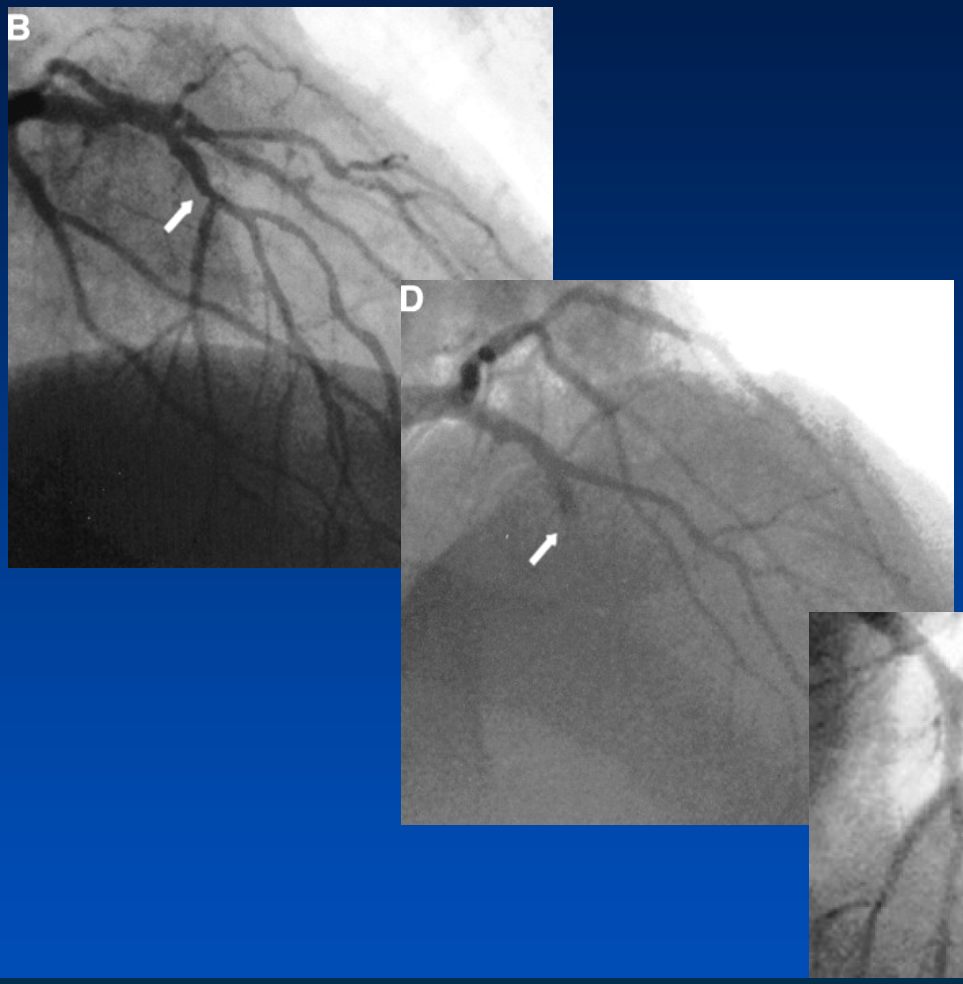


Mid-LAD 50% narrowing
70-80% diffuse LCX lesion is culprit,

LCX stenting was done

Circulation 2006;113:e61-2

1 hour later



LAD occluded 100%
AMI developed

LAD Stenting

Detection of vulnerable plaque is important to identify high risk patients.

A case report

Culprit Lesion Seen 1 Hour Before Occlusion

Limits of Coronary Angiography in Detecting Vulnerable Plaques

Enrico Romagnoli, MD; Francesco Burzotta, MD, PhD; Floriana Giannico, MD; Filippo Crea, MD

1. The mechanism responsible for the transition from stable to unstable coronary syndromes does not operate at the site of single plaque but affects whole coronary circulation
2. **Coronary angiography is limited to identify the vulnerable plaque**

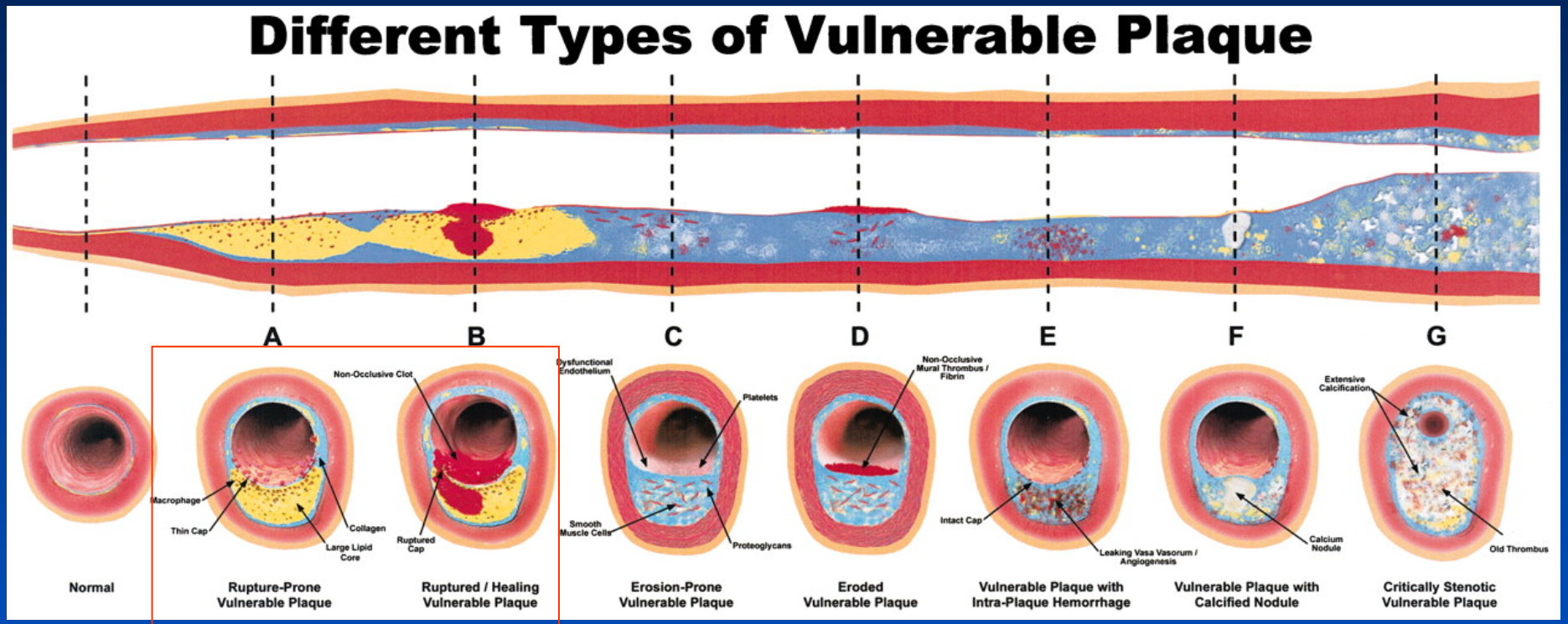
Circulation 2006;113:e61-2

Vulnerable Plaque

Nomenclature

1. Plaque disruption
2. Unstable plaque
3. Vulnerable plaque
4. Plaque rupture
5. High-risk plaque
6. Culprit plaque
7. Plaque fissure
8. Plaque erosion

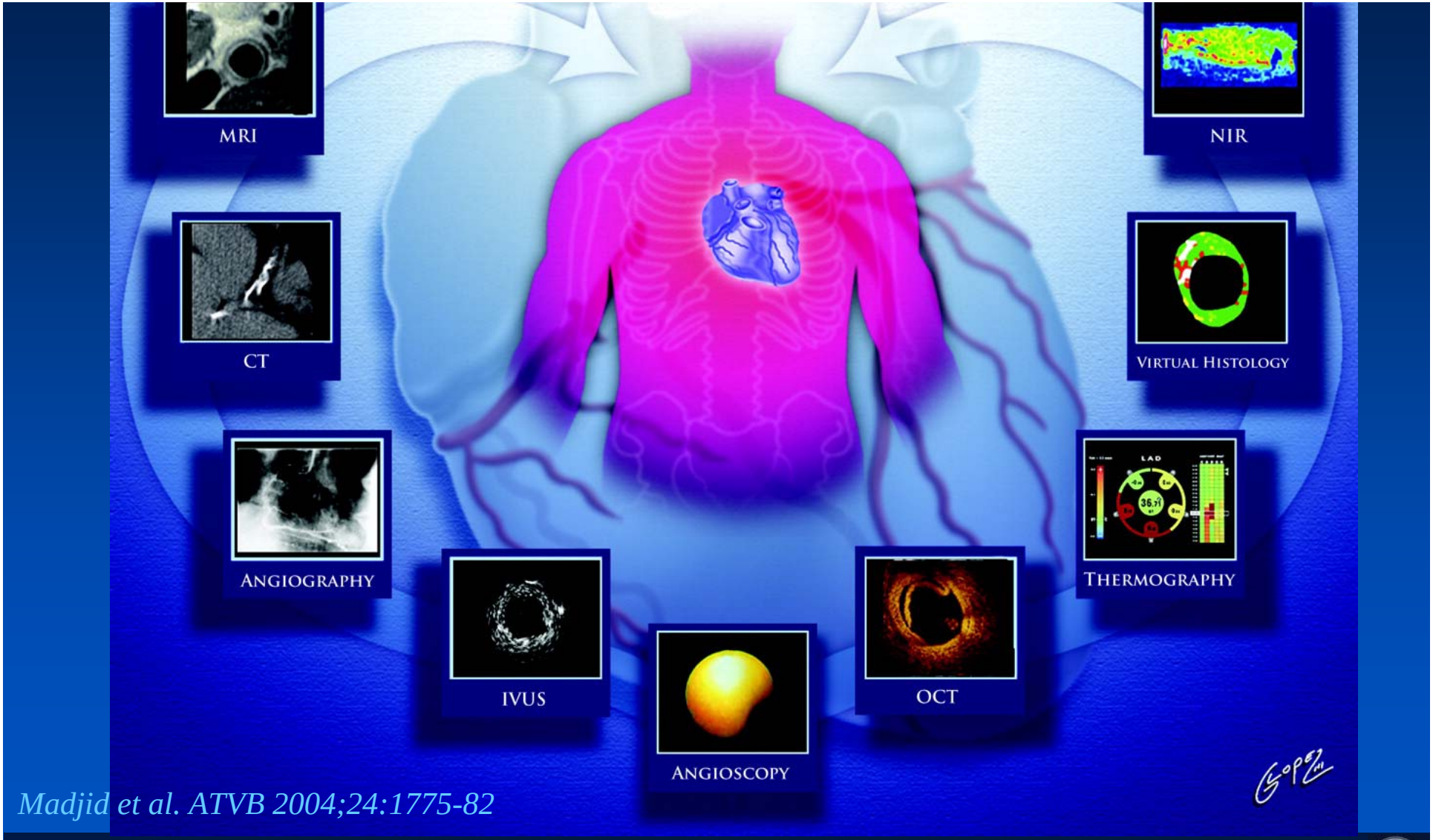
Finding Vulnerable Plaques



70% of ACS culprit lesions

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

Finding Vulnerable Plaques



Madjid et al. ATVB 2004;24:1775-82

Why
Virtual Histology ?

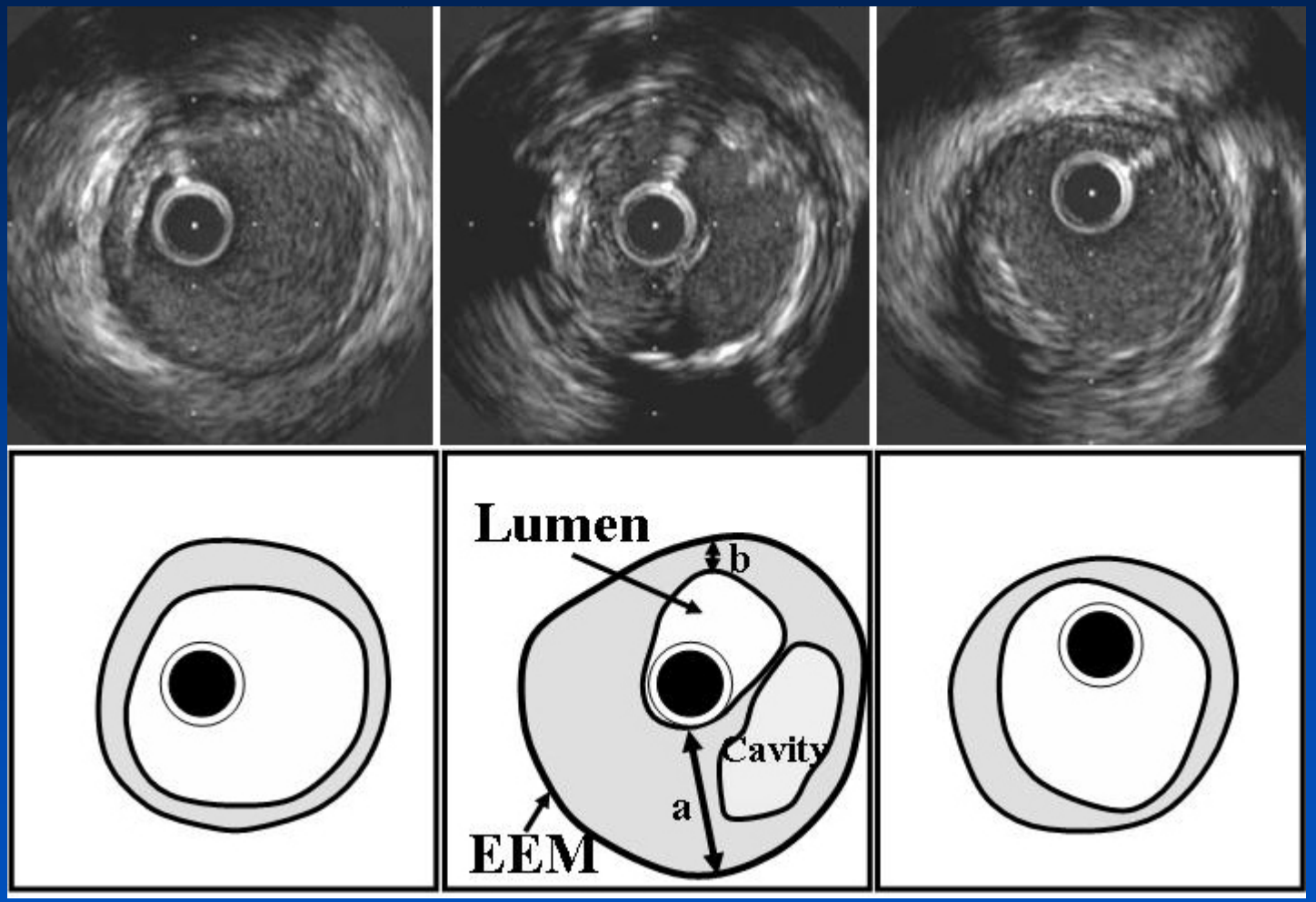
To find out Vulnerable Plaque…

Finding Vulnerable Plaques

IVUS ?

Ruptured Plaques

What does it mean ?



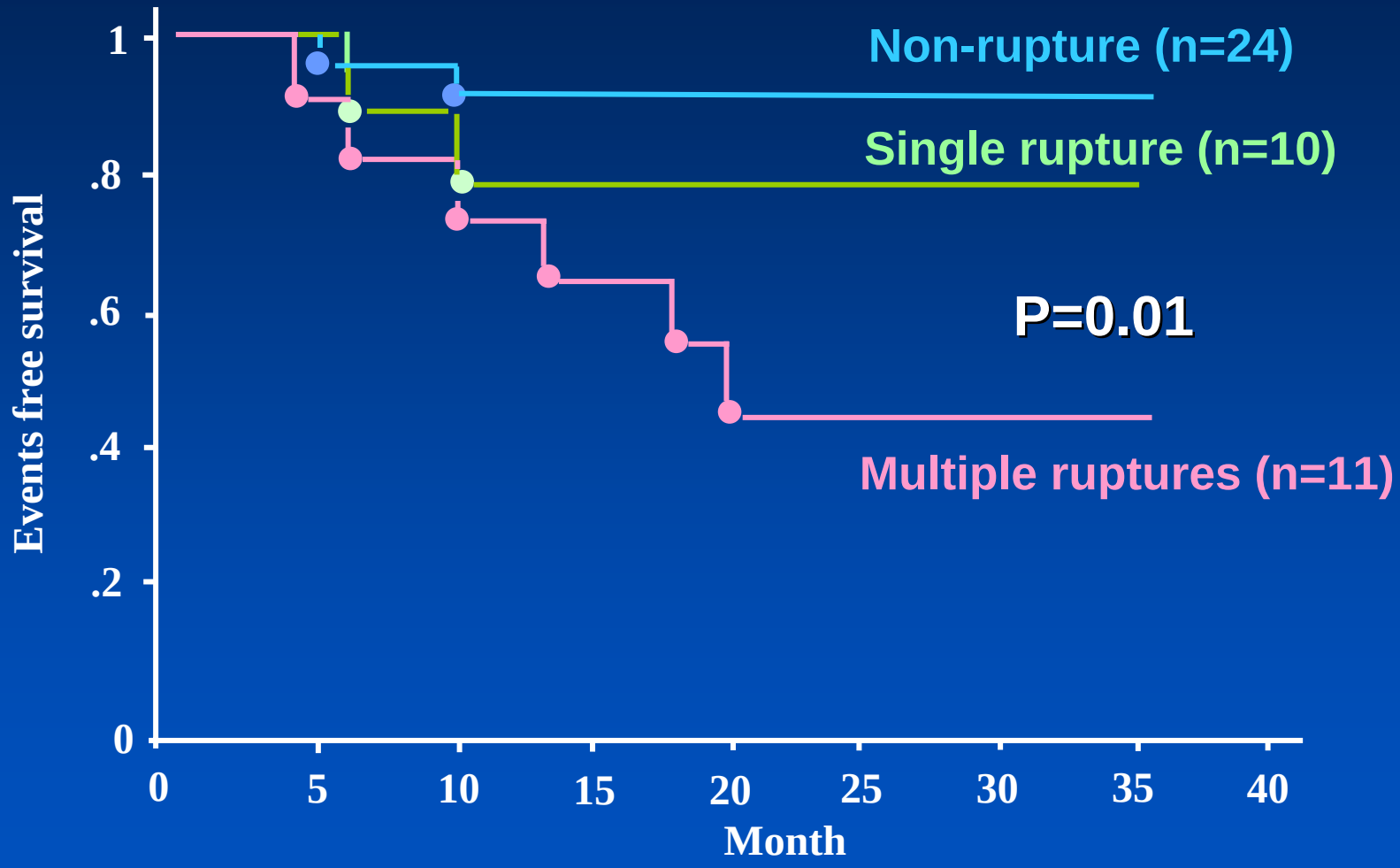
Insights into pre-rupture morphology

	Mean±1SD	CoV	10th Percentile	90th Percentile
Reference				
1 **Lumen CSA**	11.7±3.5	0.29	8.1	15.3
EEM CSA	20.2±5.6	0.27	14.2	26.7
P&M CSA	8.5±3.0	0.35	4.9	12.4
Plaque Burden	0.42±0.75	0.18	0.31	0.49
Lesion				
Lumen CSA	4.9±2.7	0.55	2.1	8.6
2 **EEM CSA**	20.8±6.0	0.29	14.3	28.5
P&M CSA	15.9±4.9	0.31	9.8	22.4
Min P&M Th	0.5±0.3	0.58	0.2	1.0
3 **Max P&M Th**	2.3±0.6	0.25	1.6	3.0
Eccentricity	0.32±0.23	0.71	0.09	0.66
4 **Plaque Burden**	0.76±0.10	0.12	0.63	0.88
AS	0.57±0.19	0.34	0.28	0.80
5 **RI**	1.10±0.20	0.18	0.87	1.38
Arc of Ca^{++}	46.9±51.2	1.09	0	106.7

99% of ruptured plaques fit 4 of these 5 parameters

IVUS in 129 arteries of 45 1st MI patients

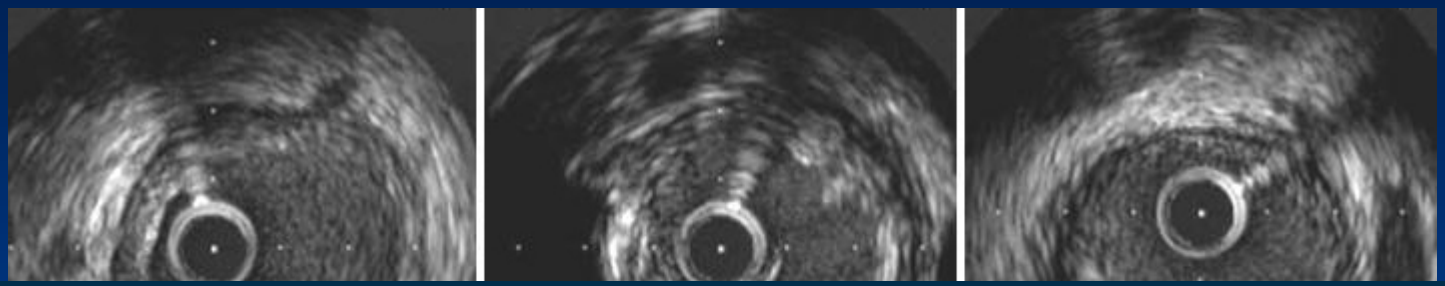
Death or ACS-Free Survival



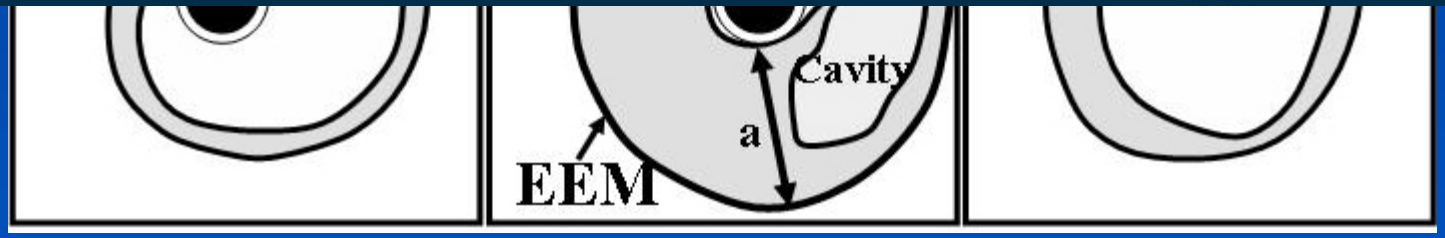
Tanaka et al. J Am Coll Cardiol 2005;45:1594-9

Ruptured Plaques

What does it mean ?



Unfortunately, it is impossible to determine whether this lesion has the histologic and mechanical substrates for a rupture-prone plaque



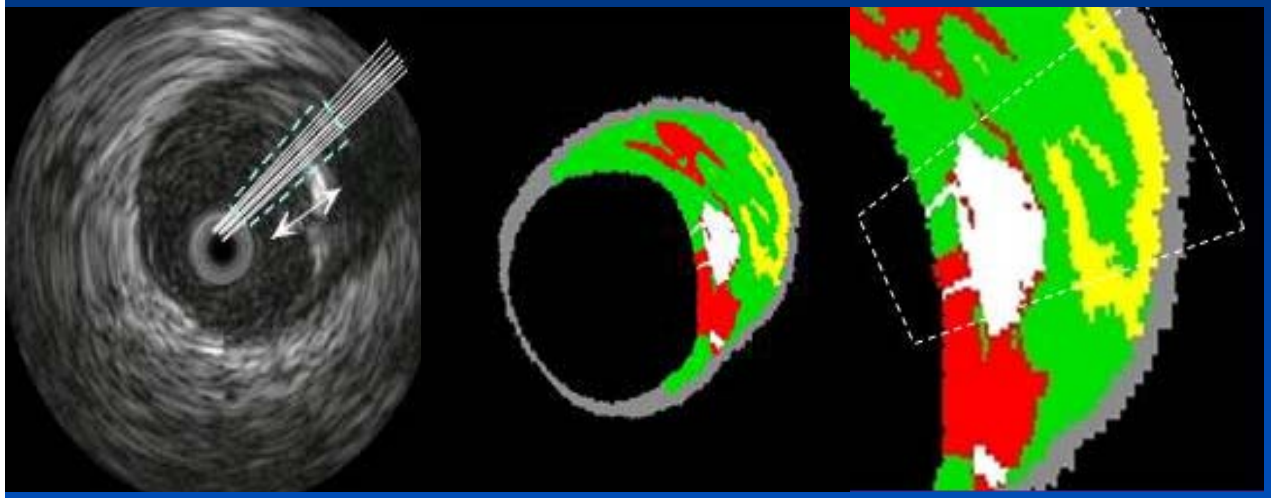
Insights into pre-rupture morphology

IVUS

- Conventional grey scale IVUS cannot detect vulnerable plaques
- Other IVUS based imaging modalities have the potential to detect vulnerable plaques,

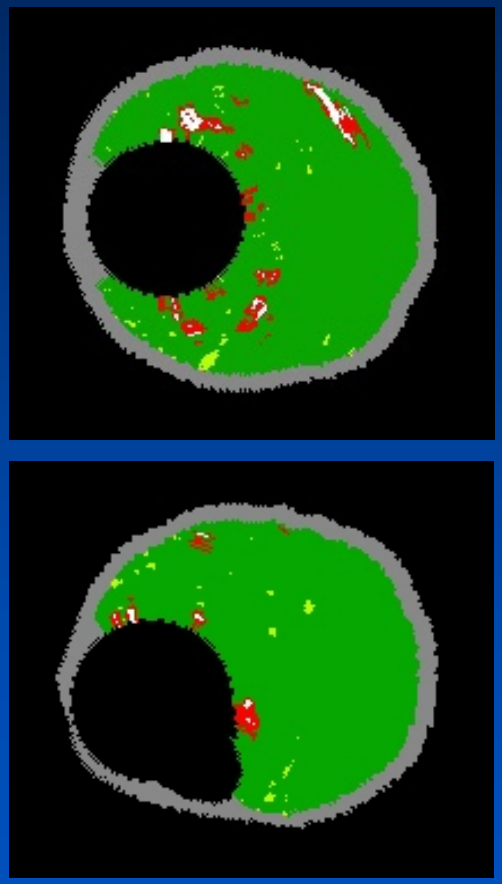
Virtual Histology -IVUS

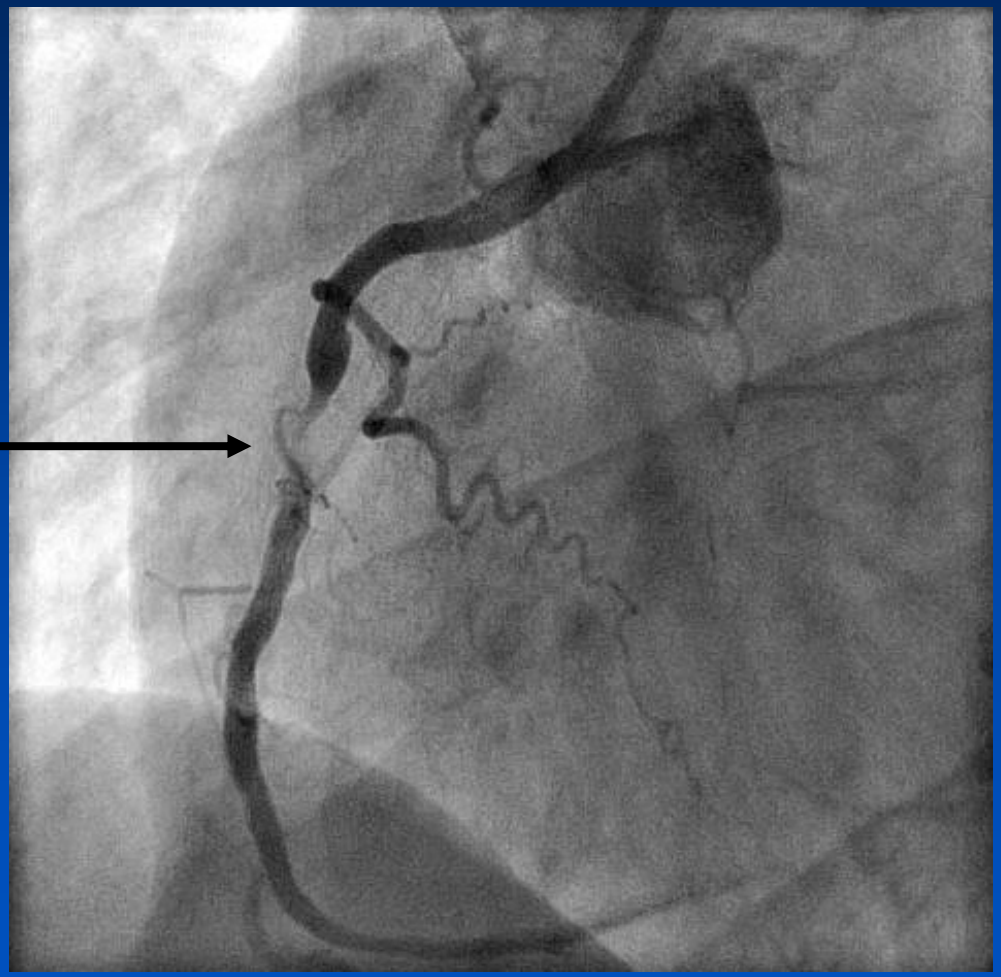
In-vivo characterization of plaque composition via advanced spectral analysis



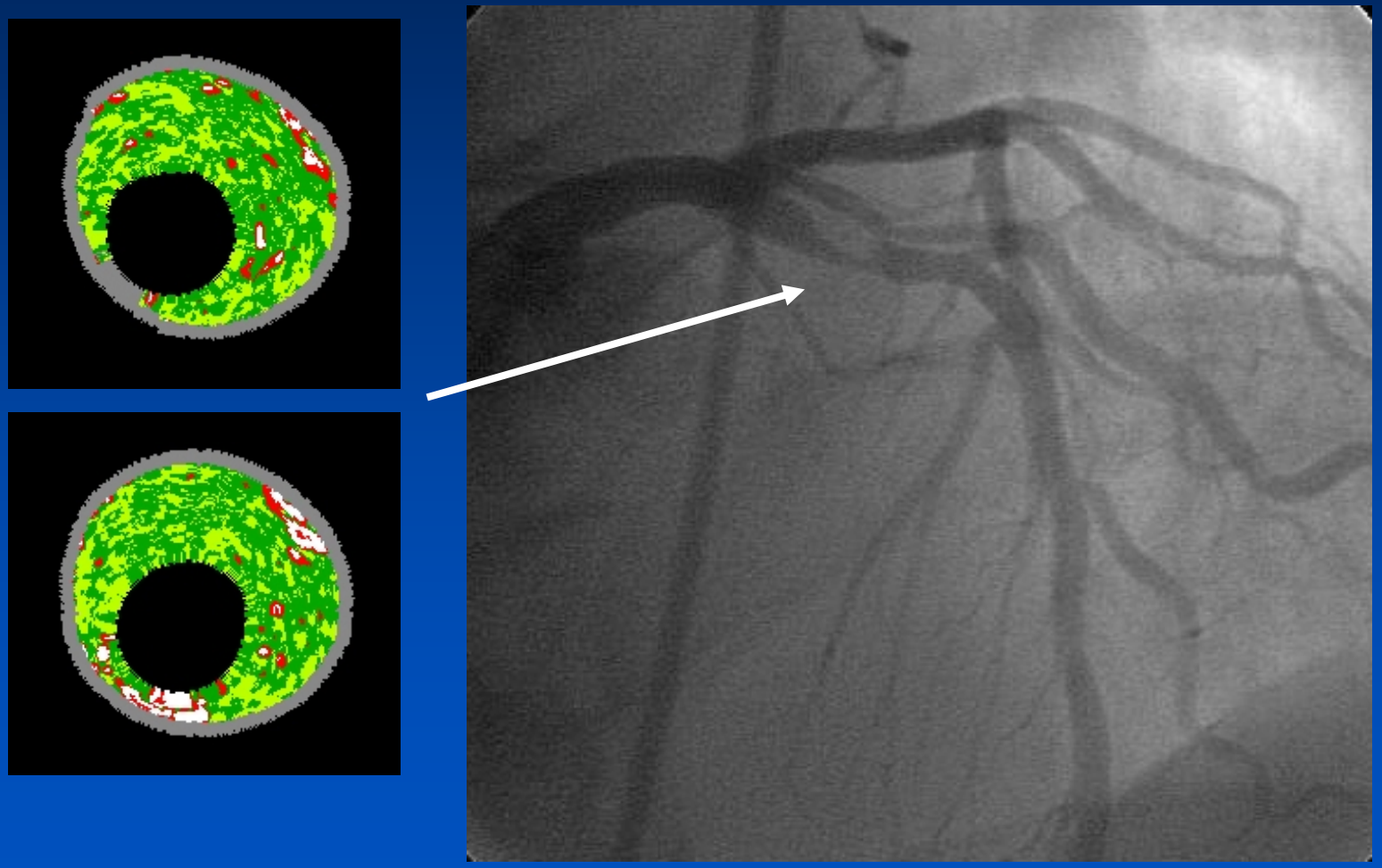
- Fibrous
- Fibro-fatty
- Necrotic
- Calcium

Fibrotic Plaque

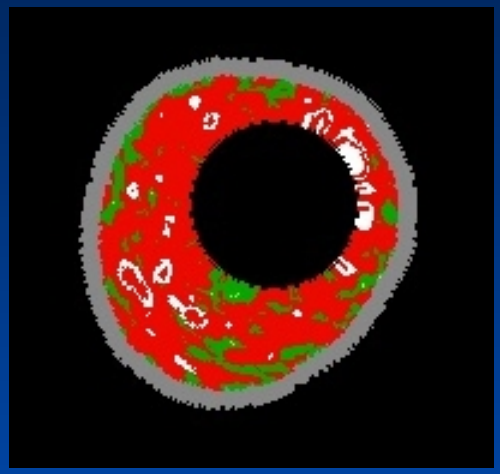


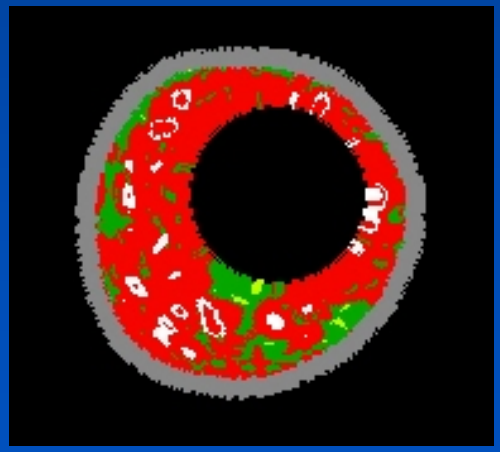


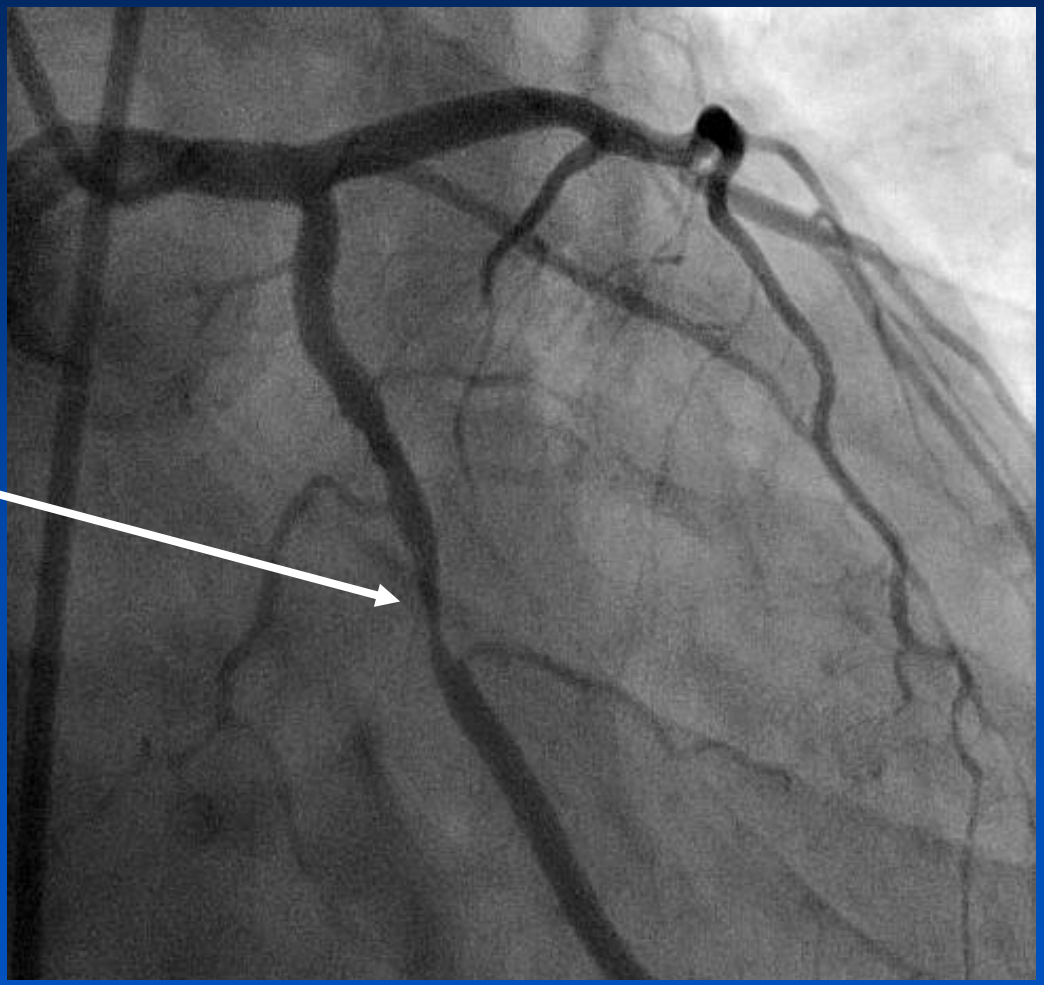
Fibrofatty Plaque



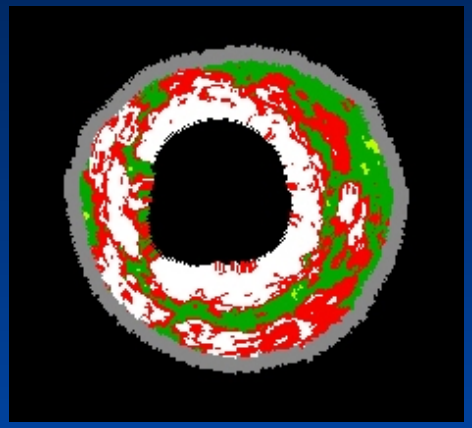
Necrotic Core

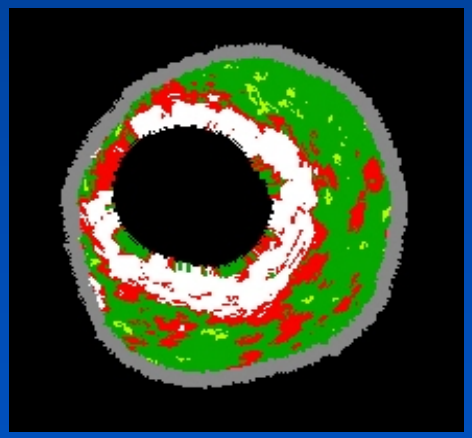


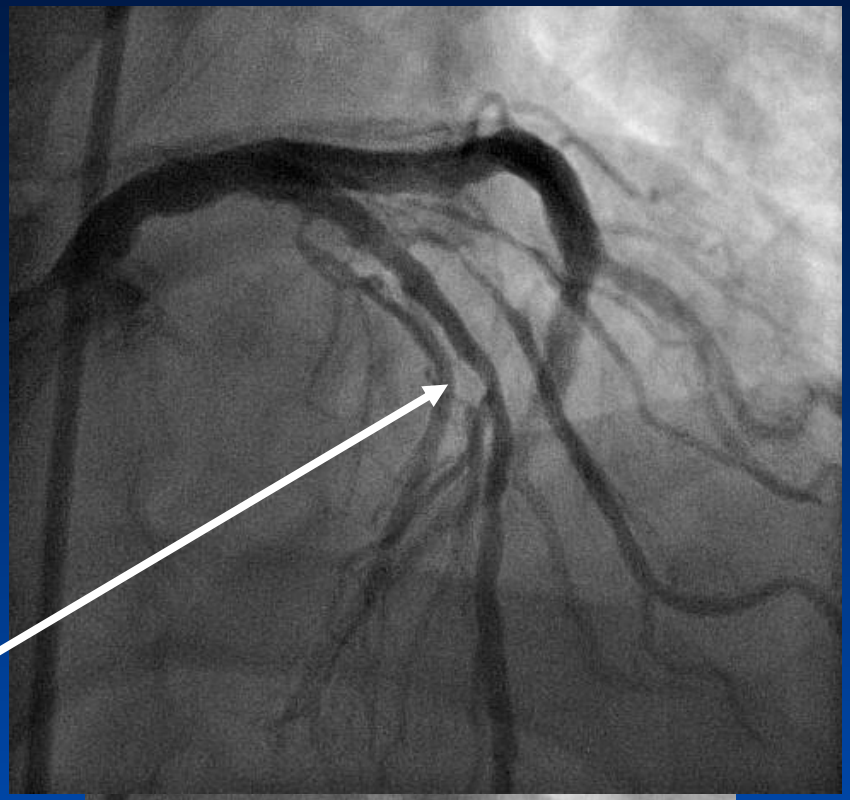


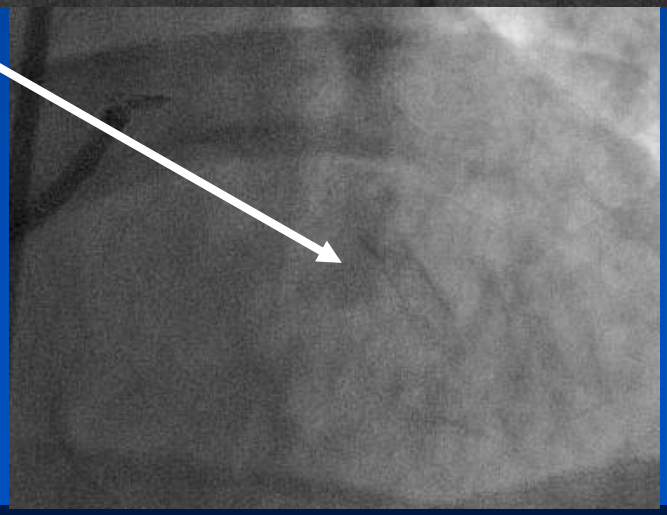


Dense Calcium



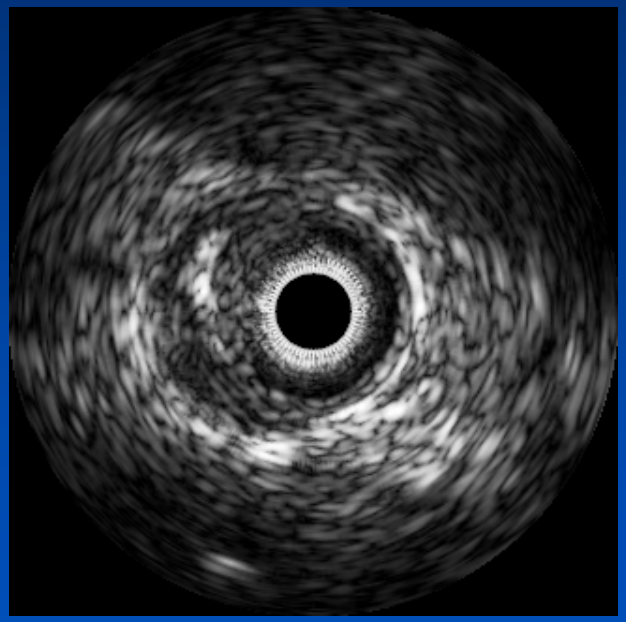


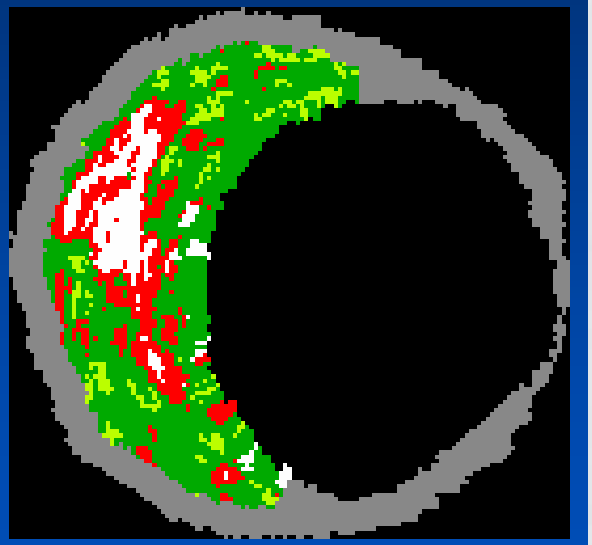




VH imaging is good correlation with pathologic findings

IVUS





Histology

In vitro Validation of VH Tissue Characterization

Eagle Eye VH Accuracy

VH IVUS vs histopathology from fresh post-mortem coronary arteries

	Sensitivity	Specificity	Predictive Accuracy
Fibrous tissue (n=162)	84.0%	98.8%	92.8%
Fibrofatty (n=84)	86.9%	95.1%	93.4%
Necrotic core (n=69)	97.1%	93.8%	94.4%
Dense calcium (n=92)	97.8%	99.7%	99.3%

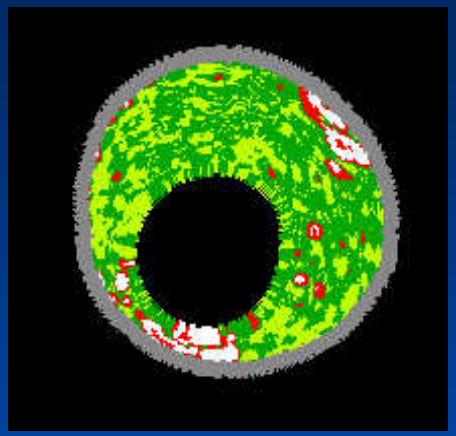
G Vince, A Nair, ATL, Volcano Therapeutics, Cleveland

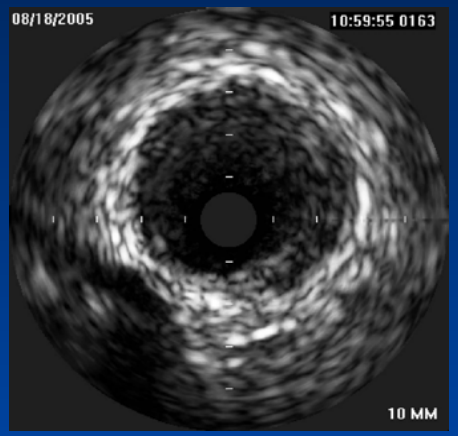
Is VH imaging good correlation with clinical manifestation too ?

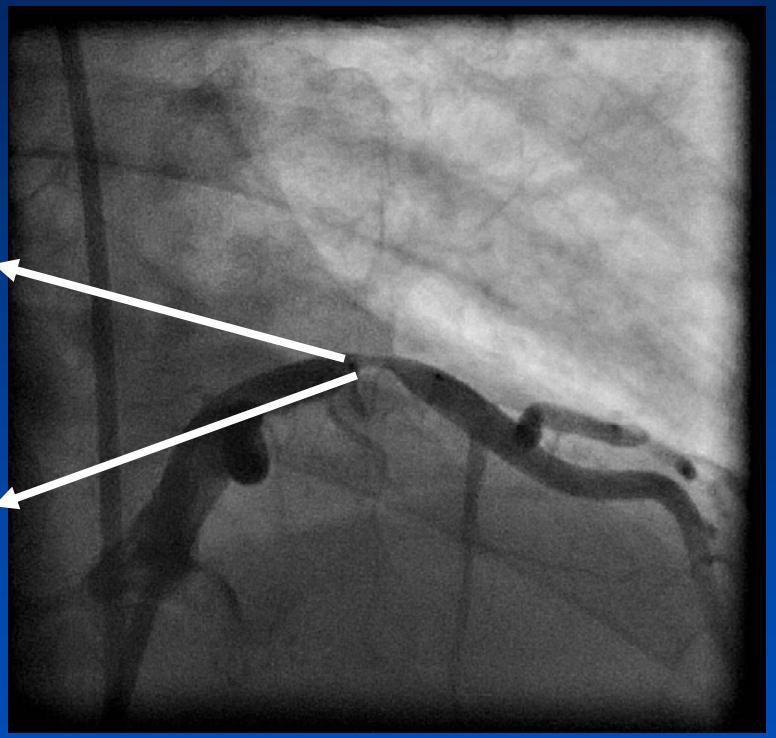
However, VH imaging is Matched and Mismatched with Clinical Manifestation

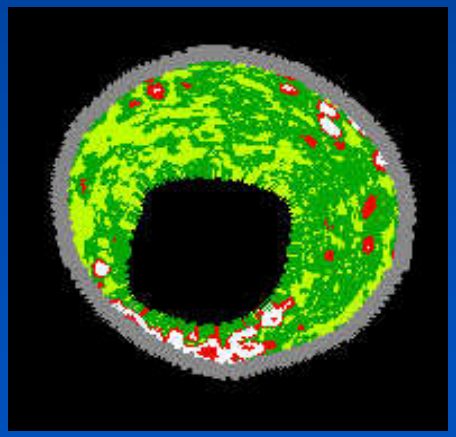
Matched with IVUS and clinical presentation

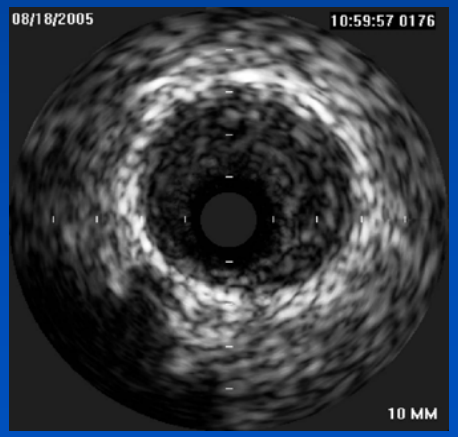
Patients with Stable Angina





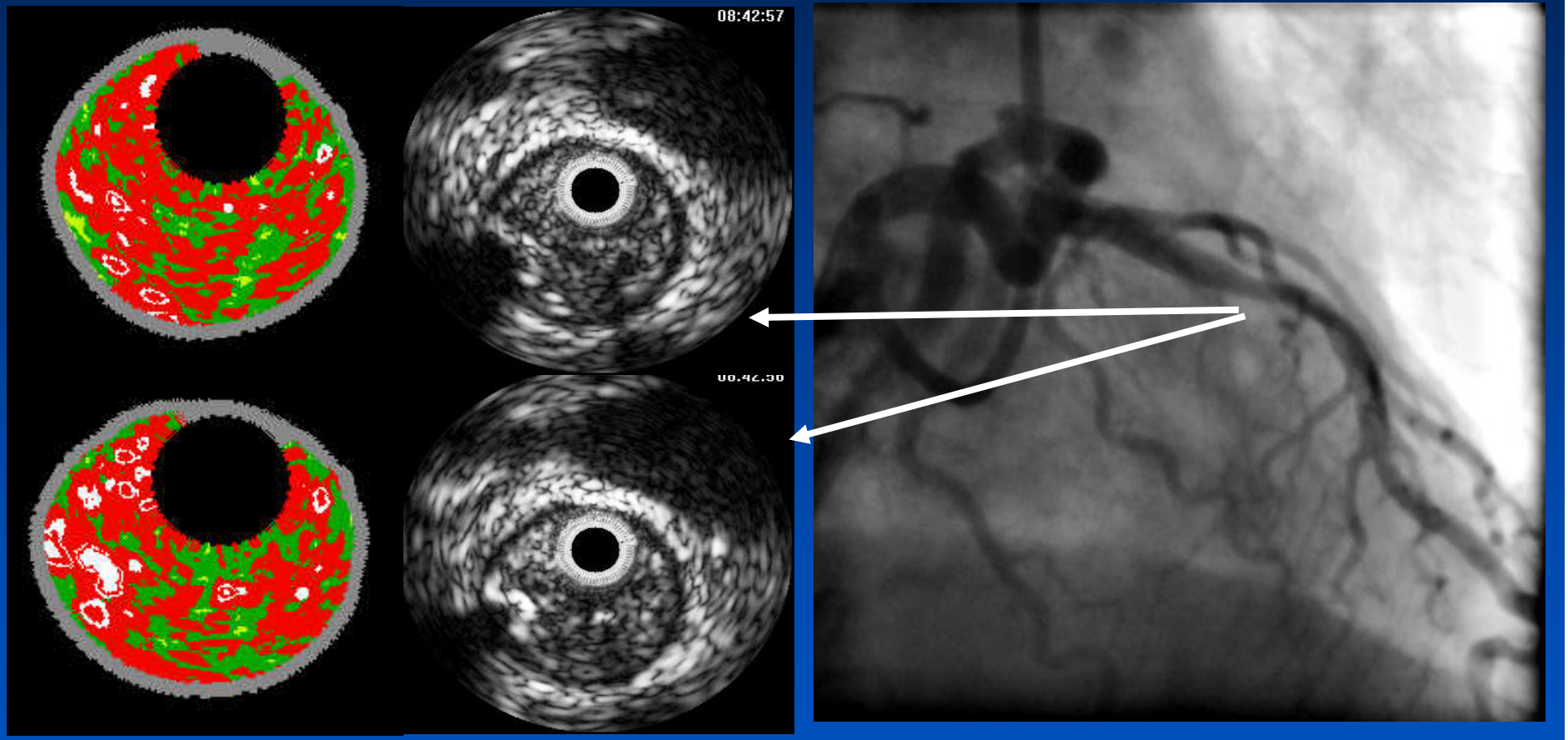




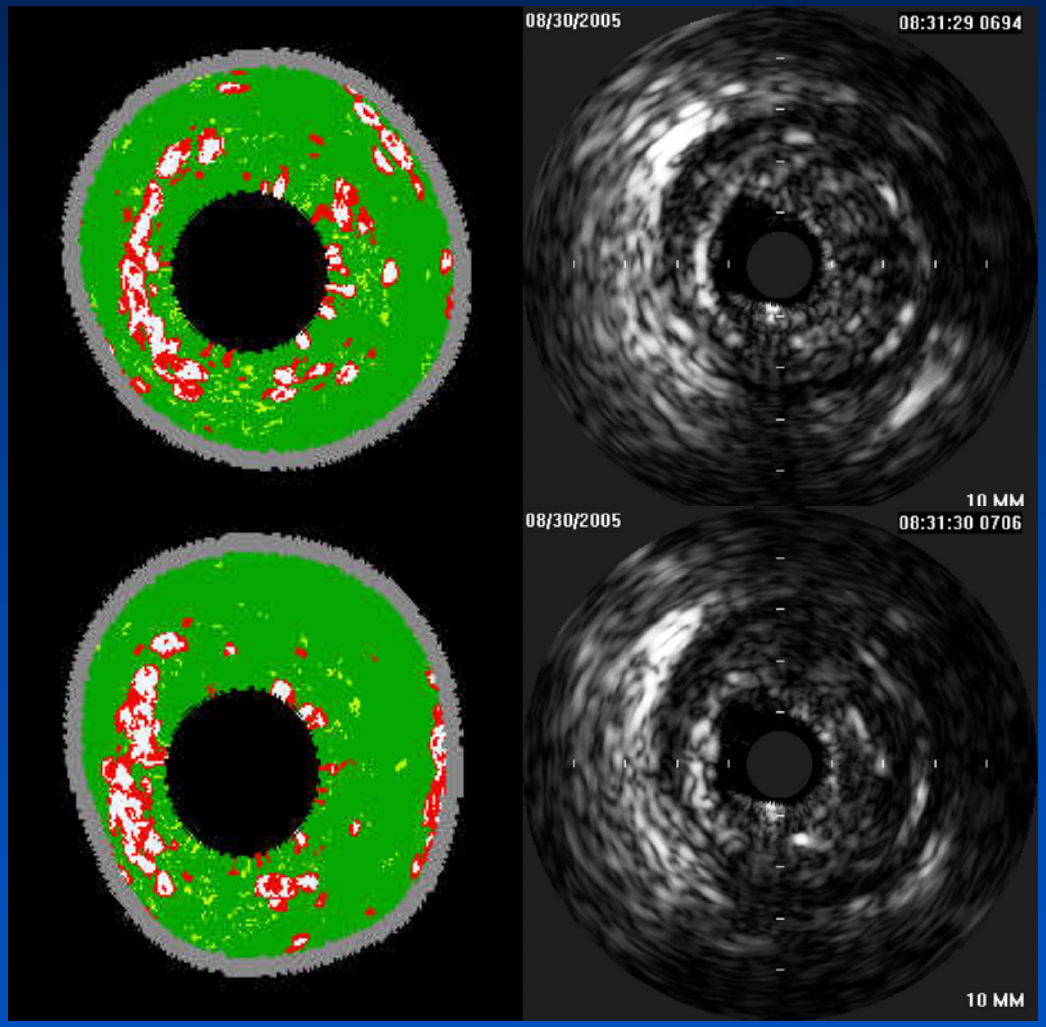


Well matched with clinical manifestation

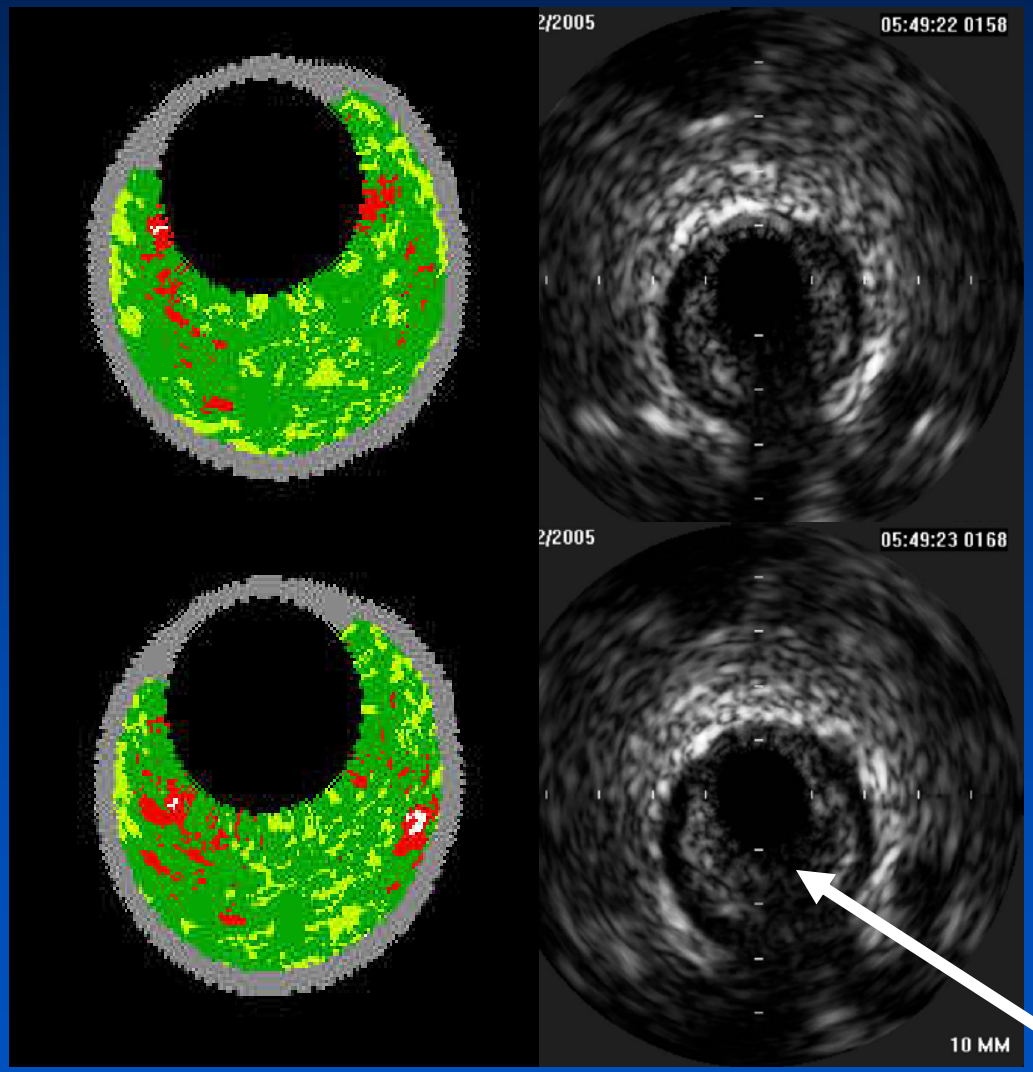
Patient with UA

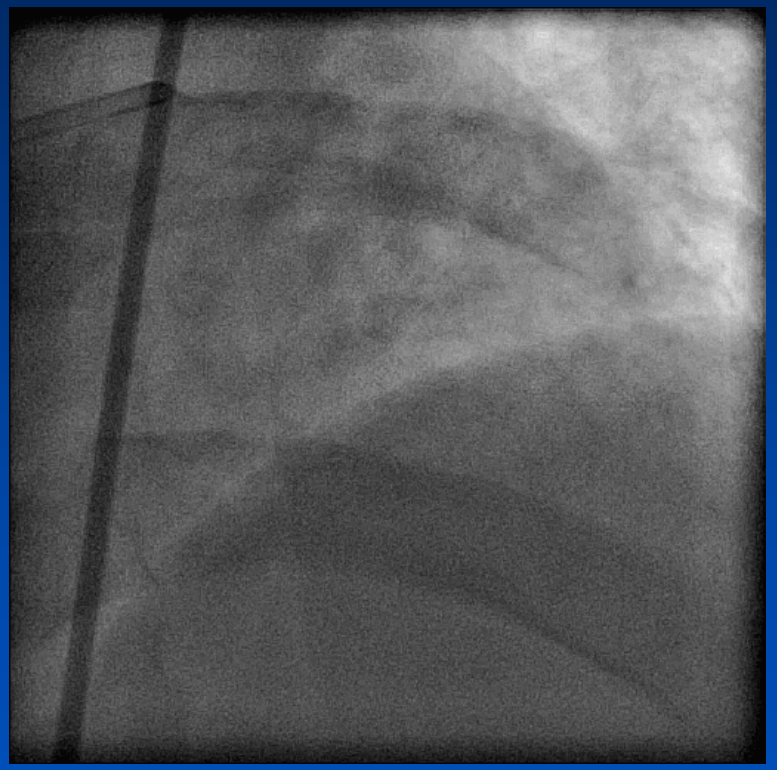


Mismatched with clinical manifestation
Patient with Unstable Angina



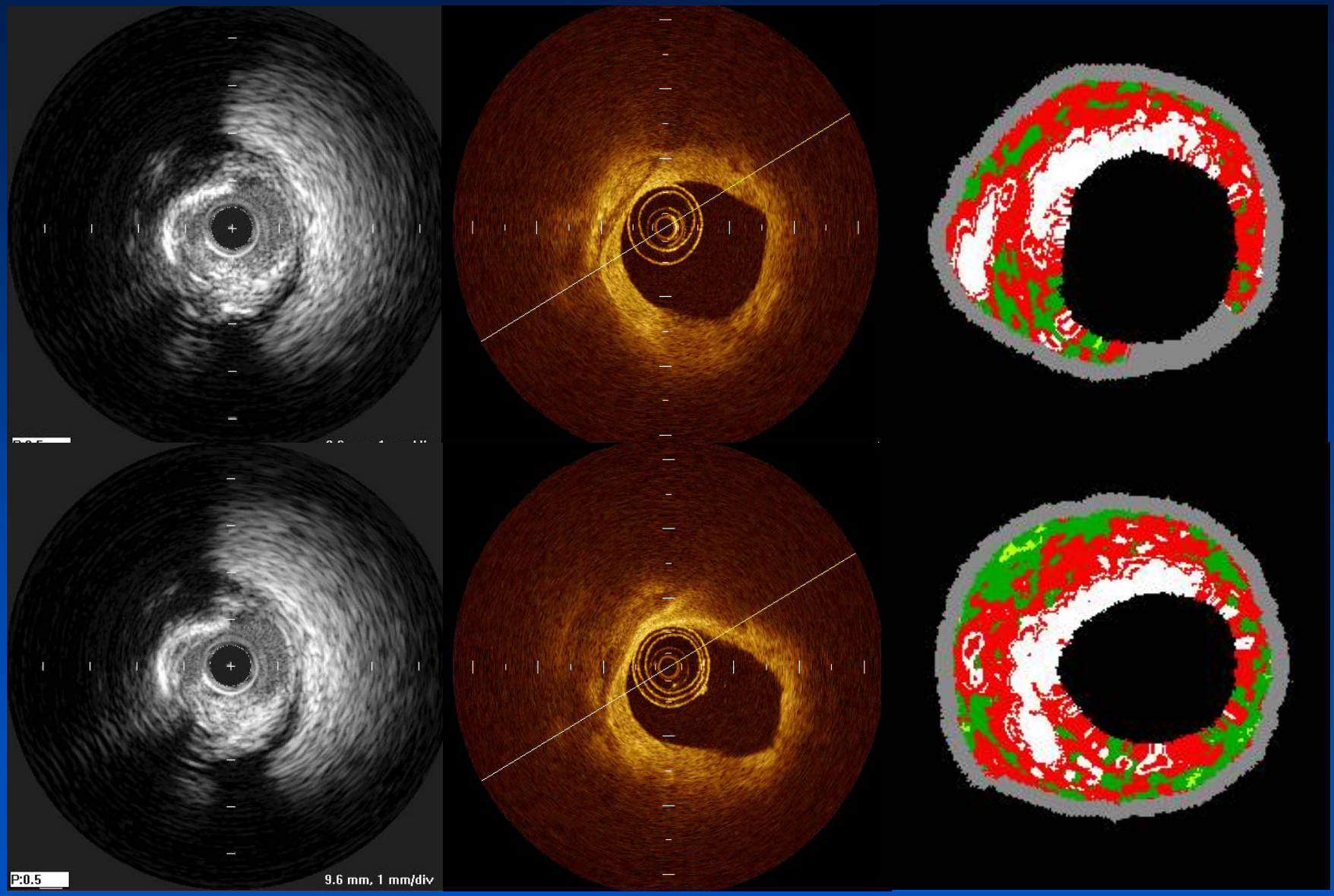
Mismatched with CAG, IVUS and clinical manifestation Patient with STEMI

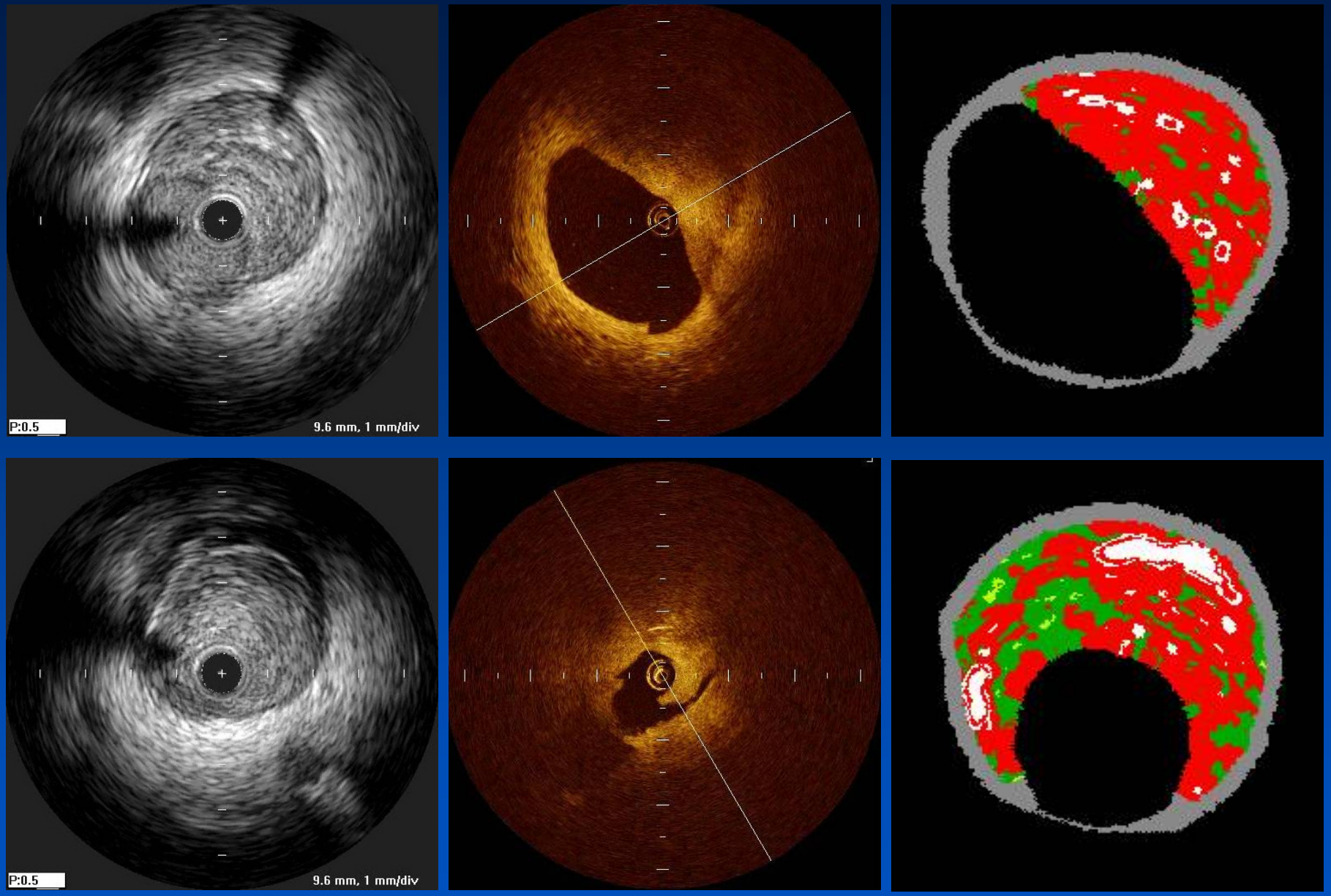




Thrombus

Matched with IVUS, OCT and VH in Patients with Stable Angina



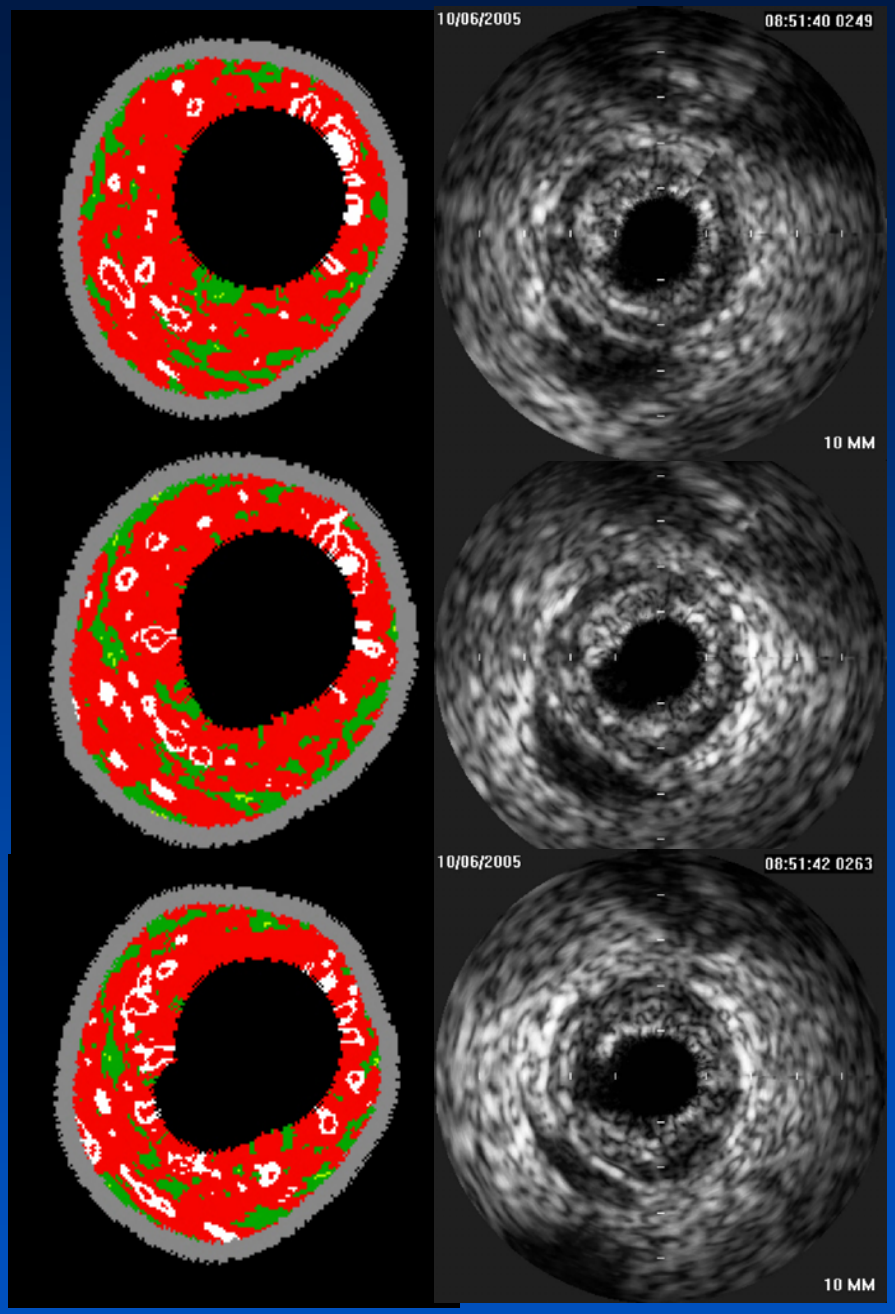

P:0.5
9.6 mm, 1 mm/div
P:0.5
9.6 mm, 1 mm/div

Vulnerable Plaque vs Vulnerable Patients?

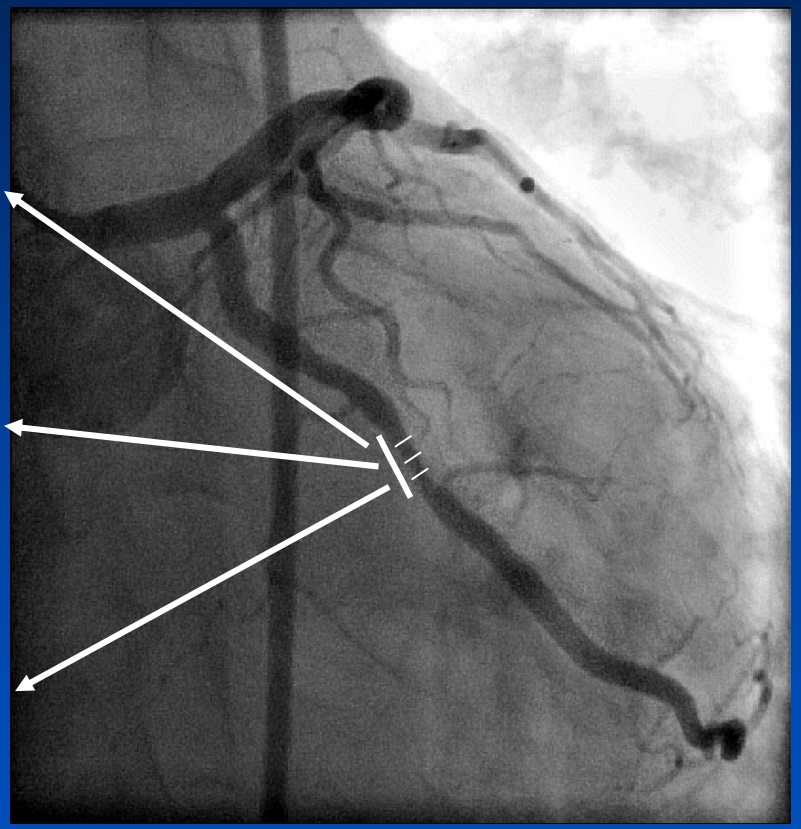
67/M, Unstable Angina

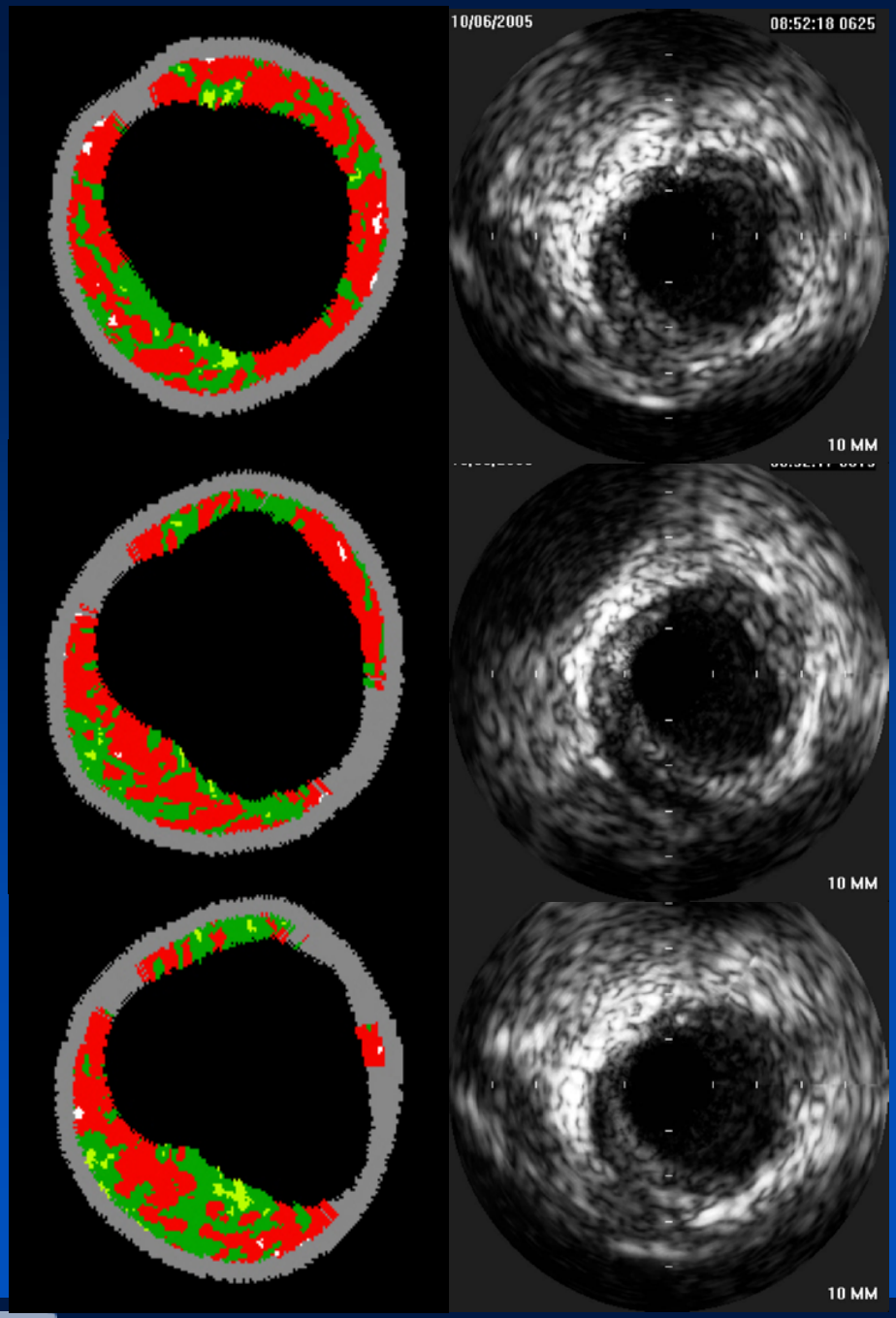
- DM for 15 years
- Hypertension under medications
- Cholesterol 238 mg/dl, LDL 162mg/dl
- Heavy smoker 1 pack/ 20 years

- No EKG changes
- No cardiac enzyme changes

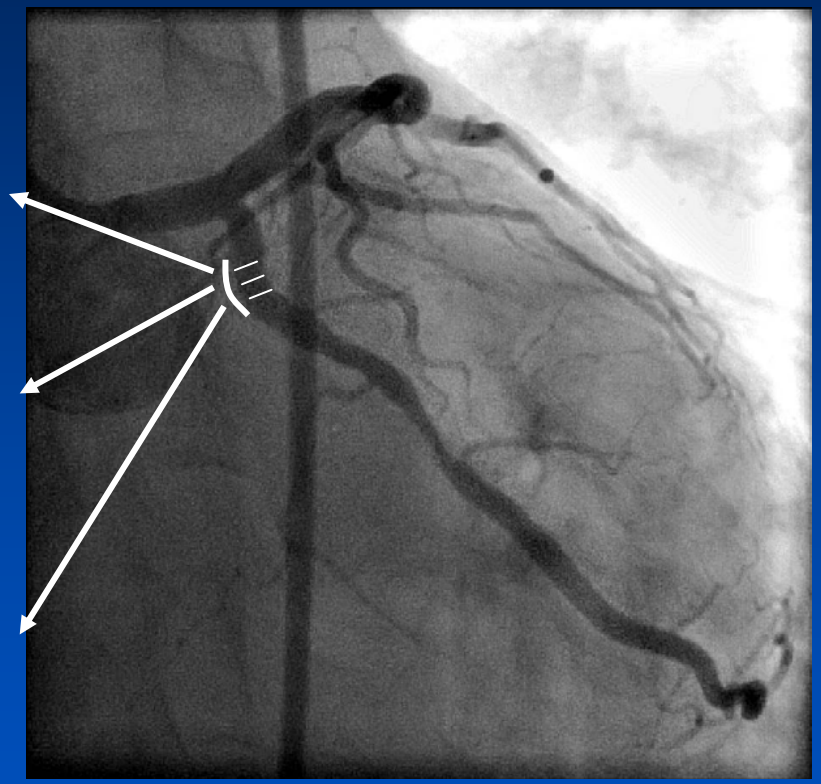


Distal LCX

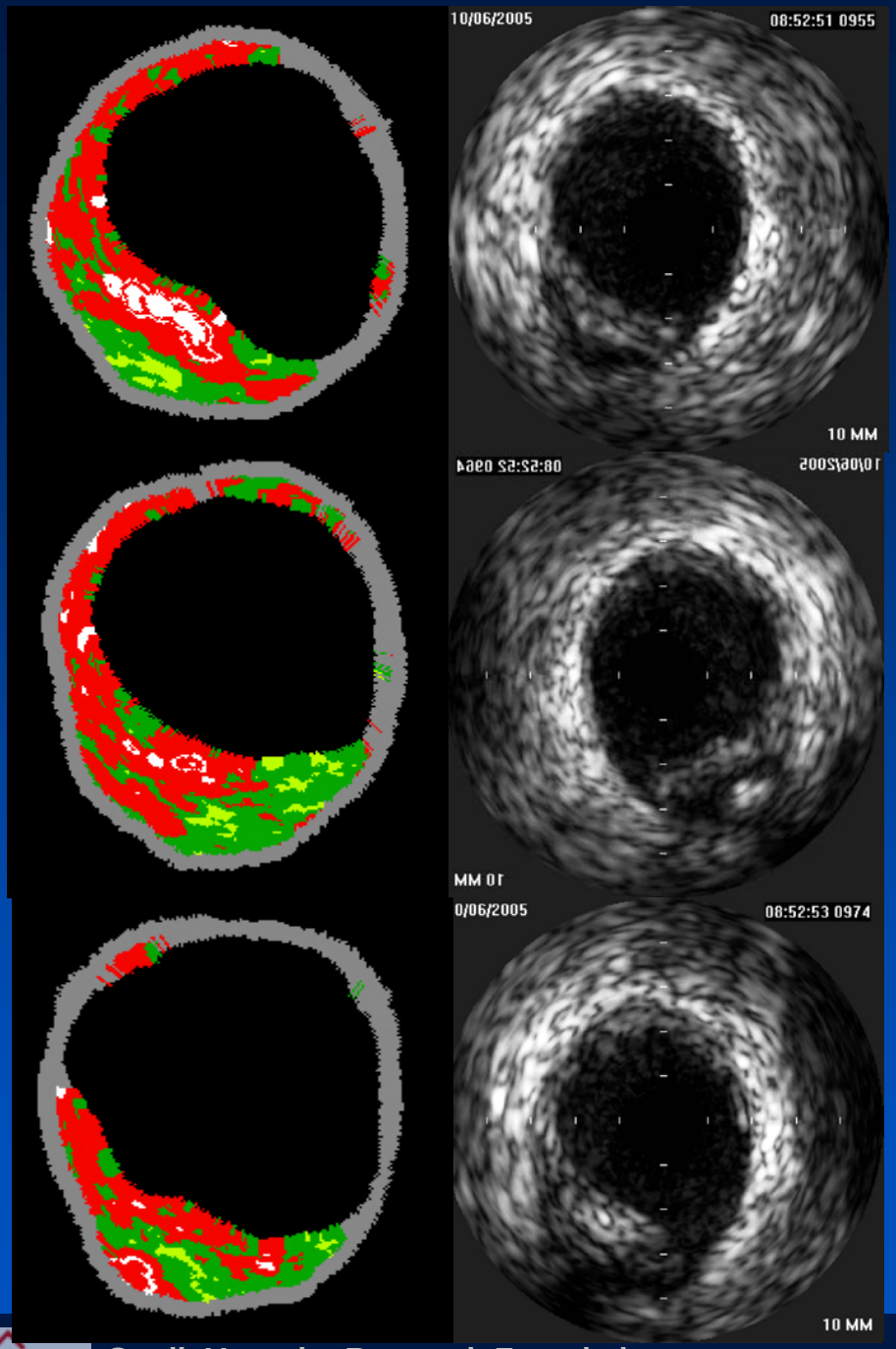


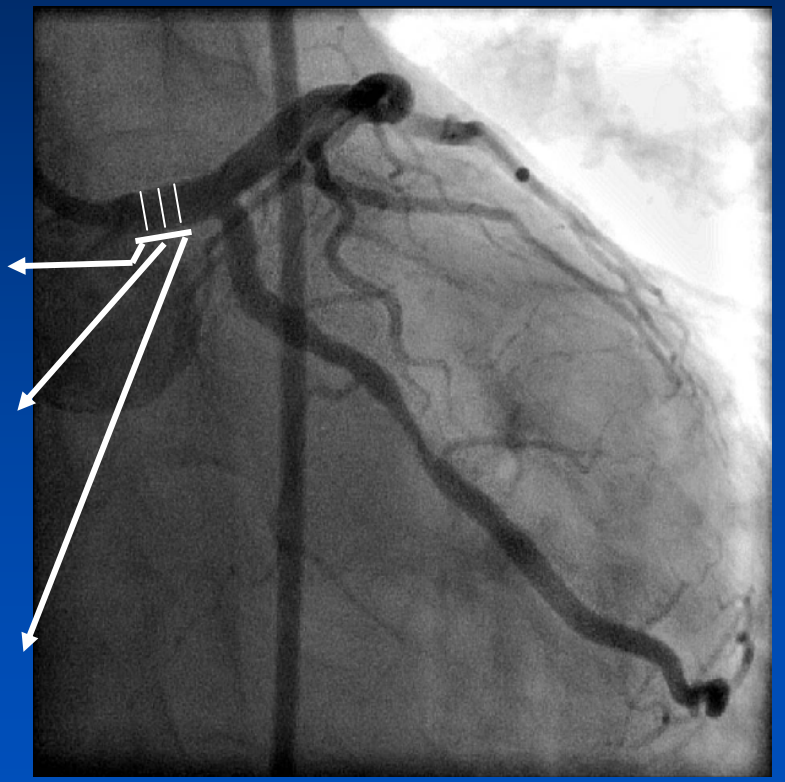


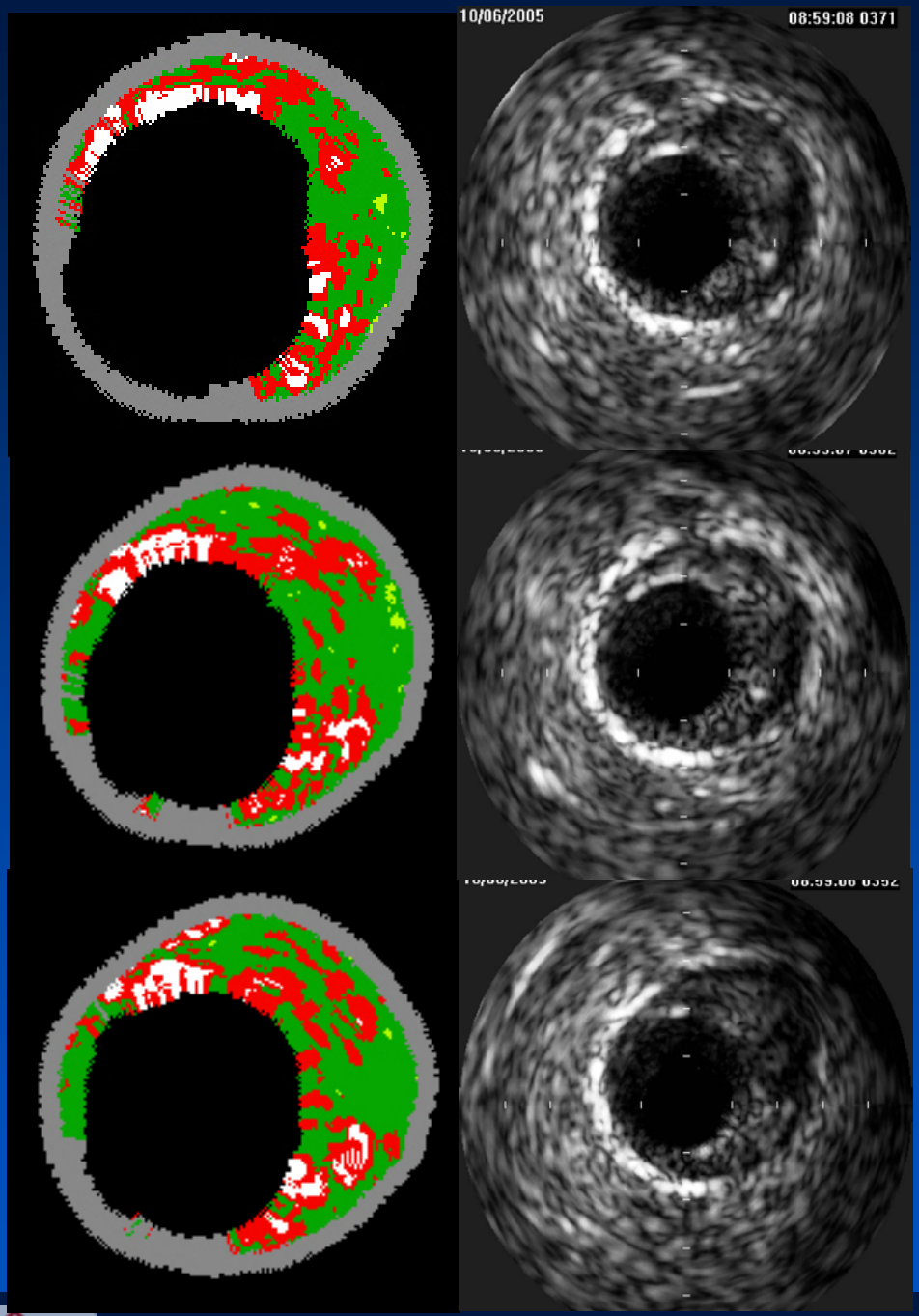
Proximal LCX



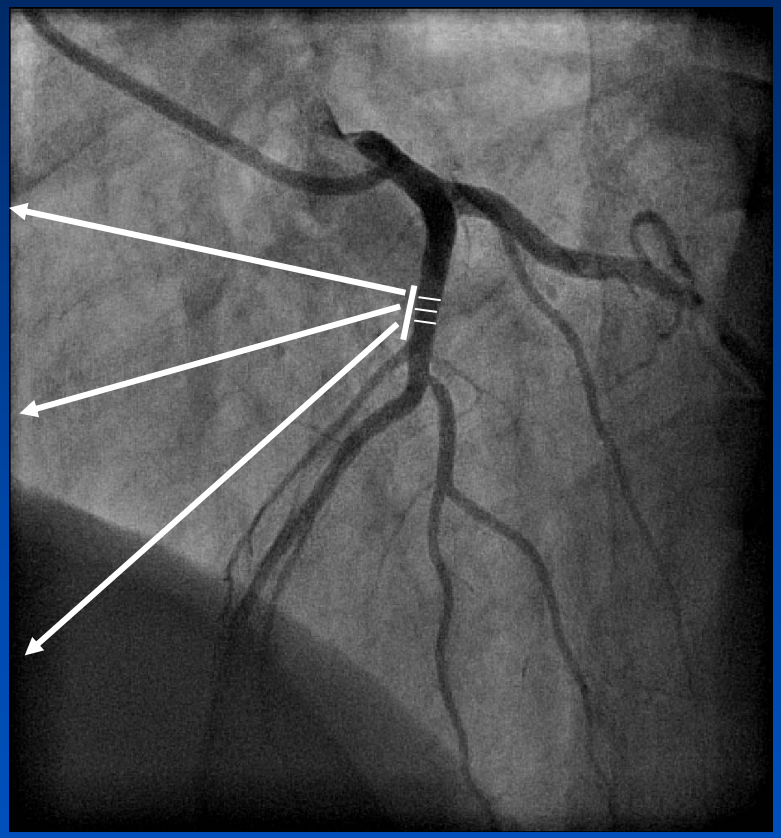
LMCA

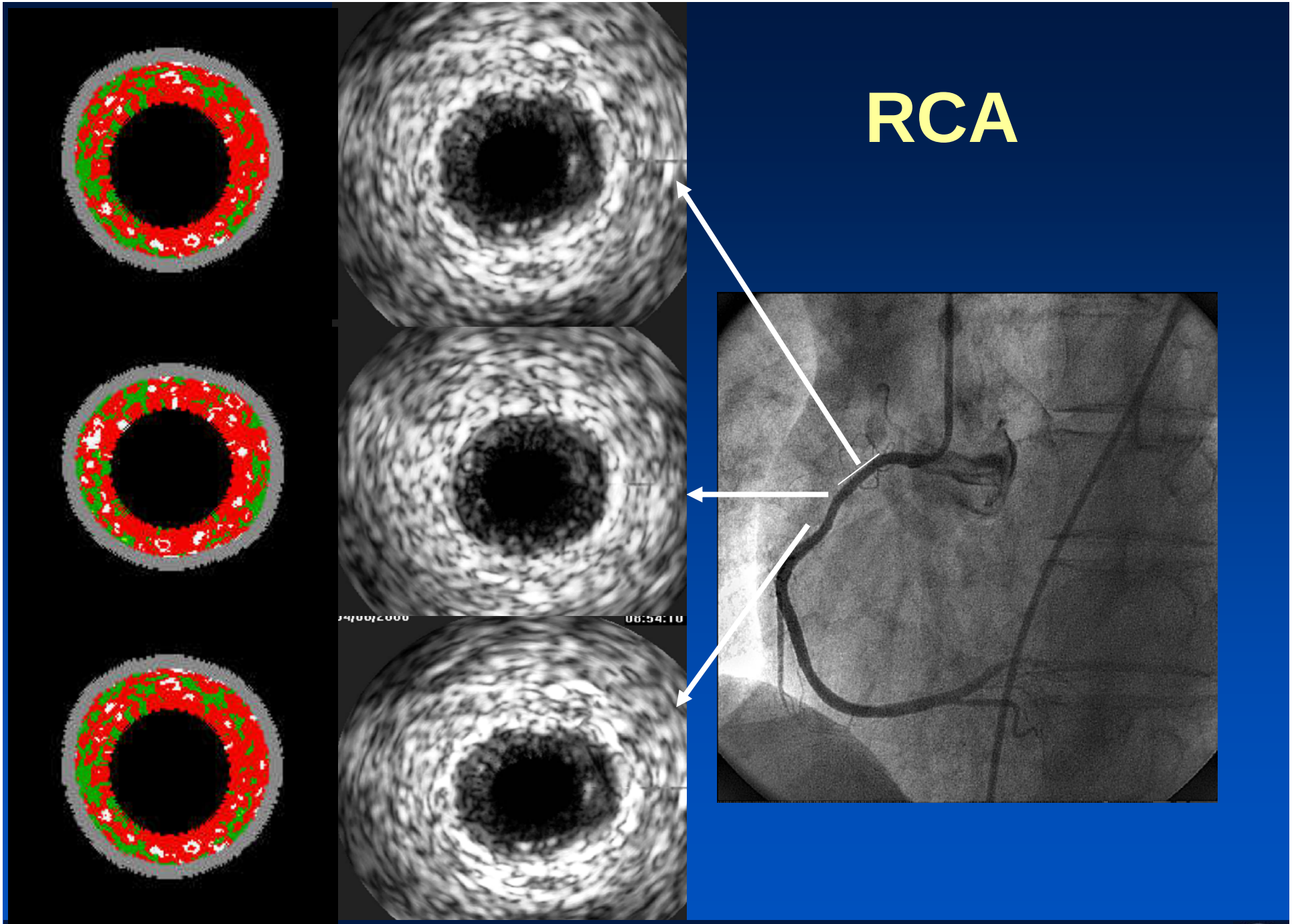






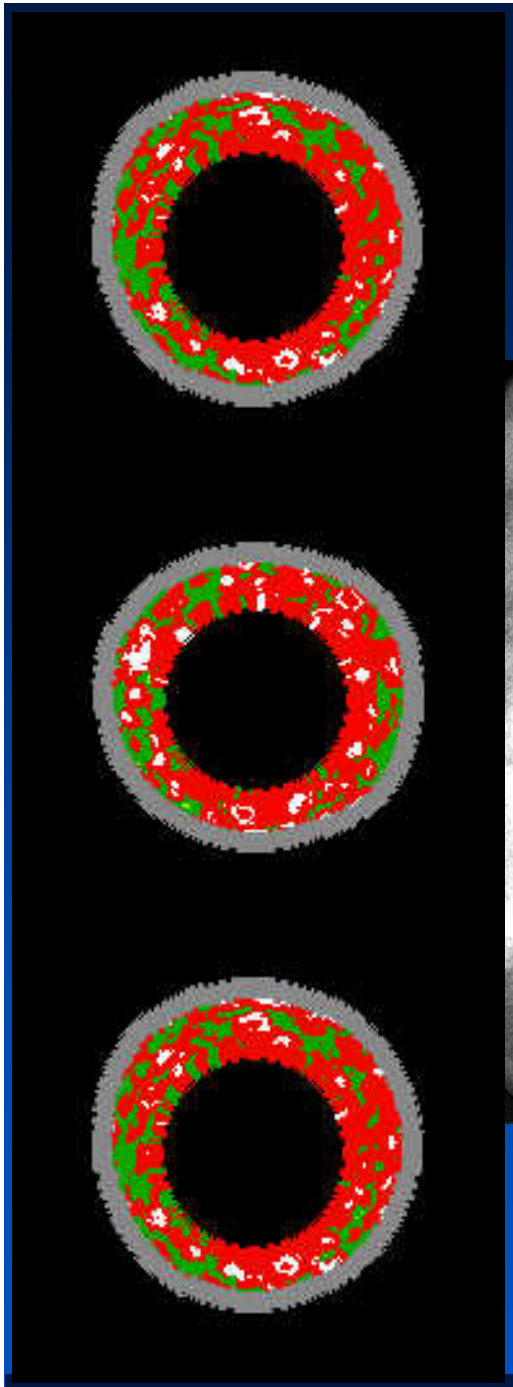
LAD



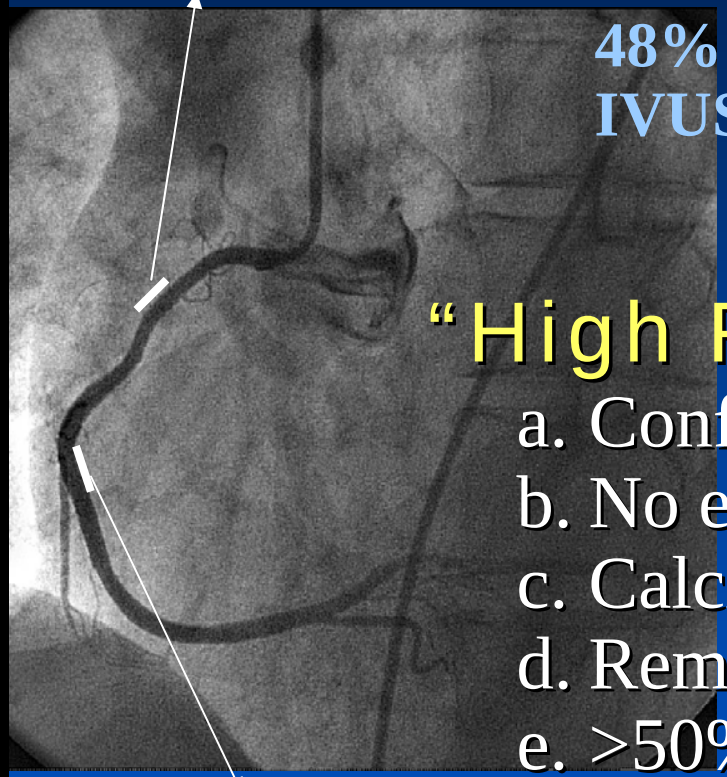

RCA

Vulnerable Plaque vs
< Vulnerable Patients

What is the Vulnerable Plaque in VH-IVUS ?



EEM CSA = 21.5mm^2
Lumen CSA = 4.9mm^2
P+M CSA = 16.6mm^2
Max P+M Thickness=1.2mm
Plaque burden=0.72
Remodeling index=1.3



EEM CSA = 13.7mm^2
Lumen CSA = 9.3mm^2
P+M CSA = 4.4mm^2

9.3-4.9/9.3=0.48
48% CSA narrowing by IVUS

"High Risk TCFA"

a. Confluent NC>10%
b. No evidence of fibrotic cap
c. Calcium >5%
d. Remodeling index >1.05
e. >50% CSA luminal narrowing by IVUS

VH Experience in Real World: *AMC Experience*

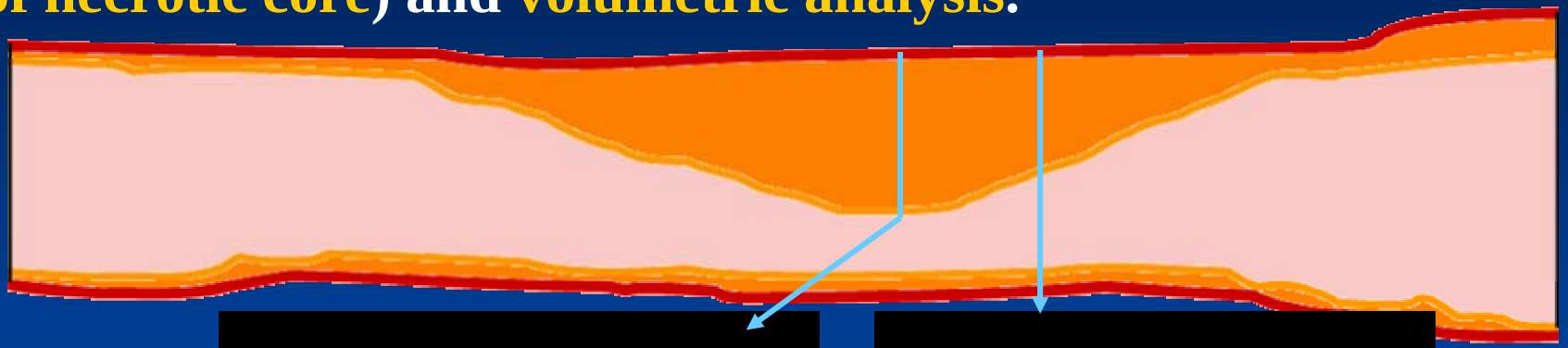
VH-IVUS (1)
Plaque Composition in Stable Angina vs. ACS

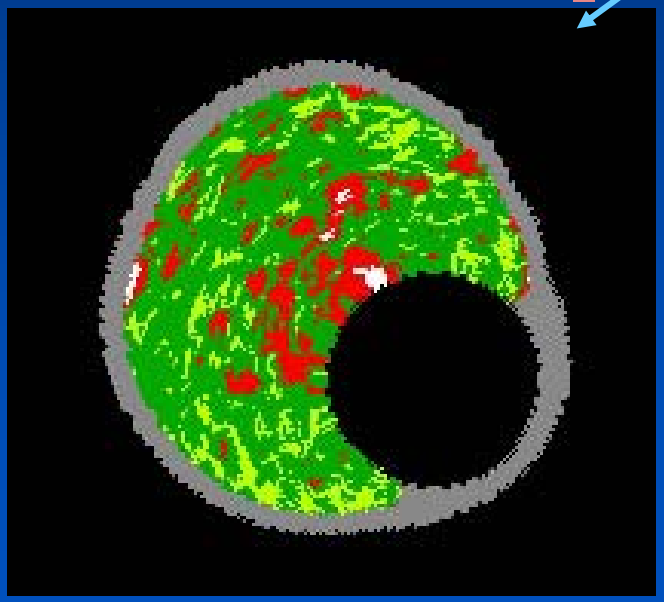
- 318 patients who underwent VH-IVUS in the de novo target/culprit lesions from May 2005 to July 2006.

- 318 patients composed of 195 SAP patients and 123 ACS patients.

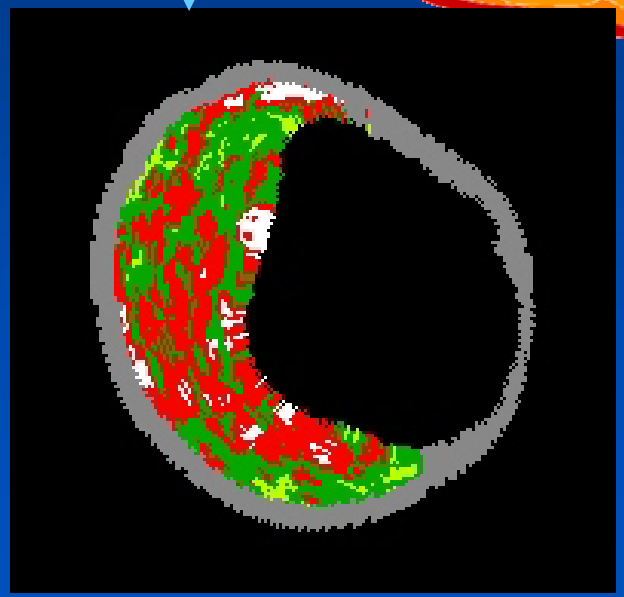
VH-IVUS Measurements

Planar VH-IVUS measurements were performed at 2 lesion segments (minimum lumen cross-sectional area and the largest of necrotic core) and volumetric analysis.

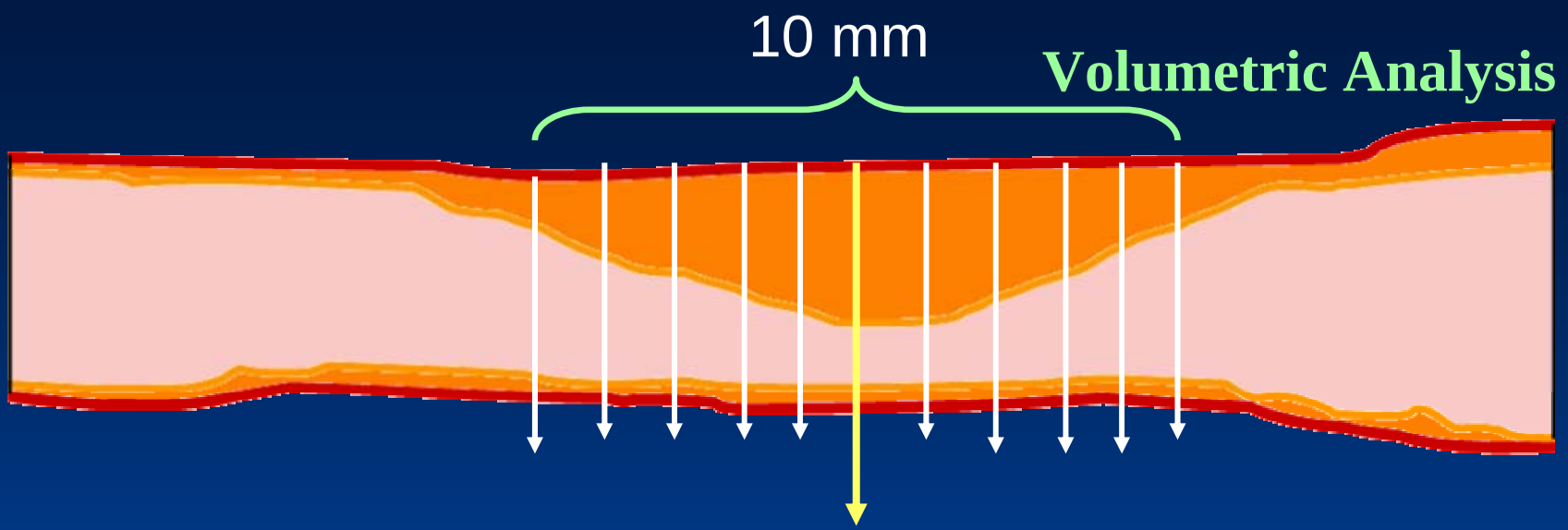




Minimal lumen CSA



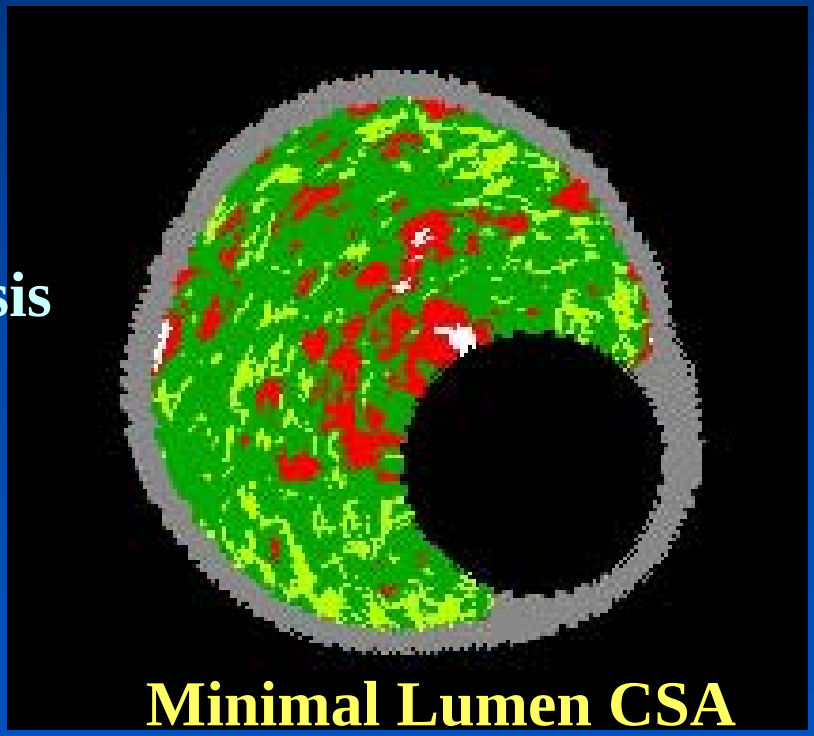
Largest necrotic core burden



VH Analysis at

(1) Minimal CSA

(2) Volumetric Analysis

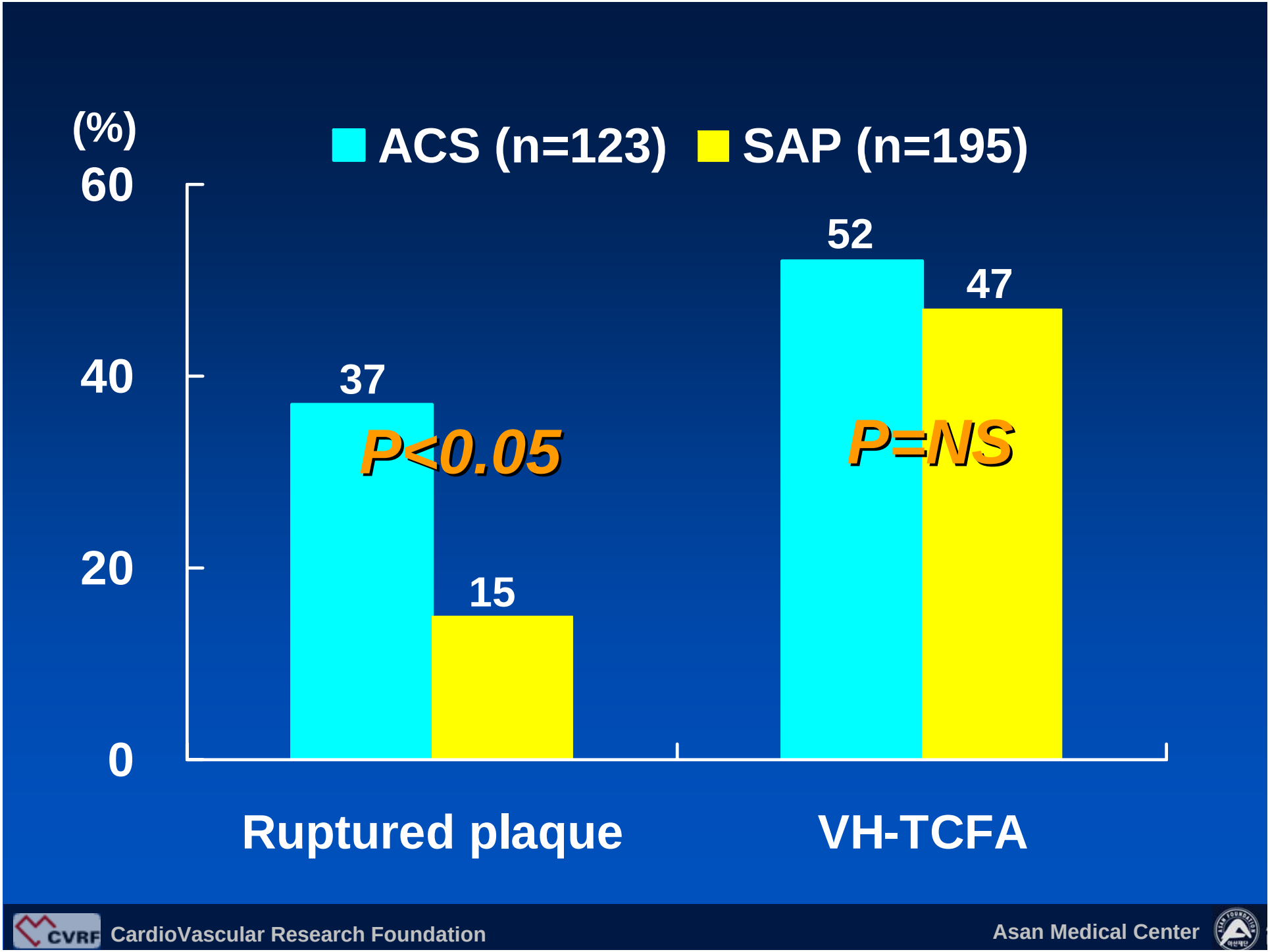


Baseline Characteristics

	ACS (n=123)	SAP (n=195)	*p*
Age (yrs)	59±11	60±9	0.7
Men	92 (75%)	136 (70%)	0.4
Diabetes mellitus	21 (17%)	48 (25%)	0.147
Hypertension	47 (38%)	97 (50%)	0.050
Smoking	65 (53%)	38 (20%)	0.001
No. of disease vessel			0.018
One vessel	71 (58%)	139 (71%)	
Two vessel	35 (28%)	44 (23%)	
Three vessel	17 (14%)	12 (6%)	

Baseline Characteristics

	ACS (n=123)	SAP (n=195)	*p*
Lipid profiles			
Total cholesterol (mg/dl)	185±42	168±35	<0.001
Triglyceride (mg/dl)	176±147	158±93	0.25
HDL-cholesterol (mg/dl)	39±11	44±13	0.004
LDL-cholesterol (mg/dl)	116±36	96±32	<0.001
hs-CRP level (mg/dl)	0.6±0.9	0.3±0.6	0.001


(%)
ACS (n=123)
SAP (n=195)
60
40
20
0
37
15
52
47
P<0.05
P=NS
Ruptured plaque
VH-TCFA

Grey-scale IVUS

AMC-VH

	ACS (n=123)	SAP (n=195)	*p*
Minimum lumen area			
EEM CSA (mm^2)	17.1±4.5	15.0±4.5	0.001
Lumen CSA (mm^2)	3.7±1.0	3.8±0.9	0.3
Plaque CSA (mm^2)	13.1±4.4	10.9±4.4	0.001
Remodeling index	1.07±0.18	1.02±0.19	0.038
Largest necrotic core			
EEM CSA (mm^2)	17.4±4.4	15.7±5.4	0.003
Lumen CSA (mm^2)	4.8±1.7	5.0±2.1	0.3
Plaque CSA (mm^2)	12.6±4.2	10.7±4.4	0.001
Volumetric analysis			
EEM CSA (mm^3)	167.7±43.8	149.2±40.5	0.001
Lumen CSA (mm^3)	59.5±15.6	60.1±14.1	0.7
Plaque CSA (mm^3)	108.3±36.7	89.1±34.4	0.001

VH-IVUS Measure in MLA

AMC-VH

	ACS (n=123)	SAP (n=195)	*p*
Absolute area (mm^2)			
Fibrotic	5.3±2.7	4.6±3.0	0.030
Fibrofatty	0.5±0.6	0.5±0.6	0.6
Dense calcium	0.8±0.7	0.6±0.6	0.001
Necrotic core	3.1±1.9	2.1±1.3	0.001
Percentage (%)			
Fibrotic	53±15	56±15	0.073
Fibrofatty	5±5	7±6	0.020
Calcific	9±7	8±8	0.4
Necrotic	33±14	29±14	0.015

VH-IVUS in largest necrotic core

	ACS (n=123)	SAP (n=195)	*p*
Absolute area (mm^2)			
Fibrotic	5.0±4.3	4.0±2.8	0.015
Fibrofatty	0.4±0.4	0.4±0.5	0.6
Dense calcium	0.9±0.7	0.7±0.7	0.003
Necrotic core	3.4±2.0	2.3±1.6	0.001
Percentage (%)			
Fibrotic	50±15	53±15	0.105
Fibrofatty	4±4	5±5	4
Calcific	10±7	9±8	0.5
Necrotic	36±13	33±14	0.034

VH-IVUS in volumetric analysis

	ACS (n=123)	SAP (n=195)	*p*
Absolute area (mm^3)			
Fibrotic	41.9±22.4	32.3±20.8	0.001
Fibrofatty	4.7±4.5	4.5±4.7	0.7
Dense calcium	6.4±5.1	4.4±4.6	0.001
Necrotic core	20.3±12.6	14.3±9.5	0.001
Percentage (%)			
Fibrotic	56±13	57±13	0.3
Fibrofatty	6±5	8±5	0.045
Calcific	9±7	9±8	0.5
Necrotic	29±12	27±11	0.081

VH Study – SAP vs. ACS

- Compared with SAP patients, plaque CSA was larger in ACS patients because of positive coronary remodeling
- Unstable lesions (plaque rupture plus VH-TCFA lesions) were more frequently observed in ACS patients than in SAP patients.
- Larger area of necrotic core and smaller area of fibrotic and fibrofatty plaque were observed in the culprit lesions of ACS patients than in the target lesions of SAP patients.
- More data should be gathered to evaluate the efficacy of VH-IVUS examination.

VH-IVUS (2)

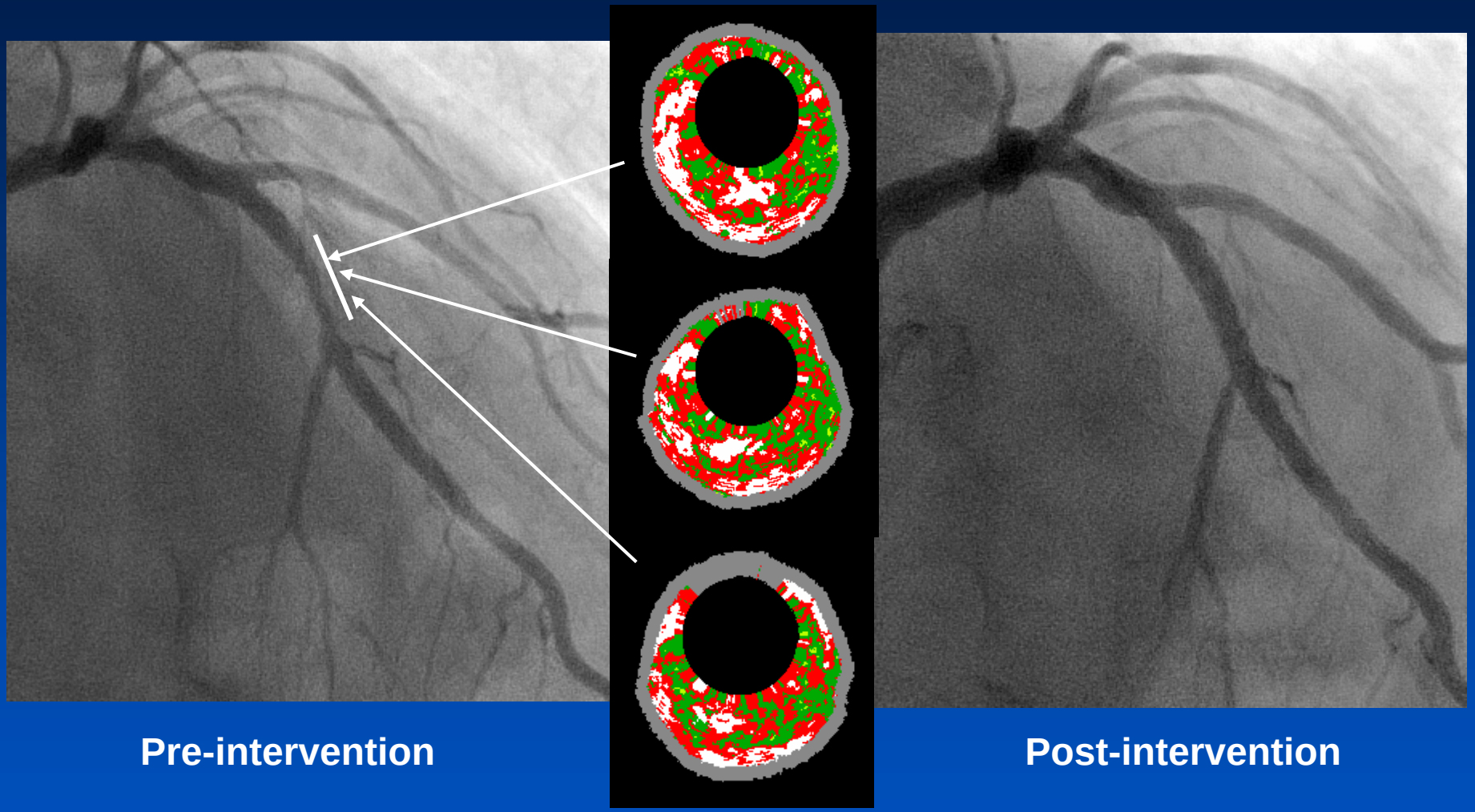
Impact of Plaque Composition on Post-myocardial Necrosis

VH Study in AMC
Plaque Composition & Myocardial Necrosis

- 305 patients with de novo lesions underwent pre-intervention VH-IVUS study at AMC. In 80 of these 305 patients, stents were implanted into ***a single de novo lesion***.

- Patients with acute or recent MI were excluded.

- To avoid confusion in determining which lesion was responsible for CK-MB elevation, patients with multi-vessel or multi-lesion PCI were also excluded from this study.



Peak CK-MB release after stent implantation was 21.2 ng/ml.

Baseline Characteristics

Age (yrs)	60±10
Men	44 (55%)
Diabetes mellitus	14 (18%)
Hypertension	42 (53%)
Smoking	28 (35%)
No. of disease vessel	
One vessel	73 (91%)
Two vessel	7 (9%)
Three vessel	0
Clinical presentation	
Stable angina	65 (81%)
Unstable angina	15 (19%)

IVUS analysis

Conventional IVUS	No (n=76)	Yes (n=4)	P
EEM area (mm^2)	13.5±3.2	16.2±4.2	0.106
Lumen area (mm^2)	3.9±0.5	3.7±0.3	0.5
Plaque area (mm^2)	9.4±3.2	12.5±4.2	0.072
EEM volume (mm^3)	136.3±29.5	161.3±46.1	0.112
Lumen volume (mm^3)	58.8±11.9	60.7±19.9	0.8
Plaque volume (mm^3)	77.5±23.5	100.6±30.0	0.062

VH-IVUS analysis

Relative amounts (%)	No (n=76)	Yes (n=4)	P
Fibrotic plaque area	57±15	52±20	0.5
Fibrofatty plaque area	6±6	1±1	0.001
Dense calcium area	9±9	9±8	1.0
Necrotic core area	28±13	39±14	0.097
Fibrotic plaque volume	58±13	56±15	0.8
Fibrofatty plaque volume	7±5	2±1	0.001
Dense calcium volume	9±8	10±8	0.7
Necrotic core volume	26±11	32±8	0.3

VH-IVUS analysis

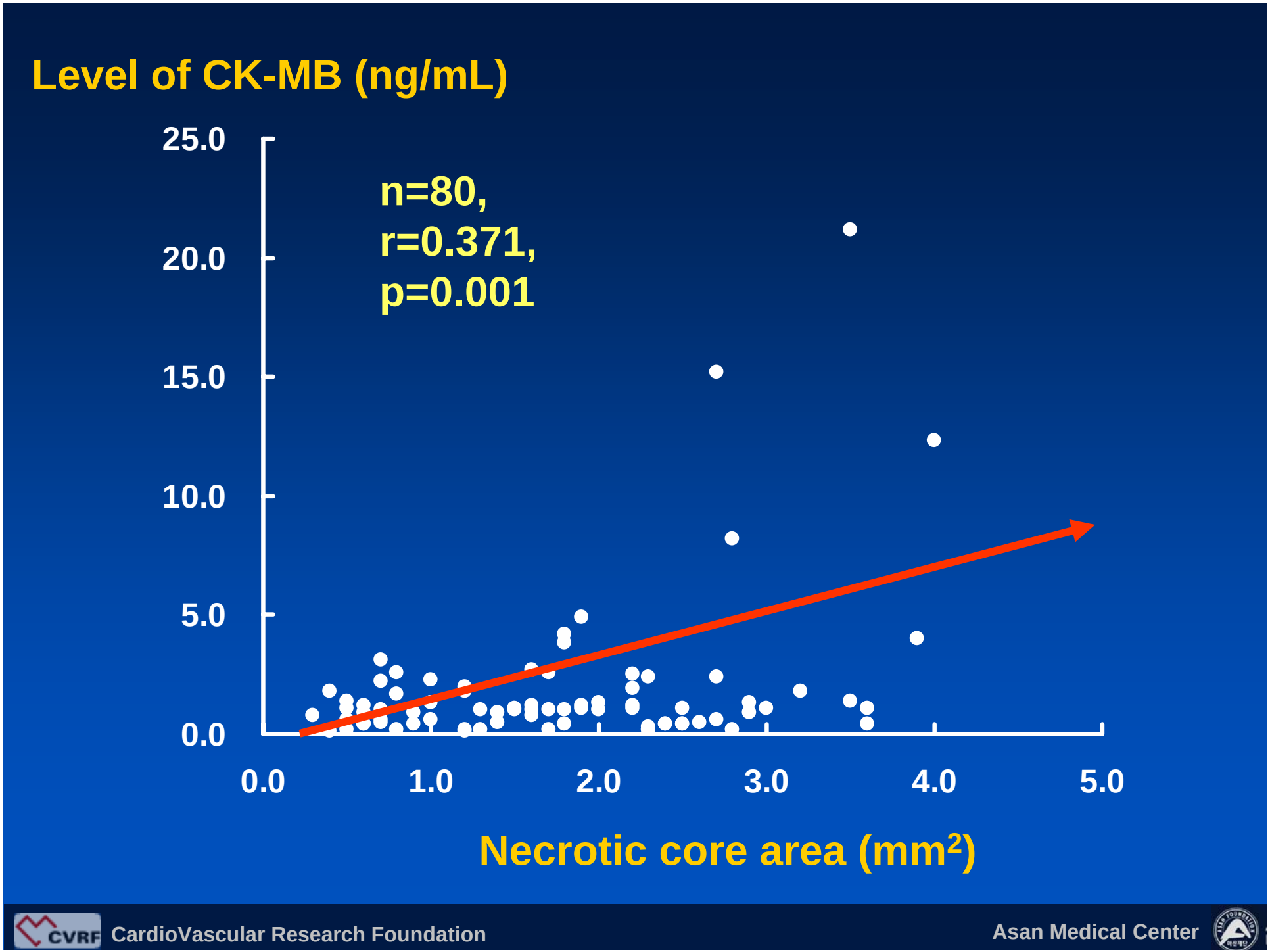
Absolute amounts	No (n=76)	Yes (n=4)	P
Fibrotic plaque area (mm^2)	3.9±2.2	5.3±4.2	0.24
Fibrofatty plaque area (mm^2)	0.5±0.5	0.1±7	0.21
Dense calcium area (mm^2)	0.5±0.7	0.6±0.6	0.8
Necrotic core area (mm^2)	1.7±0.9	3.3±0.6	0.001
Fibrotic plaque volume (mm^3)	26.7±14.8	39.4±23.6	0.11
Fibrofatty plaque volume (mm^3)	3.4±2.9	1.3±0.9	0.005
Dense calcium volume (mm^3)	3.8±4.0	5.6±2.8	0.4
Nnecrotic core volume (mm^3)	11.7±6.7	19.7±3.9	0.021

Correlates of post-PCI CK-MB level

	r	95% CI	p
Grey scale IVUS			
EEM area (mm^2)	0.232	0.012 – 0.444	0.039
Lumen area (mm^2)	0.144	-2.248 - 0.483	0.202
P&M area (mm^2)	0.274	0.056 – 0.476	0.014
Plaque burden (%)	0.249	0.972 – 14.859	0.026
Remodeling index	0.262	1.472 – 11.764	0.013
EEM volume (mm^3)	0.203	-0.002 – 0.044	0.071
Lumen volume (mm^3)	0.036	-0.050 – 0.069	0.8
P&M volume (mm^3)	0.239	0.003 – 0.061	0.033

Correlates of post-PCI CK-MB level

	r	95% CI	p
VH- IVUS			
Fibrotic plaque area (mm^2)	0.182	-0.056 – 0.567	0.11
Fibrofatty plaque area (mm^2)	0.079	-1.921 – 0.926	0.5
Dense calcium area (mm^2)	0.064	-0.809 – 1.446	0.6
Necrotic core area (mm^2)	0.371	0.546 – 1.957	0.001
Fibrotic plaque volume (mm^3)	0.195	-0.005 – 0.087	0.087
Fibrofatty plaque volume (mm^3)	0.099	-0.356 – 0.138	0.4
Dense calcium volume (mm^3)	0.139	-0.068 – 0.290	0.220
Necrotic core volume (mm^3)	0.278	0.029 – 0.232	0.013


Level of CK-MB (ng/mL)
25.0
20.0
15.0
10.0
5.0
0.0
n=80,
r=0.371,
p=0.001
0.0
1.0
2.0
3.0
4.0
5.0
Necrotic core area (mm²)

Predictors of post-PCI CK-MB level

Multivariable linear regression analysis - including all variables with p<0.2 in univariable analysis - indicated that the *absolute necrotic core area* was the only independent predictor of CK-MB enzyme level after PCI (r=0.371, 95% CI= 0.546 to 1.957 and p=0.001).

VH Study – Postmyocardial necrosis

- Post-PCI CK-MB enzyme level correlated with a larger pre-PCI necrotic core area at the minimal lumen site as assessed by VH-IVUS analysis.

- More aggressive medical treatment (i.e. use of platelet glycoprotein IIb/IIIa inhibitors or a larger loading dose of clopidogrel or statin before PCI) and less aggressive procedures may be warranted to prevent higher CK-MB elevations in these lesion subsets.

Vulnerable Plaque
: Major limitations

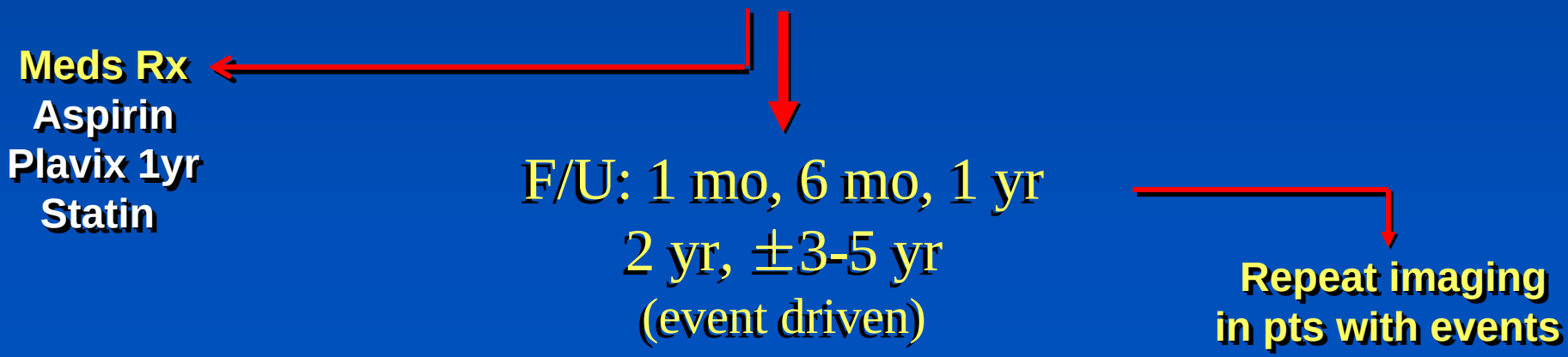
- **Everything that we know about vulnerable plaque mainly come from in vivo detection of plaque rupture in patients presented with ACS**
- **NOT from prospective identification of vulnerable plaques before they rupture and/or thrombus formation**

PROSPECT

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

Natural history study in pts with ACS

700 pts with ACS and 1 or 2 vessel CAD undergoing PCI will have QCA of entire coronary tree, culprit artery imaging (post PCI), and both non-culprit arteries also imaged using IVUS, Virtual histology, Palpography, ± Thermography (EU only)



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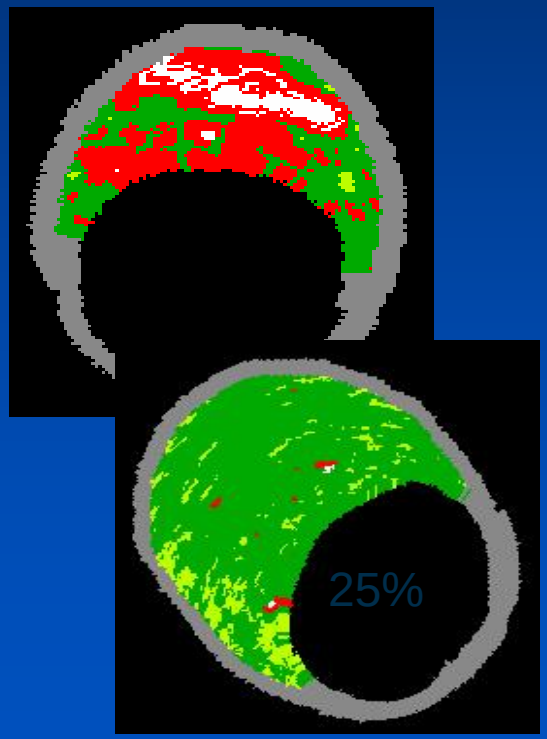

At the end of the study, we hope to say "If you see this kind of a plaque, there is a X % likelihood of that plaque to cause a thrombotic clinical event within a year"