Virtual Histology (and other IVUS-derived technologies): Basics and Potential for Detection of Vulnerable Plaques

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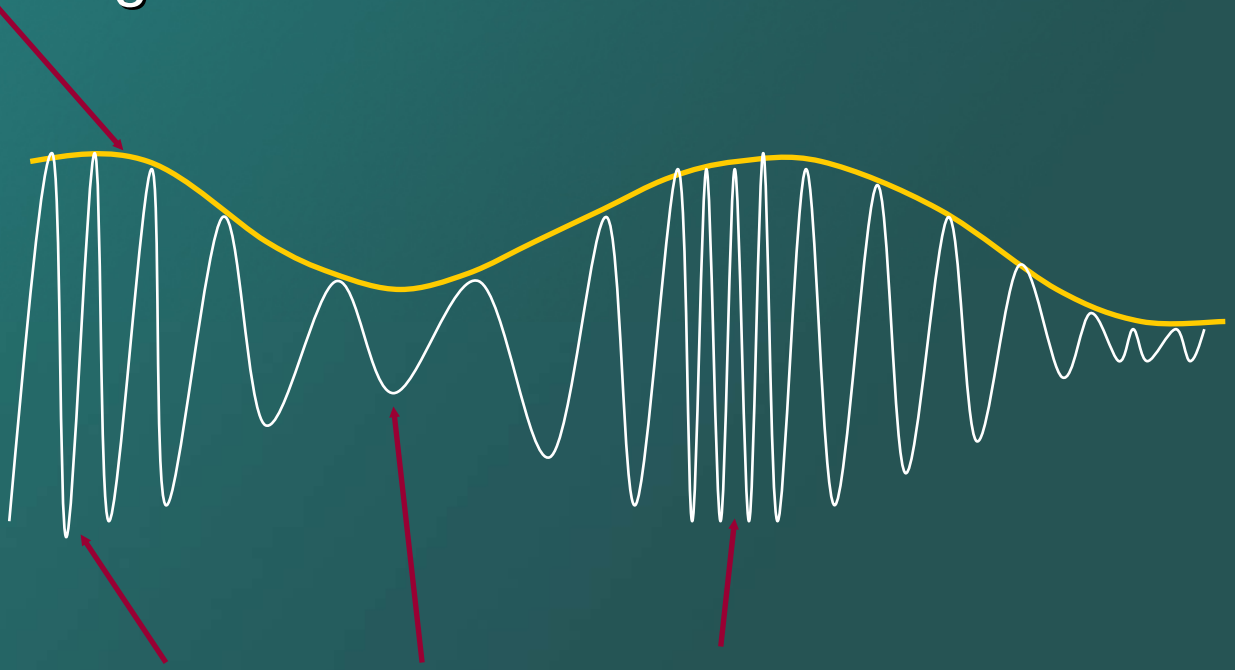
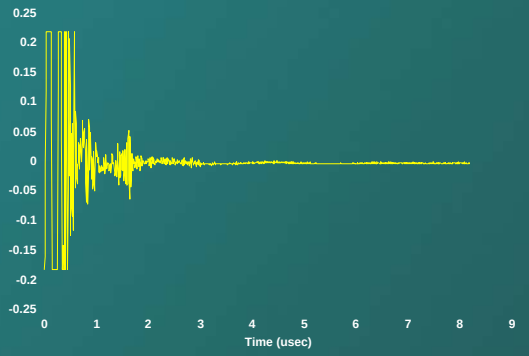
Cardiovascular Research Foundation

- **Greyscale IVUS provides precise morphometric cross-sectional imaging of coronary arteries. However, greyscale IVUS is limited in its ability to assess plaque composition in individual patients and lesions.**

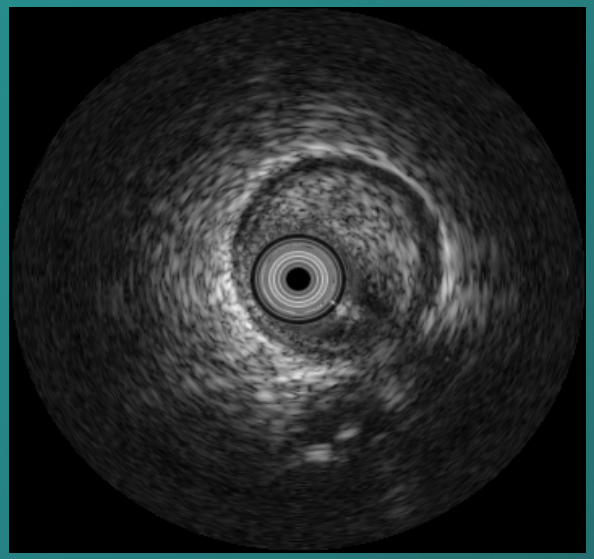
Only the envelope amplitude (echo intensity) is used to form the **gray-scale IVUS** image





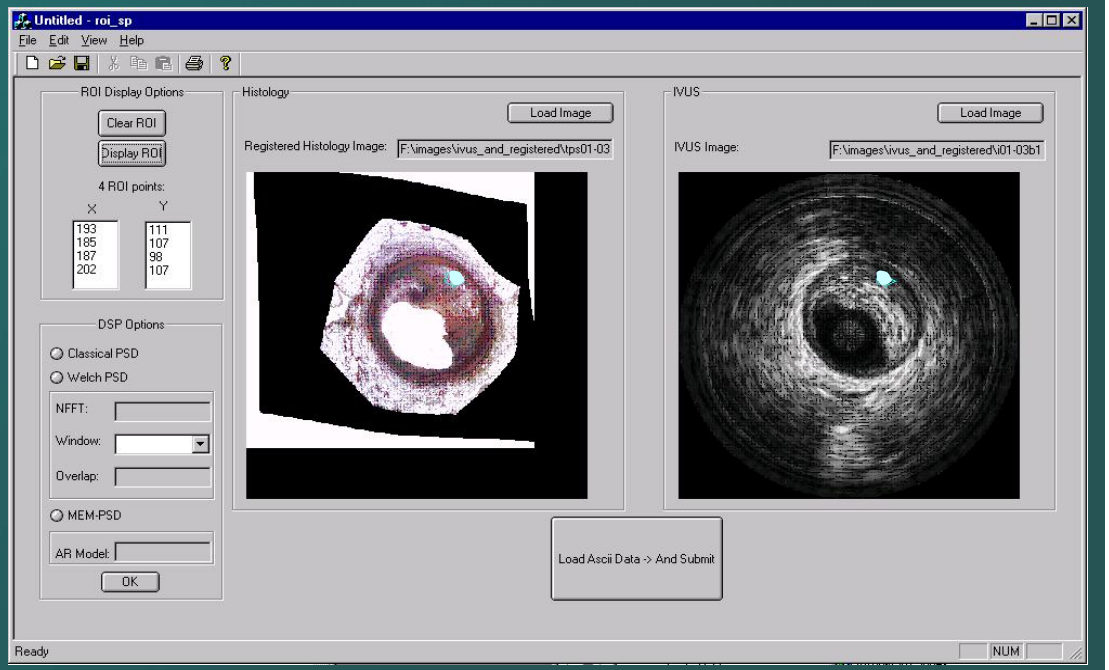
Among reflected ultrasound signals of the same intensity, frequency can also vary depending on the tissue

IVUS B scan



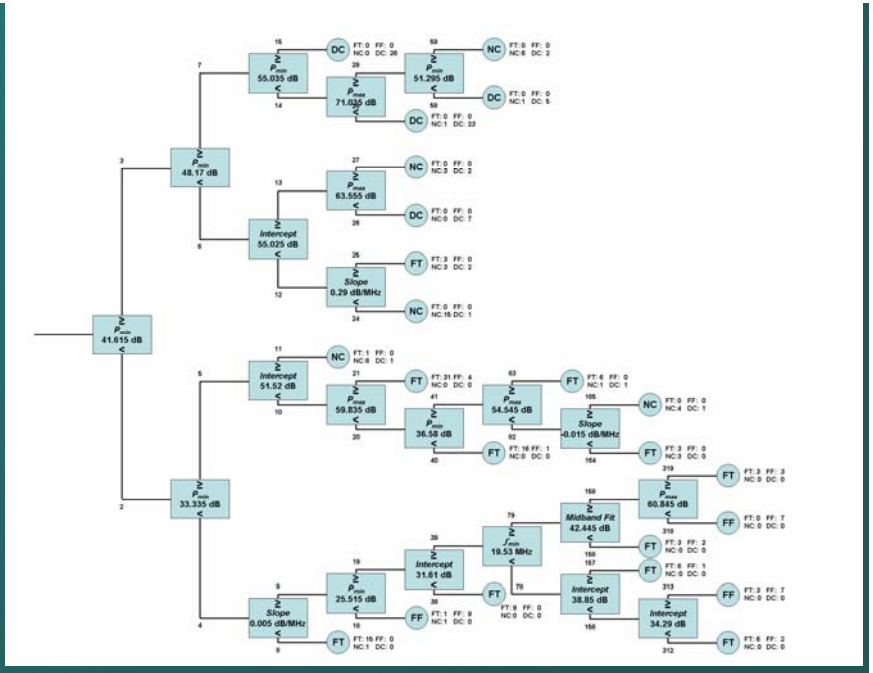
Movat pentachrome stain

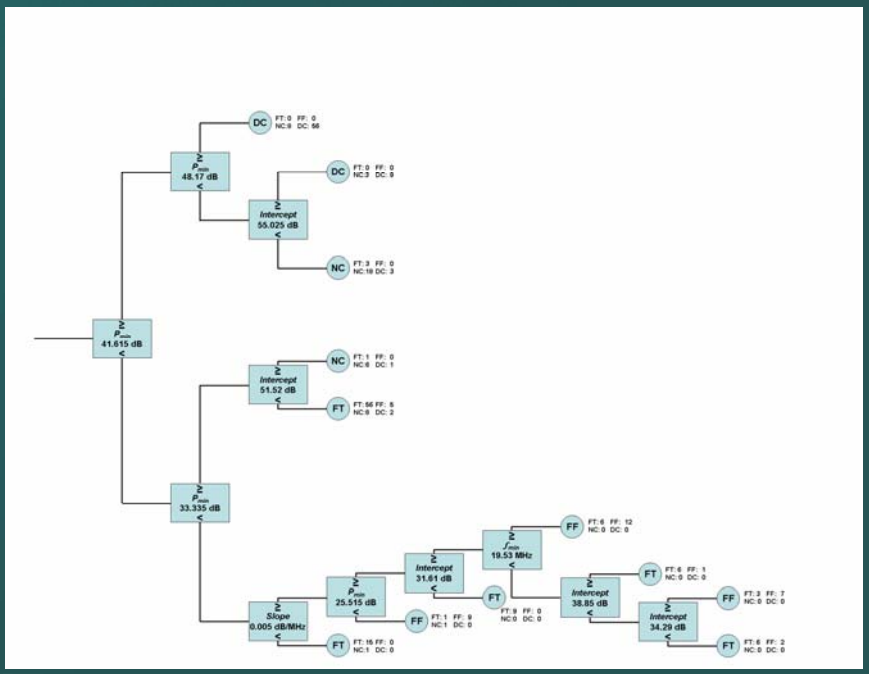
Thin plate spline morphing of the histologic image



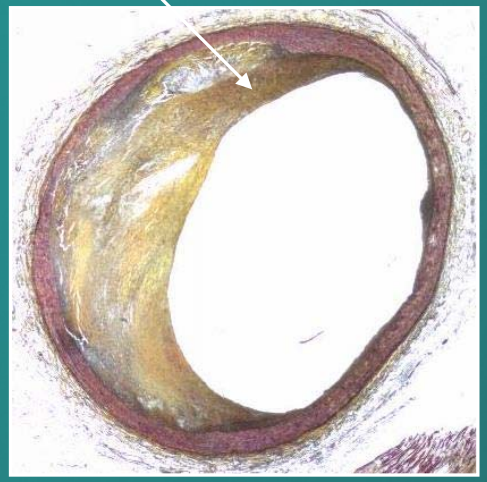
Two examples of plaque composition classification trees based on these 8 parameters

- maximum power
- corresponding frequency
- minimum power
- corresponding frequency
- Slope
- *y*-intercept
- mid-band fit
- integrated backscatter



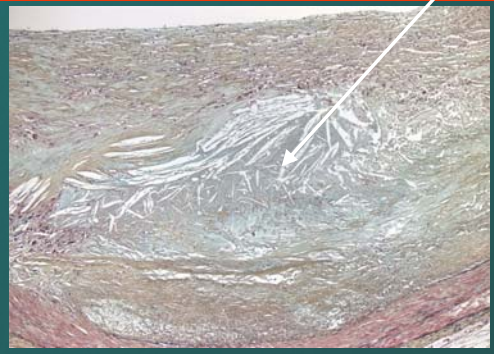


Fibrous Tissue



Densely packed bundles of collagen fibers with no evidence of intra-fiber lipid accumulation. No evidence of macrophage infiltration. Appears dark-yellow/green on Movat stained histology section and dark green on VH-IVUS.

Necrotic Core

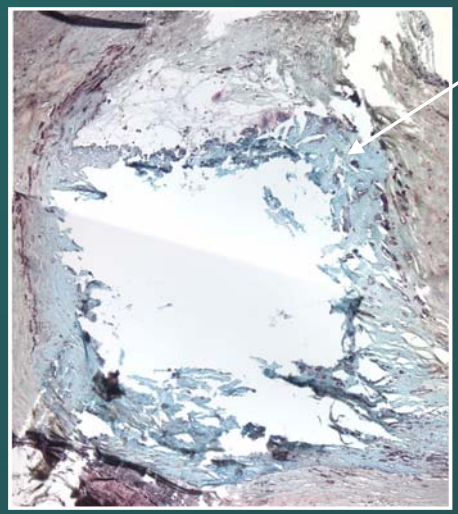


Highly lipidic necrotic region with remnants of foam cells and dead lymphocytes present. No collagen fibers are visible and mechanical integrity is poor. Cholesterol clefts and micro calcifications are clearly visible. Red on VH-IVUS.

Fibro-Fatty

Loosely packed bundles of collagen fibers with regions of lipid deposition present. These areas are cellular and have no cholesterol clefts or necrosis present. Increase in extra cellular matrix. Appears turquoise on Movat stained histology section. Light-green on VH-IVUS.

Dense Calcium



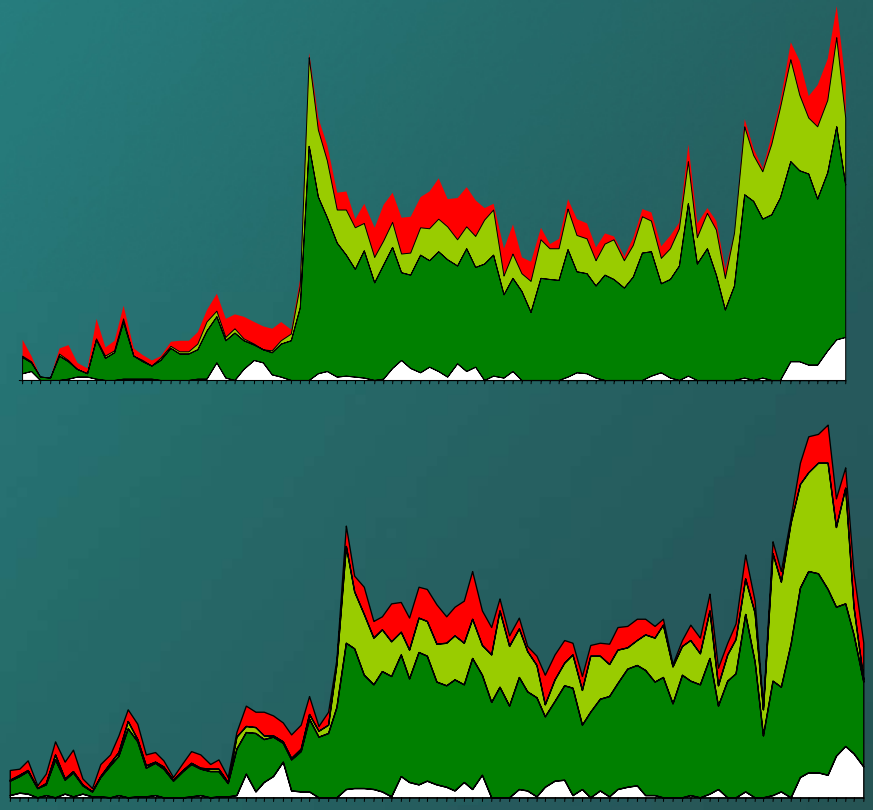
Focal area of dense calcium. Appears purple or deep blue on Movat. Usually falls out of histology section, but calcium crystals are evident at borders. White on VH-IVUS.

Eagle Eye (20MHz Electronic Array Transducer)

VH IVUS vs histopathology from fresh 51 fresh, post mortem LADs (115 sections and 407 regions of interest)

	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%

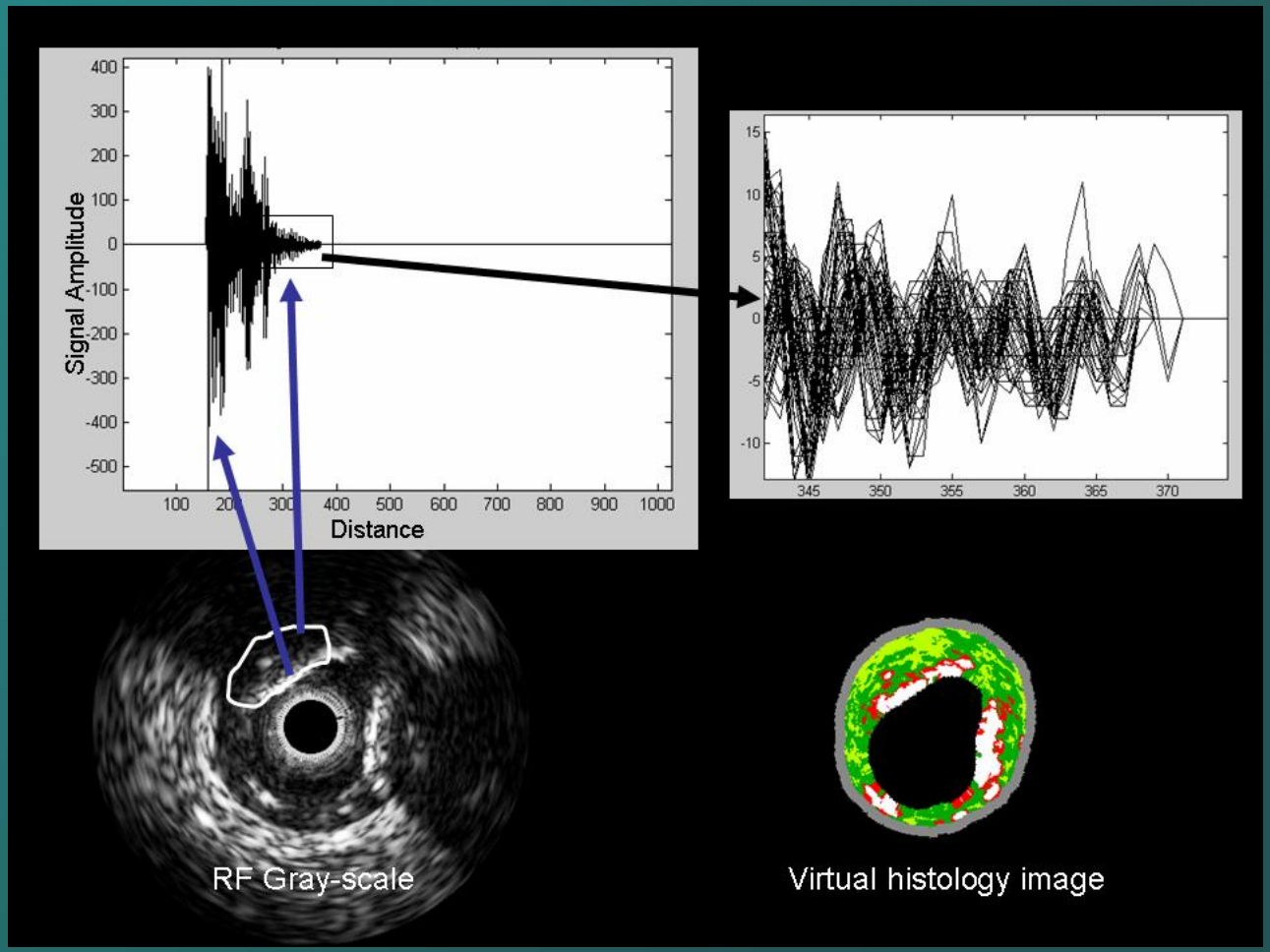
In Vivo Reproducibility
Two 20MHz catheters and two pullbacks



Limitations

- Requires ECG-gated motorized catheter pullback
- Currently limited to 20MHz solid-state catheter systems (Volcano)
- No classification for blood, stent metal, or thrombus (depends on thrombus age, but most often appears “green” or fibrotic)
- Totally dependent on accurate borders
  - If the lumen is drawn “too large,” a fibroatheroma may be converted into a TCFA
- Limited by the resolution of IVUS – cannot classify a structure that is below the resolution of greyscale IVUS
- Will classify all plaque within the inner and outer borders regardless of signal strength - i.e., behind calcium

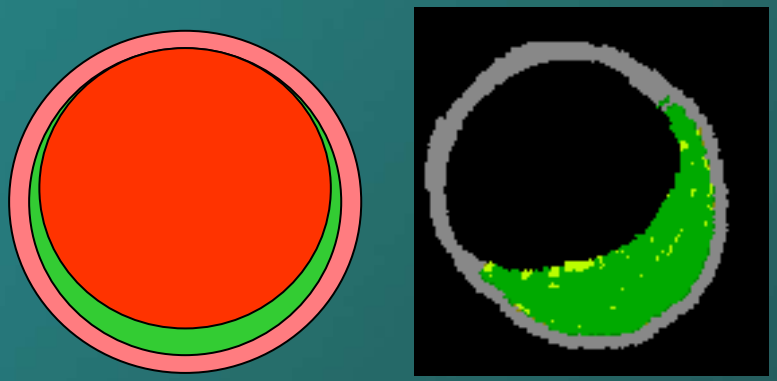
More than 80% of the 20 ROIs within the acoustic shadowing (behind calcium) demonstrated a signal of very low amplitude; however, a coherent periodic pattern between successive scan lines and a slight signal increase in the region of adventitia indicated that these ROIs contained not only noise, but also reflected ultrasound waves.



Lesion Classification - I

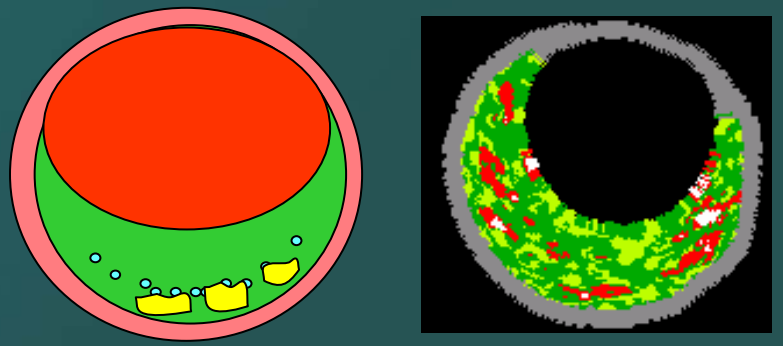
Adaptive Intimal Thickening

Nearly all fibrous tissue with intimal thickness <600 microns



Pathologic Intimal Thickening

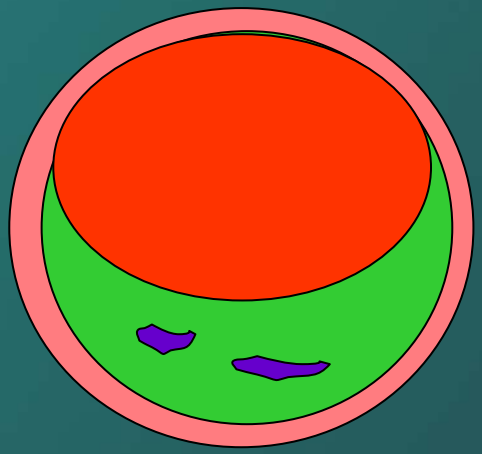
Intimal thickness >600 microns with a mixture of fibrous, fibrofatty (<10%), confluent necrotic core (<10%), and calcium (<10%)

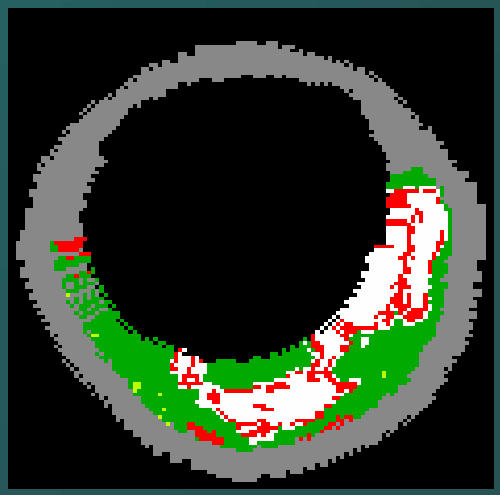


Lesion Classification - II

Fibrocalcific

Mainly fibrotic plaque with one or more dense calcific elements which together are >10% of total plaque. (Necrotic core or fibrofatty plaque <10% of total plaque.)

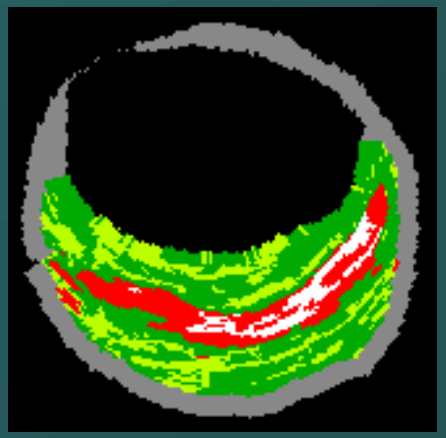




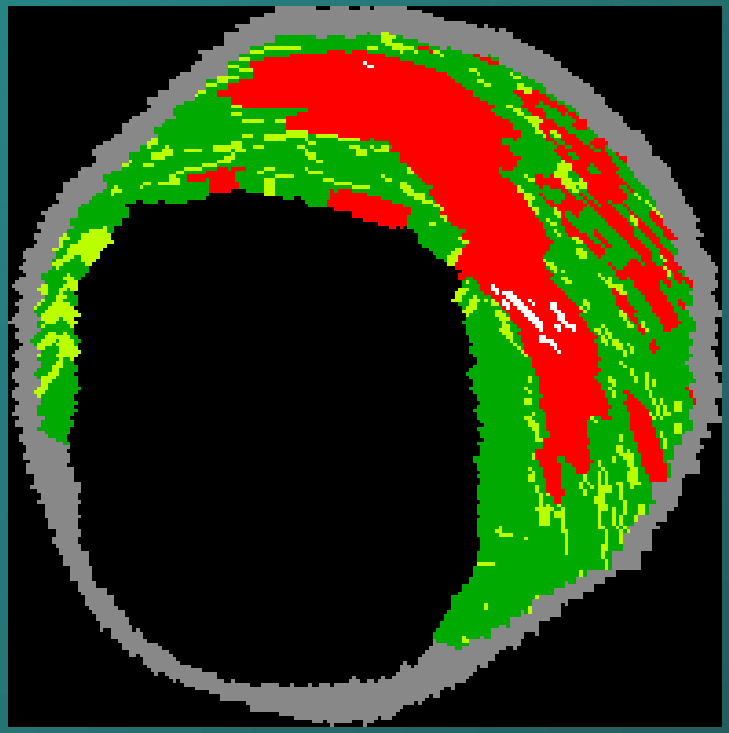
Lesion Classification - III

Fibroatheroma

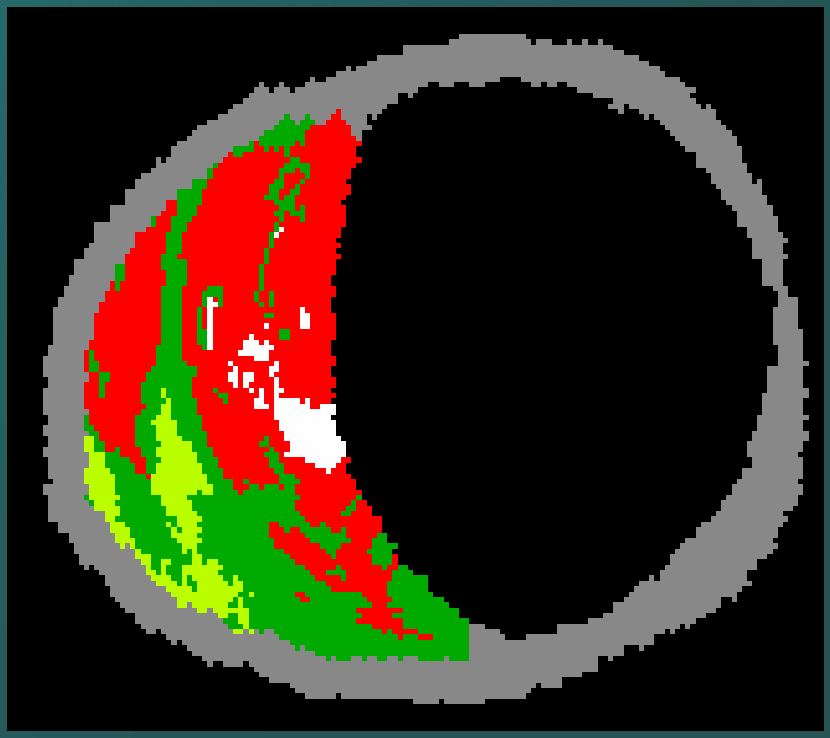
Significant necrotic core (confluent NC >10% of total plaque) within fibrotic or fibrofatty tissue



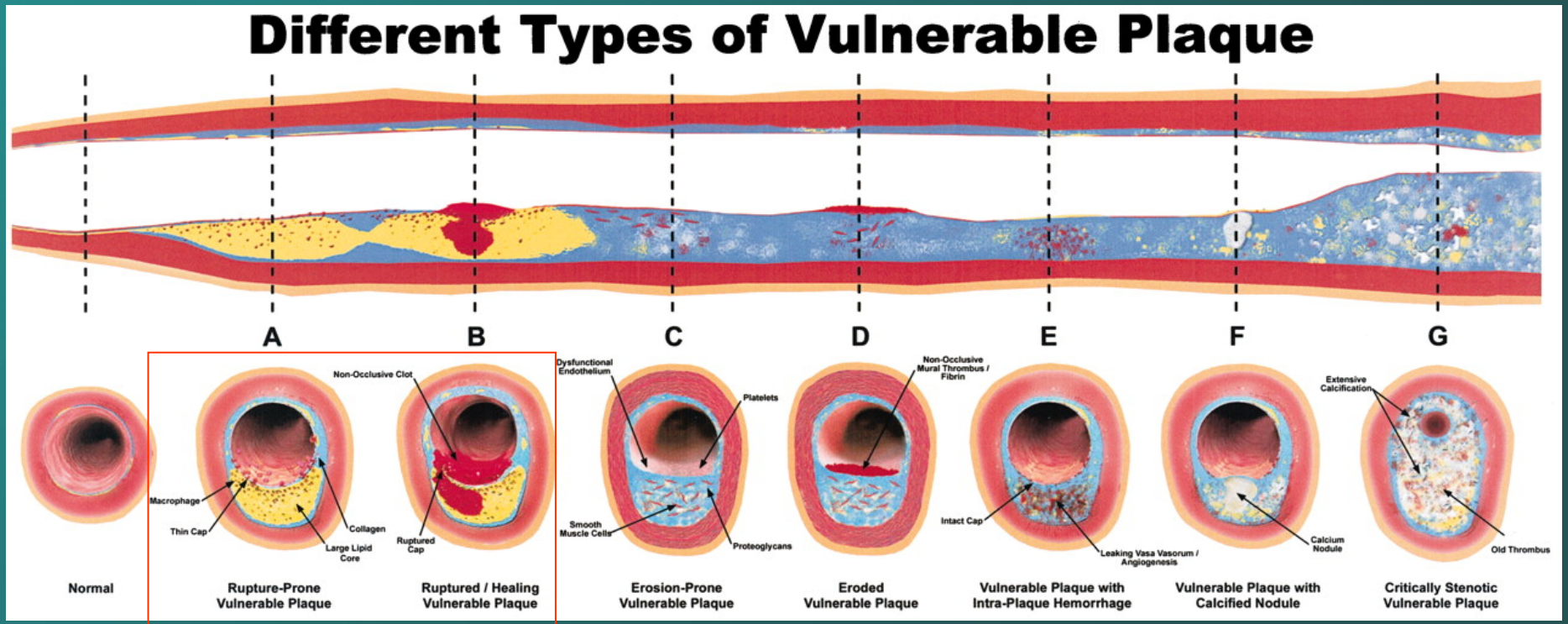
Fibroatheroma with evidence of thick fibrous cap



Fibroatheroma without evidence of thick fibrous cap



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



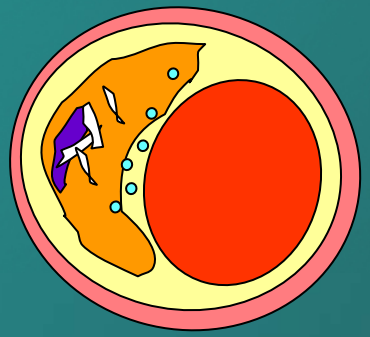
70% of ACS culprit lesions

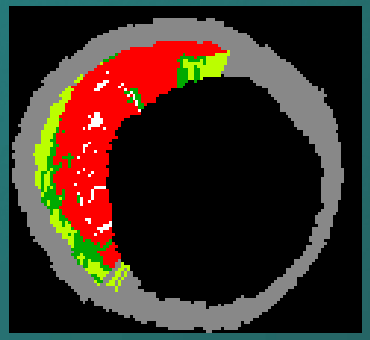
30% of ACS culprit lesions

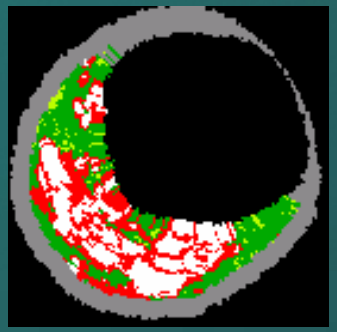
(Naghavi et al. Circulation 2003;108:1664-72)

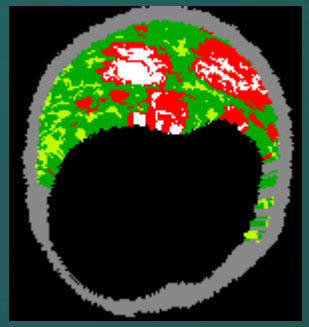
Thin Cap Fibroatheroma (TCFA)

"Thin Cap Fibro-Atheroma (TCFA)" or "Vulnerable Plaque" – Confluent Necrotic Core >10% of total plaque over >10% of circumference, and located at or near the lumen in 3 consecutive frames. Based on the presence or absence of Ca, the length of the NC, or signs of previous ruptures, TCFA can be further sub-classified for the purpose of risk assessment





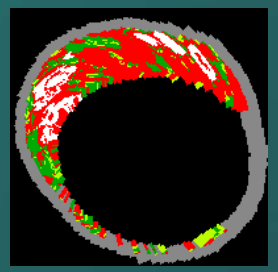


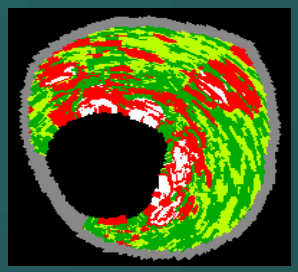


<10% calcium >10% calcium multiple layers

Still further sub-classification can be based on presence of luminal narrowing.

"TICFA without significant narrowing" - plaque burden <50% on IVUS and/or less than 25% narrowing on angiogram. (Pathologic data suggests that TCFA without significant plaque burden are less "vulnerable")



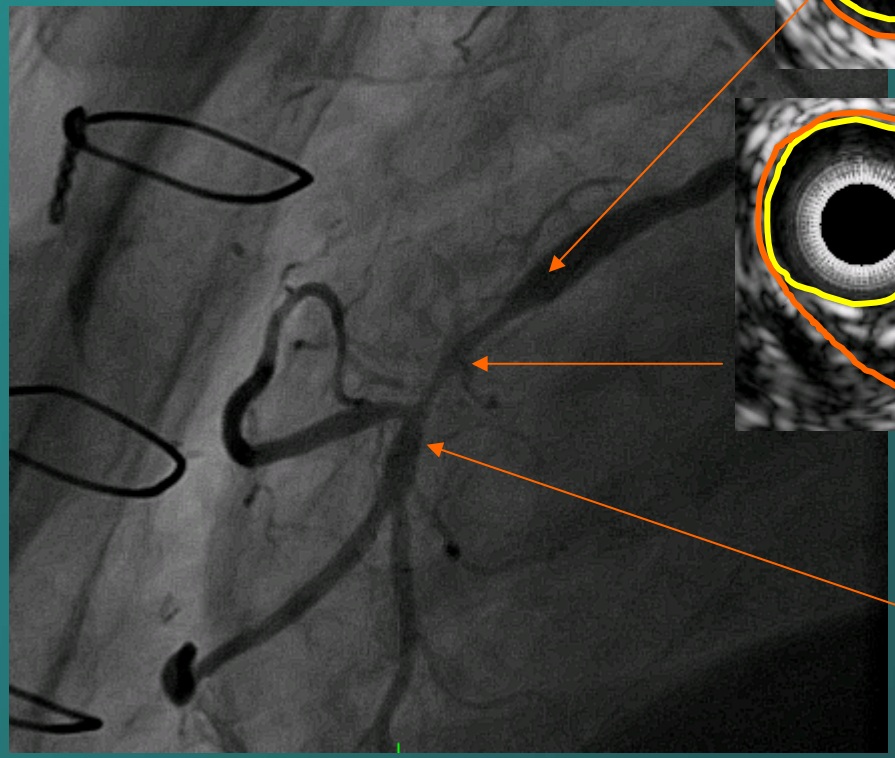


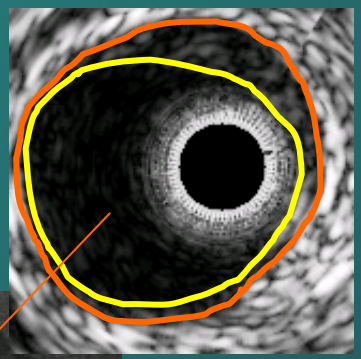
"Highest Risk TCFA"

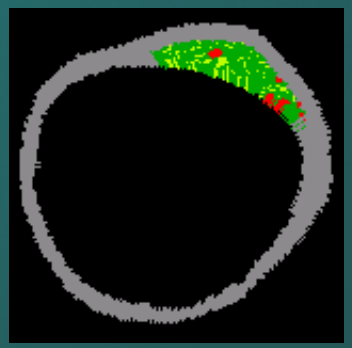
a. **Confluent NC>20%**
b. **No evidence of fibrotic cap**
c. **Calcium >5%**
d. **Remodeling index >1.05**
e. **>50% plaque burden by IVUS**

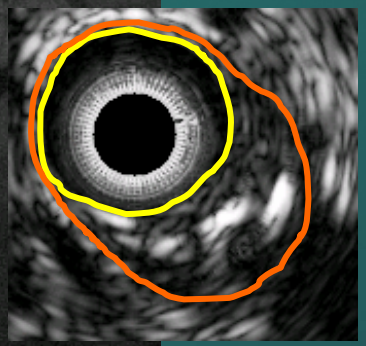
(Pathologic data suggests that TCFA with significant plaque burden are the most vulnerable)

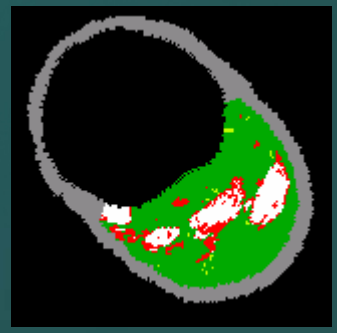
Multiple small calcific deposits by greyscale IVUS, multiple necrotic cores by VH-IVUS

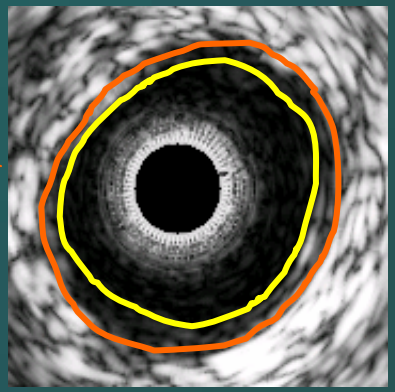


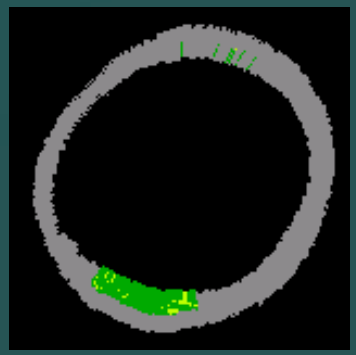








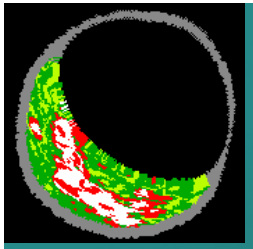




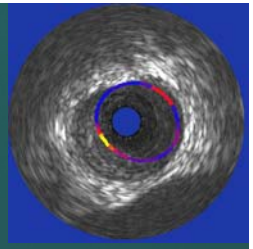
Healed ruptures are common in patients with acute events

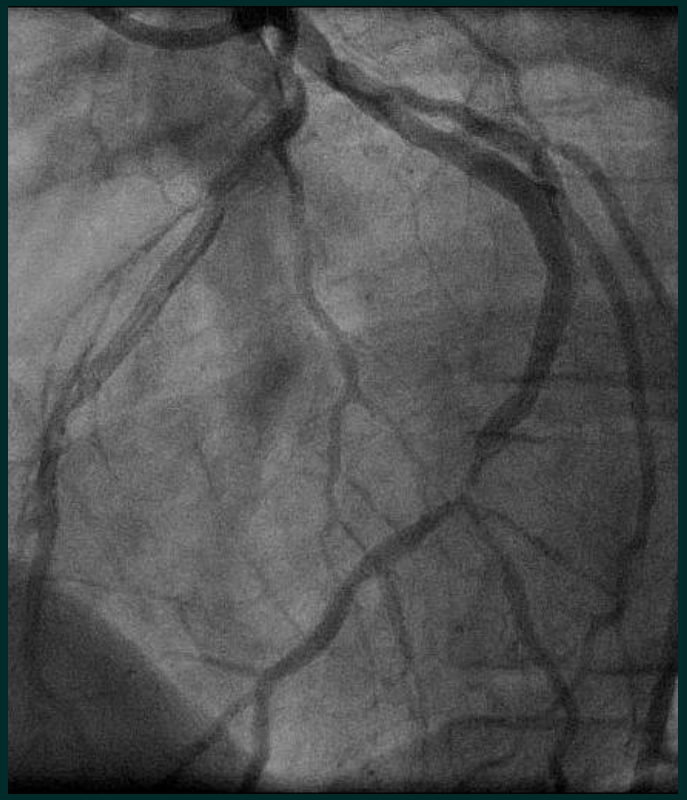
- In 142 men with sudden cardiac death, the mechanism of death was presumed to be acute plaque rupture with acute thrombus in 44, acute plaque erosion with acute thrombus in 23, stable plaque with healed MI in 41, and stable plaque without MI in 34
- There were 189 healed rupture sites. ***Healed ruptures were present in 75% of hearts with acute plaque rupture and 80% of hearts with stable plaque and healed MI***
- ***Of the 44 acute rupture sites, 9 showed 1 healed previous rupture site, 9 showed 2 healed previous rupture sites, 9 showed 3 healed previous rupture sites, and 6 showed 4 healed previous rupture sites.***
- Acute ruptures at sites of ≥3 healed previous ruptures demonstrated greater underlying plaque burden (94±4%) than those without healed previous rupture (74±12%).

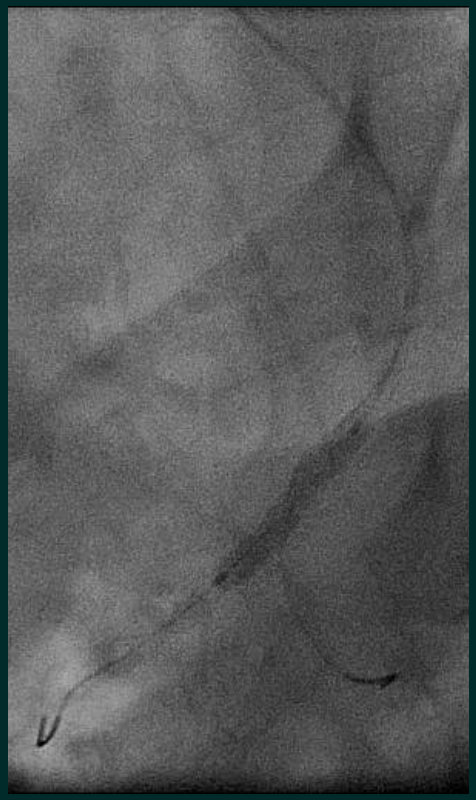
(Burke et al. Circulation 2001;103;934-40)

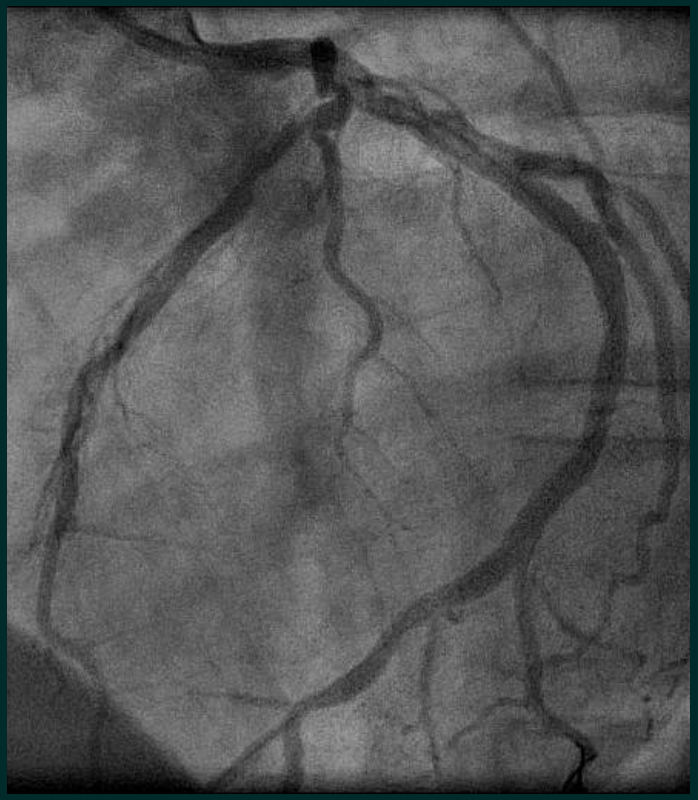


PROSPECT: Case example
74. y.o. ♂ with NSTEMI

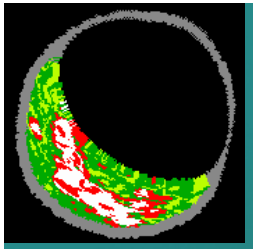








Pre PCI **Stent** **Post PCI**



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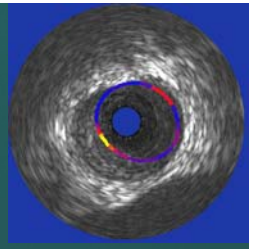
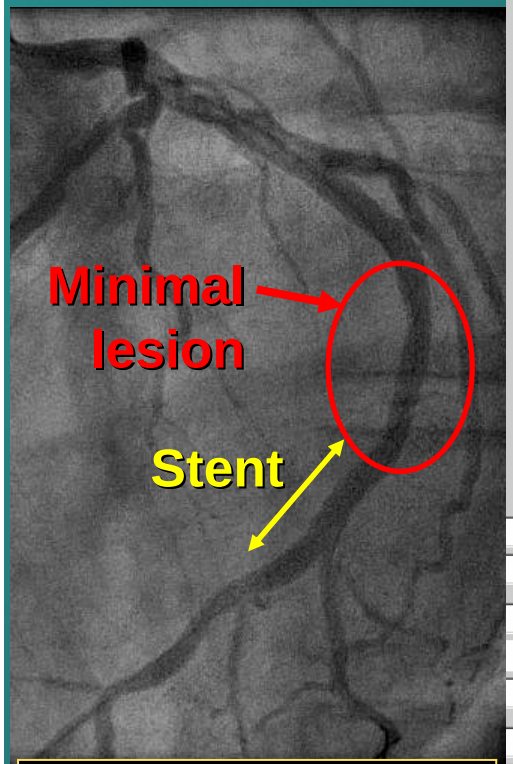
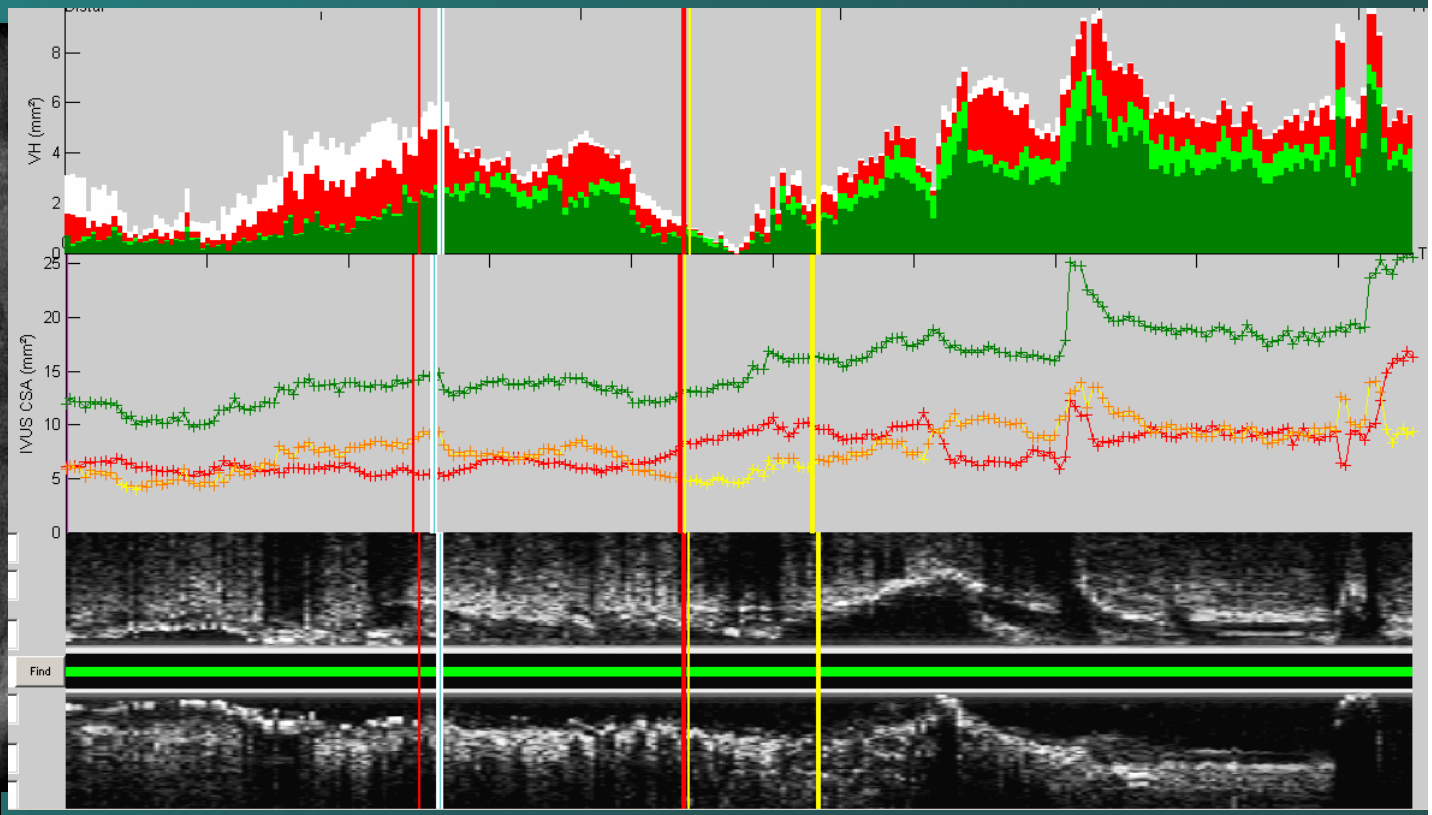


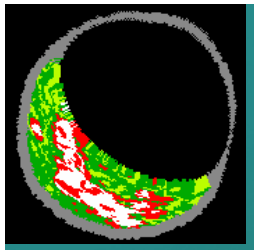




QCA
RVD 2.67 mm
MLD 2.52 mm
DS 9.4%

Stent → ← **Fibroatheroma**

CARDIOVASCULAR RESEARCH FOUNDATION



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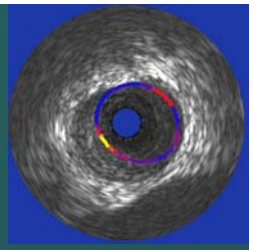
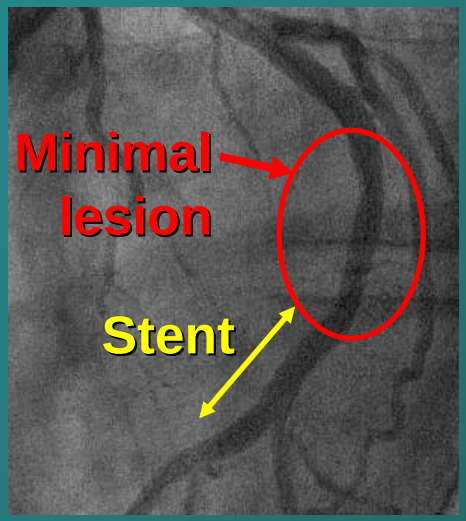
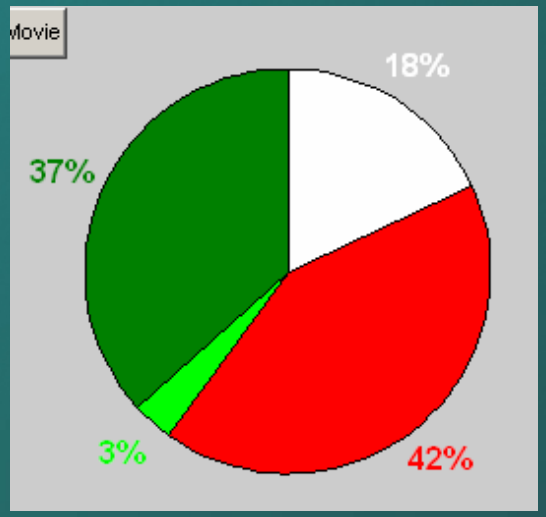
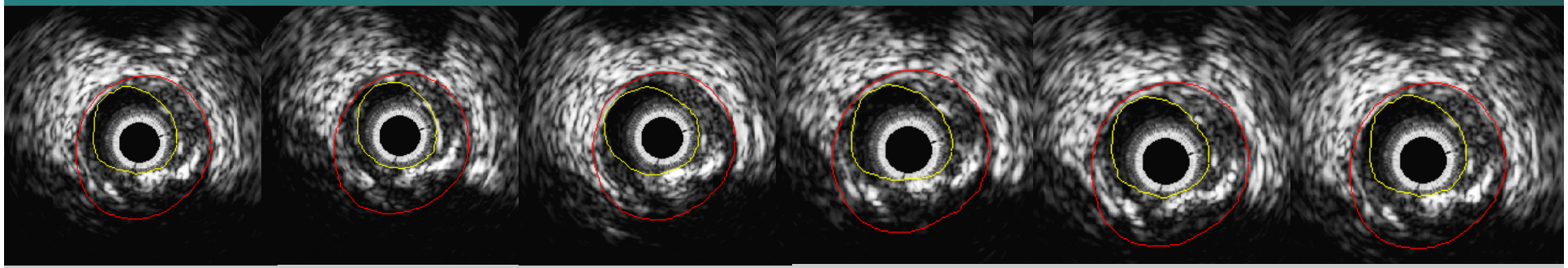
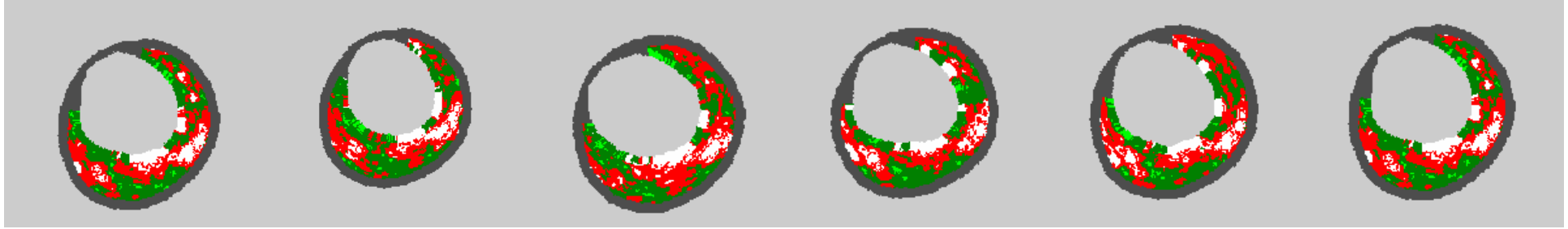


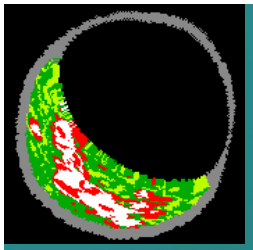




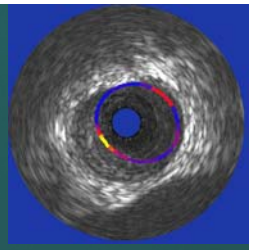
VH-TCFA
Calcified
Multiple layered
F 37%
FF 3%
NC 42%
DC 18%



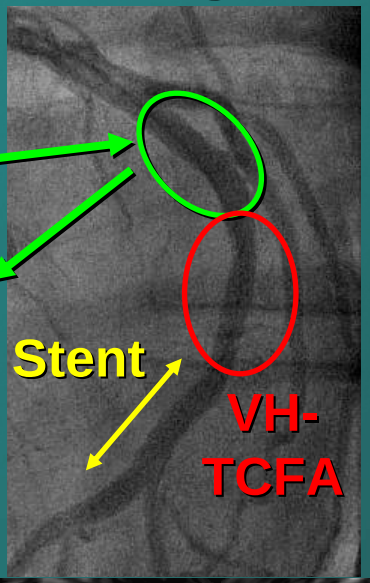




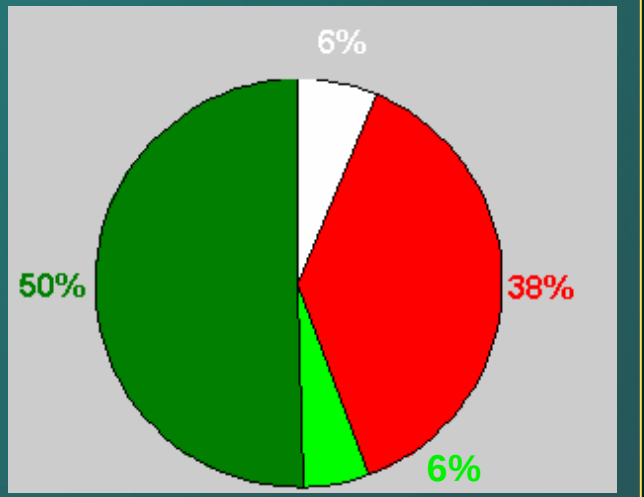
PROSPECT: Case example
74. y.o. ♂ with NSTEMI



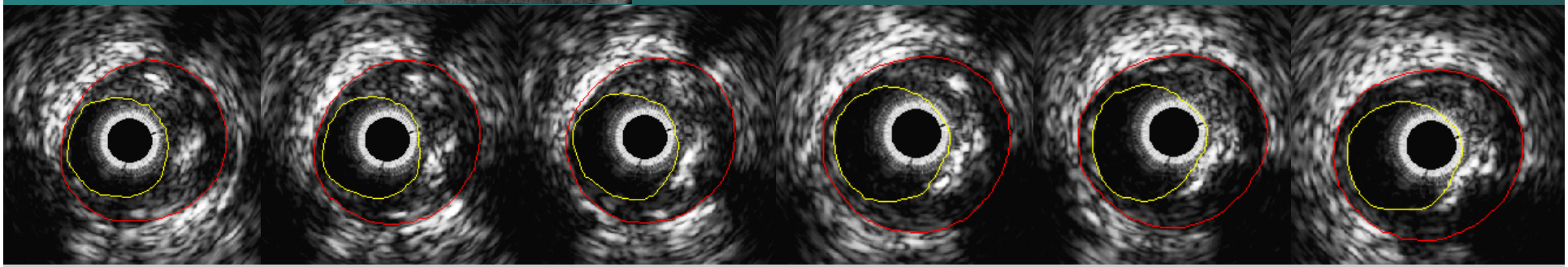
Nearly Normal vessel

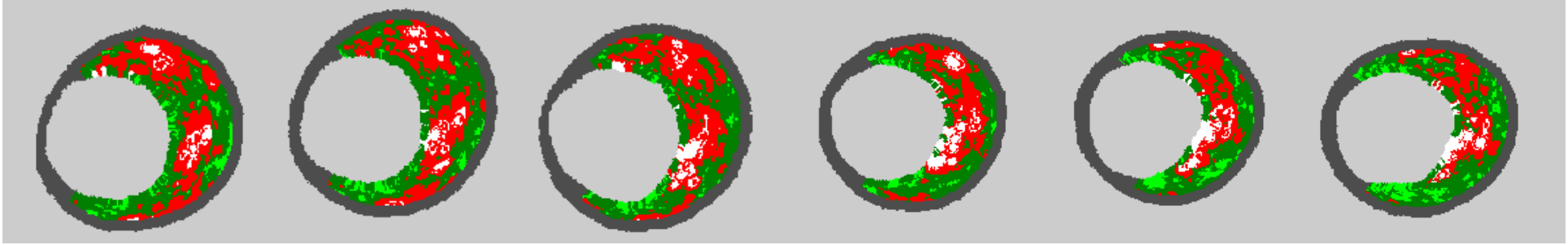


QCA
RVD 2.88 mm
MLD 2.81 mm
DS 2.4%

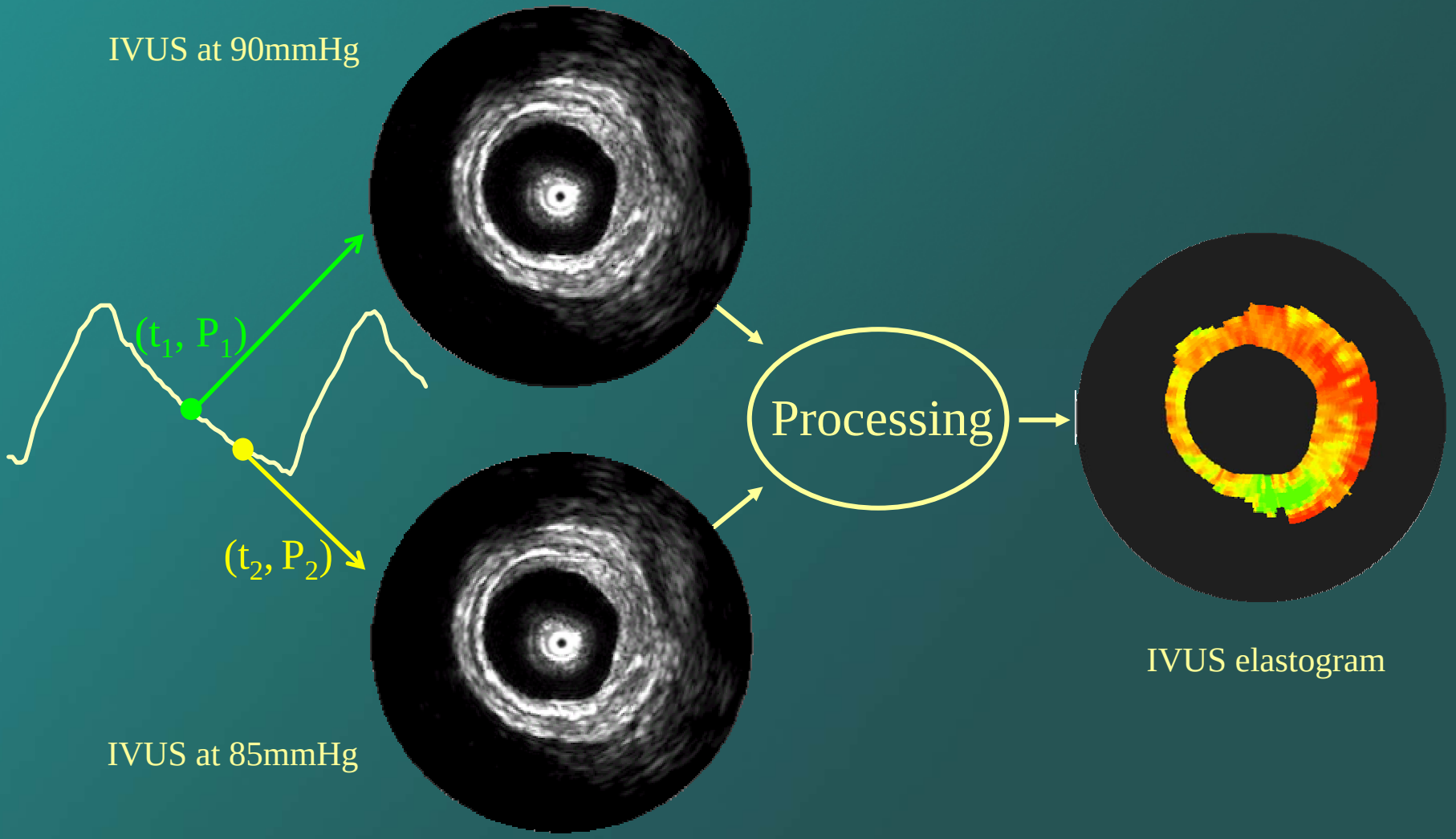


2nd VH-TCFA
Non calcified
Multiple layered
F 50%
FF 6%
NC 38%
DC 6%

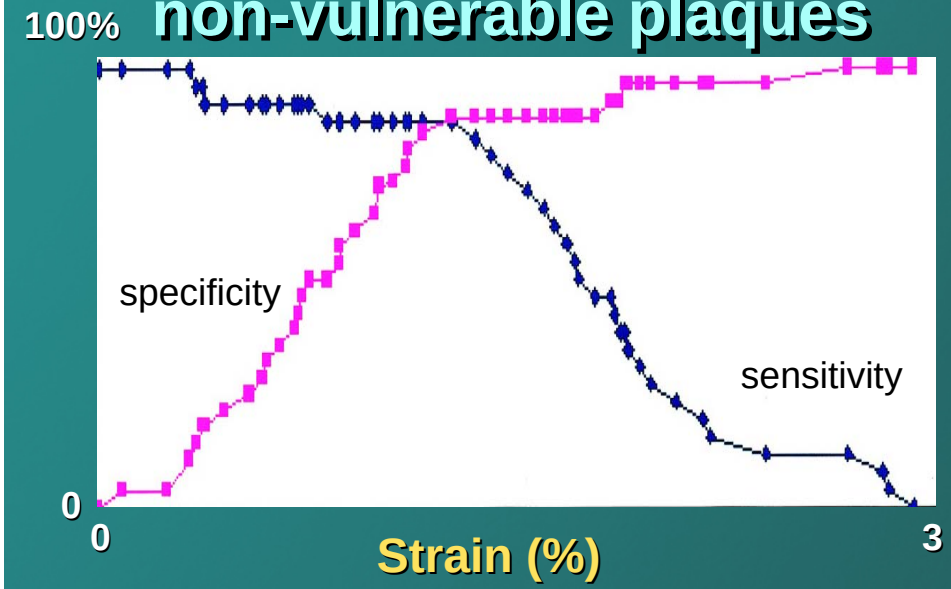


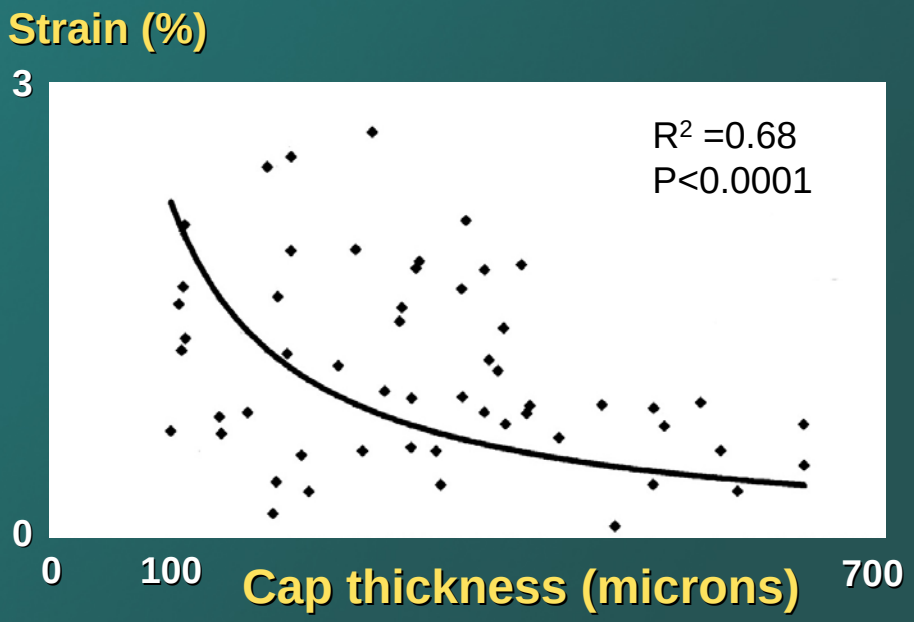


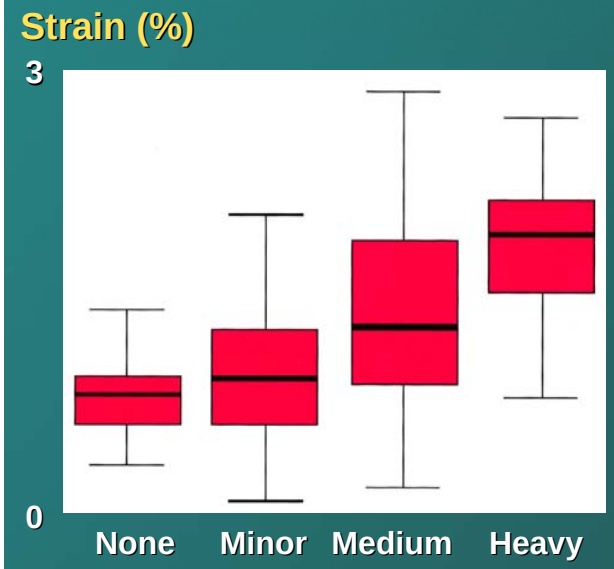
Principles of Palpography

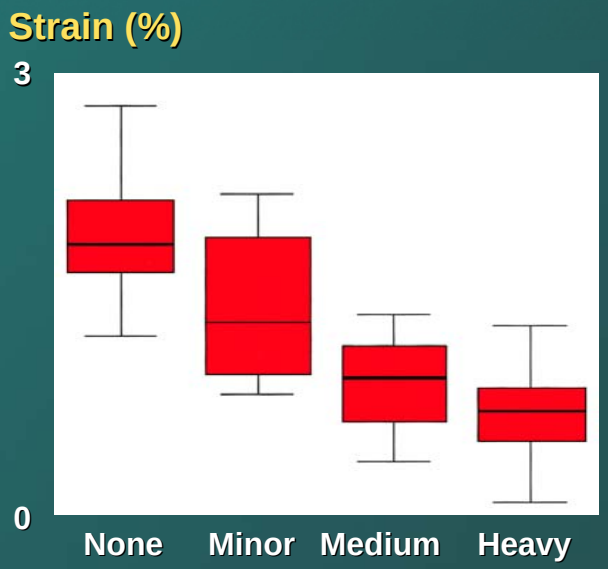


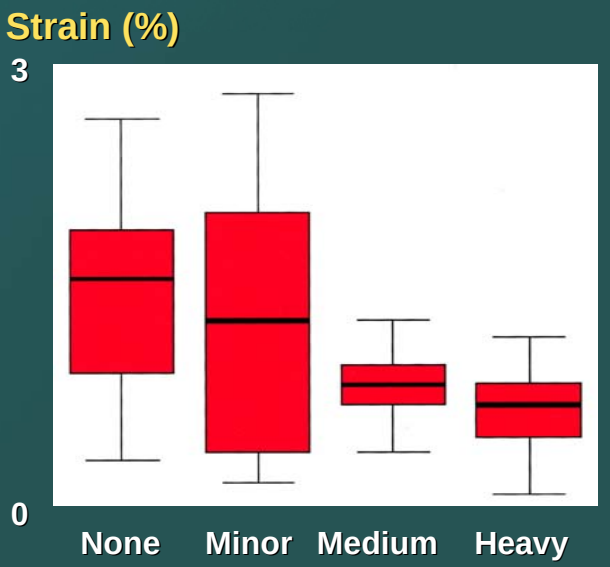
26 vulnerable vs 28 non-vulnerable plaques



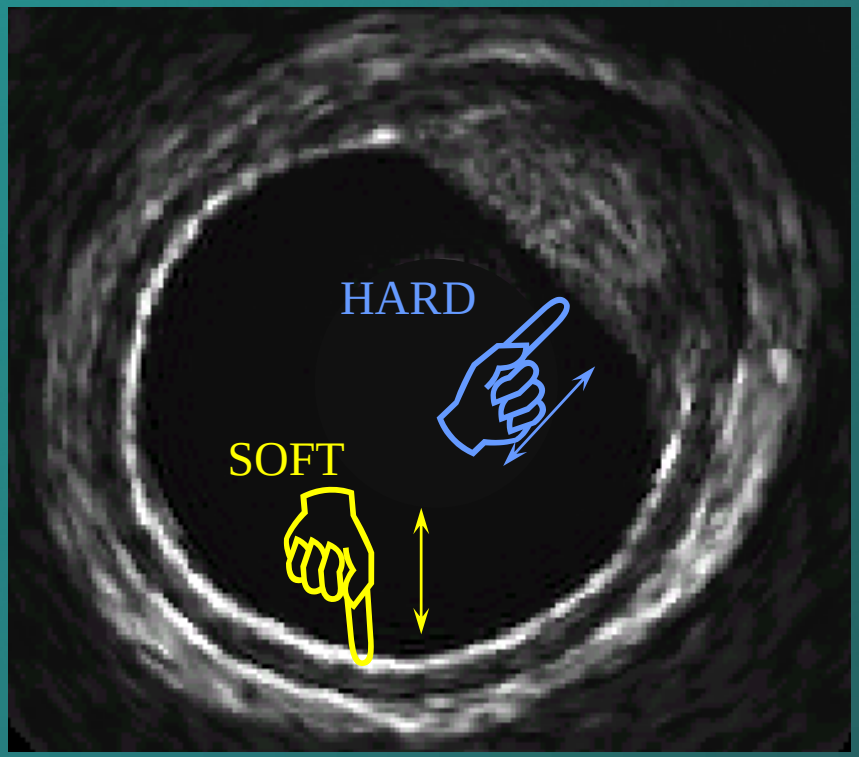


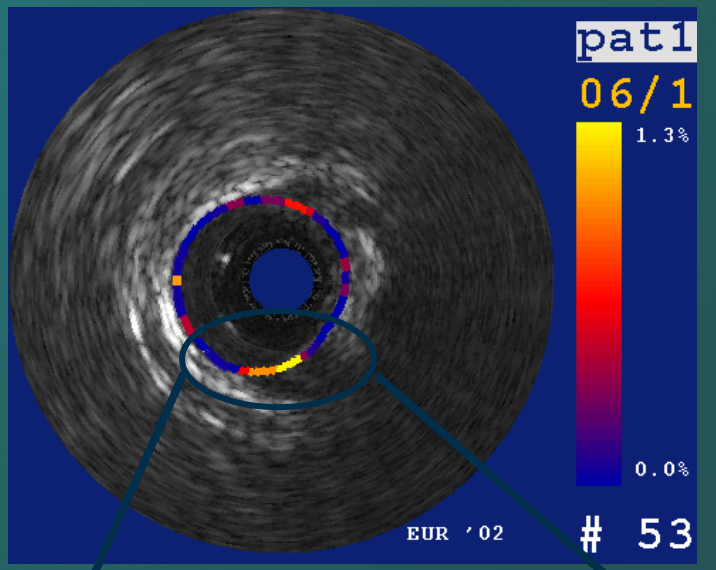


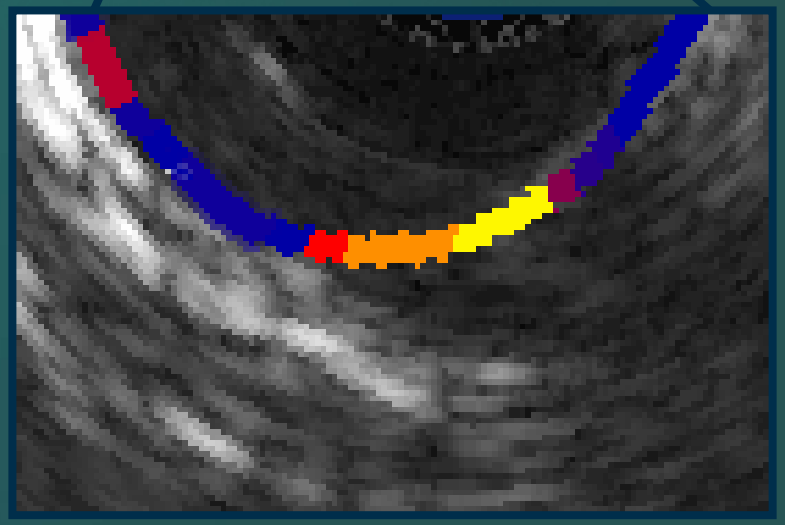




(Schaar et al. Circulation 2003;108:2535-41)

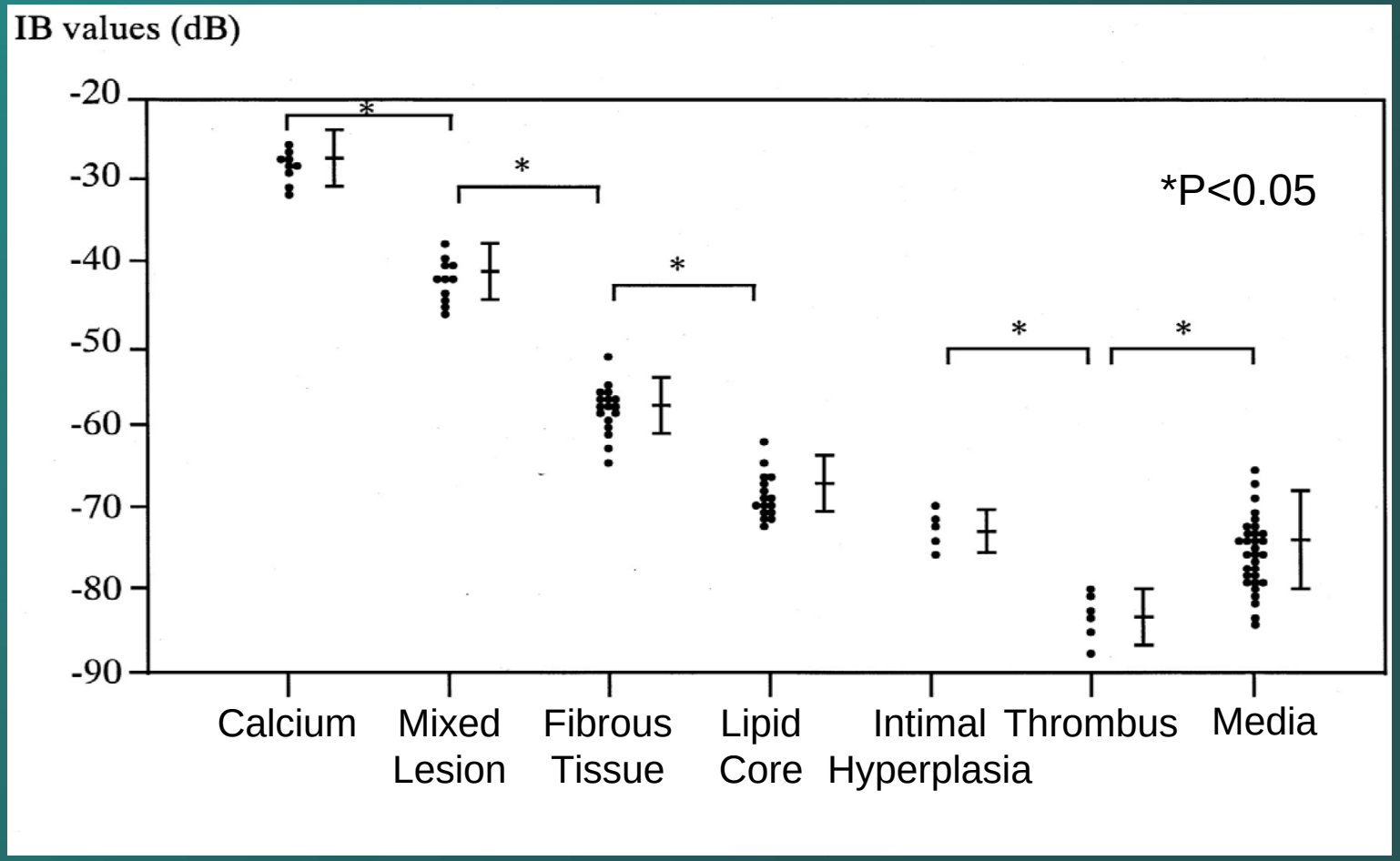






Independent predictors of strain were macrophages (p=0.006) and smooth muscle cells (p=0.0001)

Integrated Backscatter (IB) IVUS values for various tissue types



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

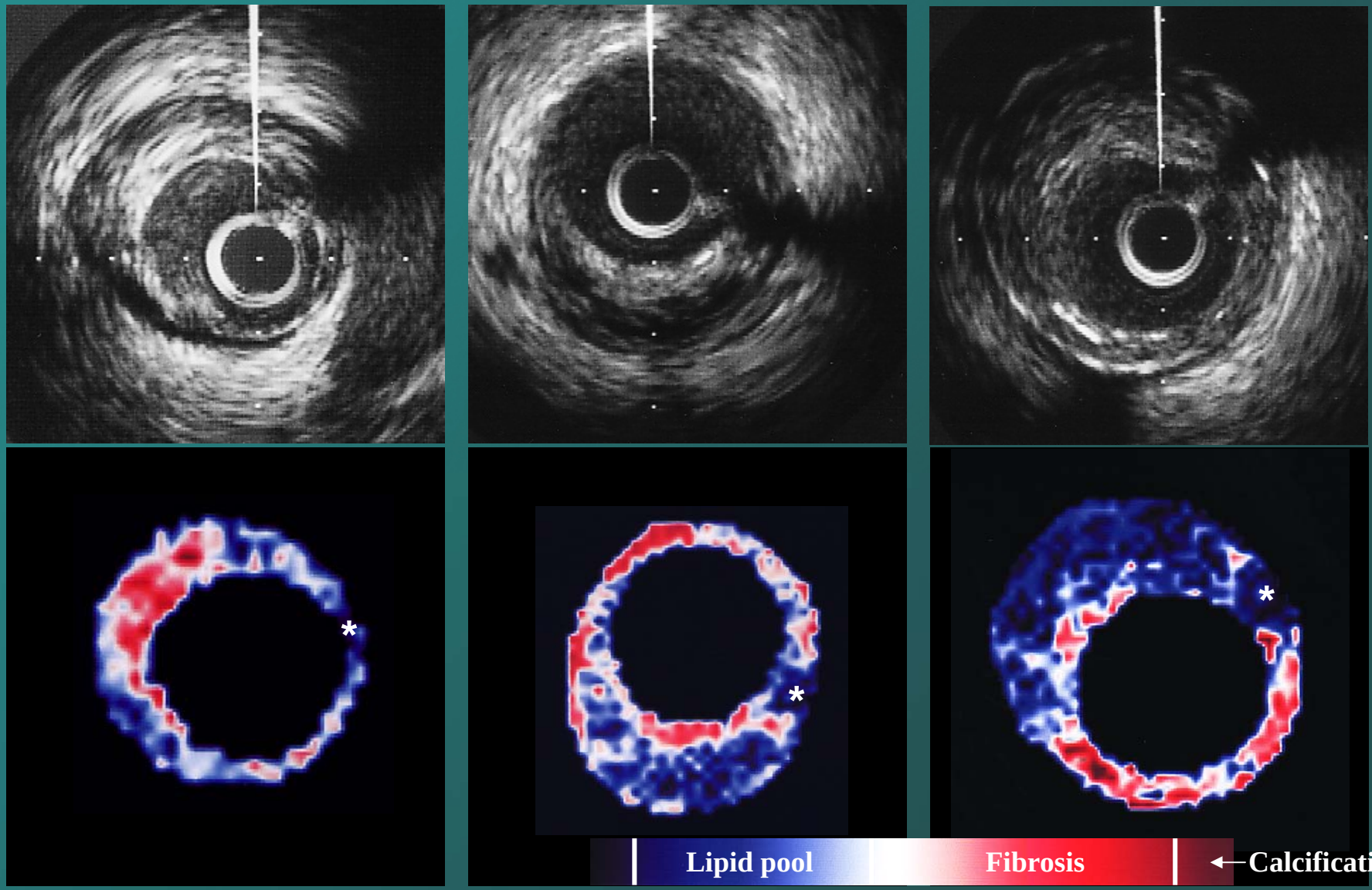
Diagnostic accuracy of real-time IB (Integrated Backscatter)-IVUS

	Sensitivity	Specificity	PPV	NPV
Calcification (n=144)	95%	99%	93%	99%
Fibrosis (n=335)	94%	93%	93%	94%
Lipid pool (n=205)	90%	92%	85%	90%

(Kawasaki et al. Circulation2002;105:2487-92)

Stable Plaque

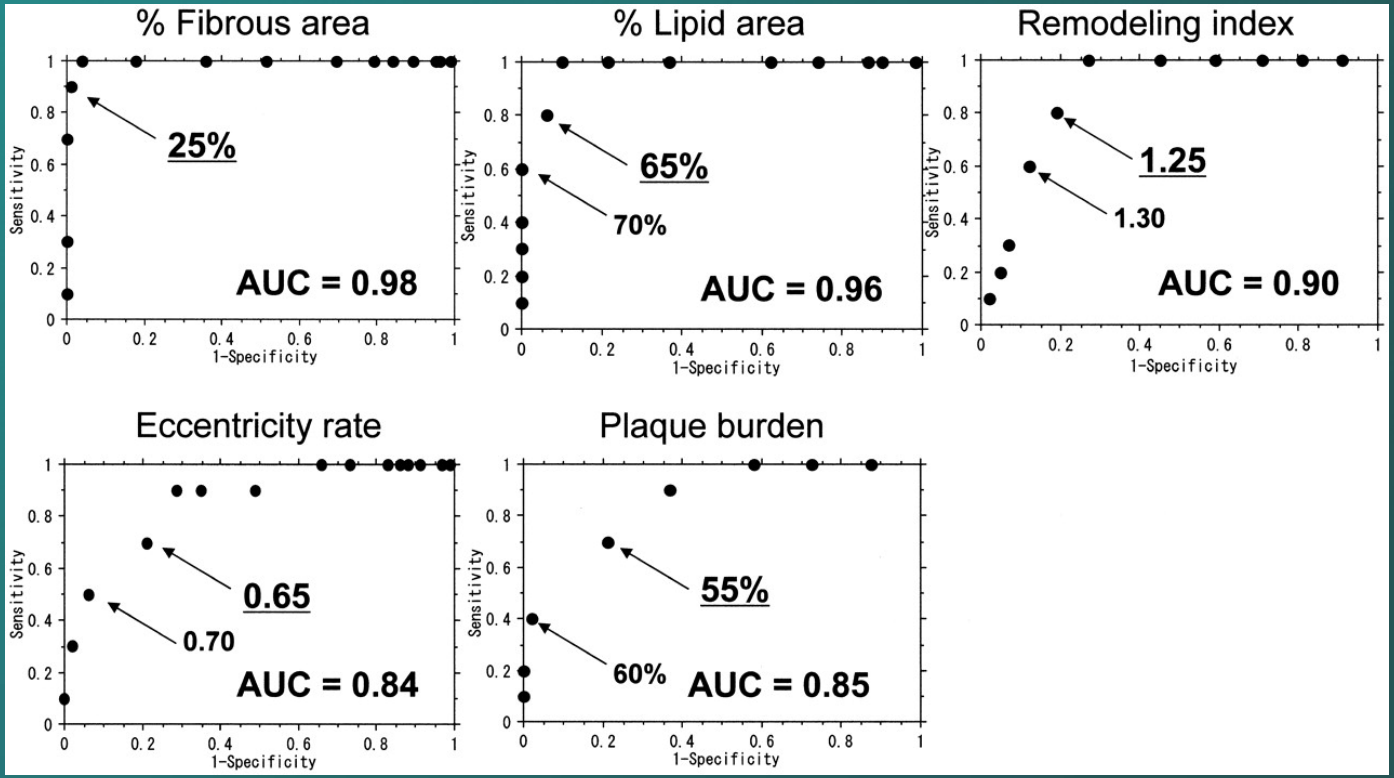
Vulnerable Plaque Causing ACS



* guidewire artifact

(Sano et al. J Am Coll Cardiol 2006;47:734-41)

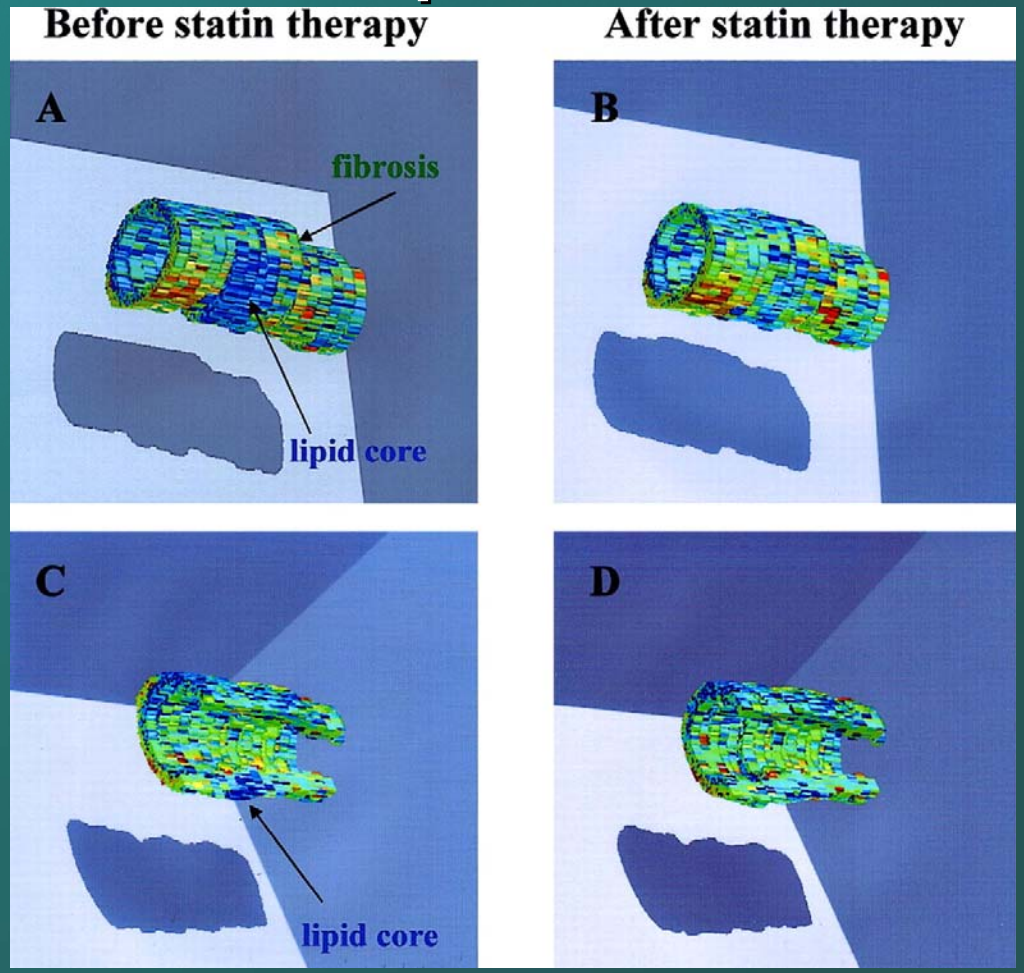
IVUS predictors of vulnerable plaques



	Sens	Spec	PPV	NPV	Accuracy
%fibrous area (<25%)	90%	96%	69%	99%	95%
%lipid area (>65%)	80%	90%	42%	98%	89%

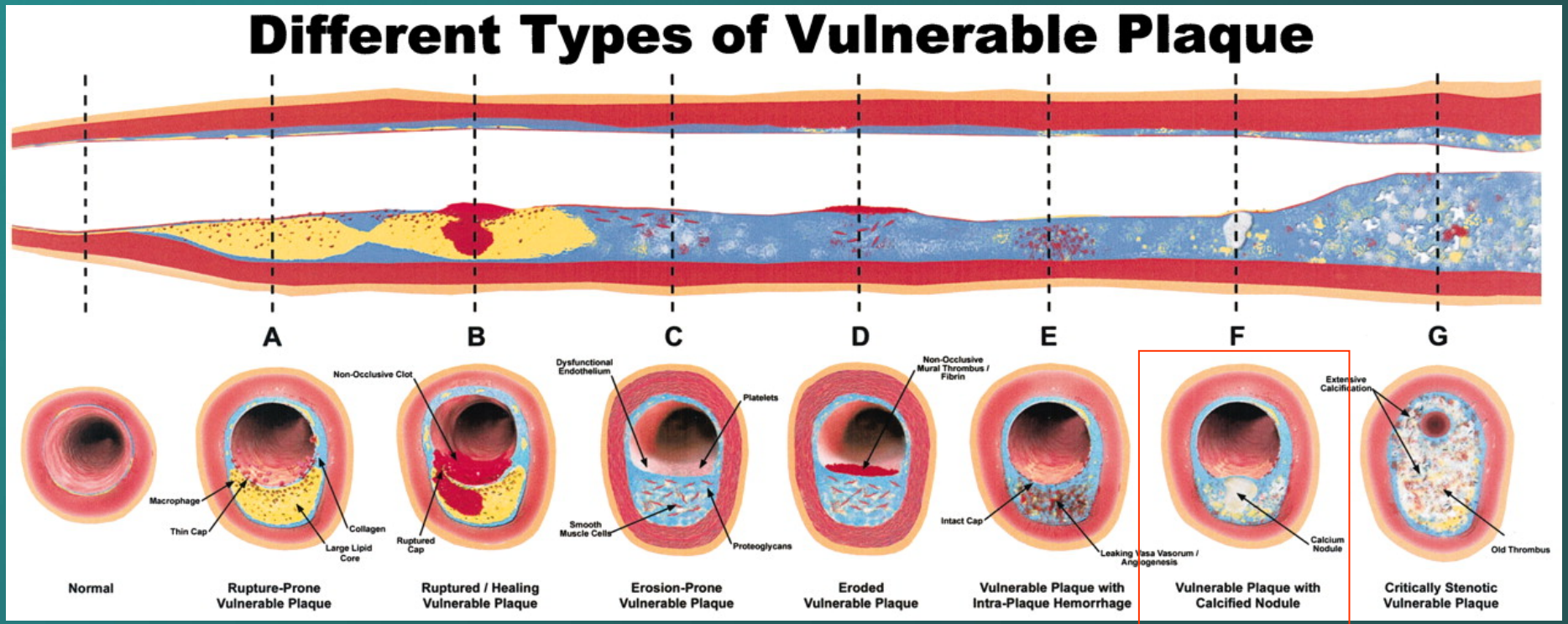
(Sano, K. et al. J Am Coll Cardiol 2006;47:734-741)

Statin therapy increased the volumes of fibrous and “mixed” lesion components and reduced the lipid content



(Kawasaki, M. et al. J Am Coll Cardiol 2005;45:1946-1953)

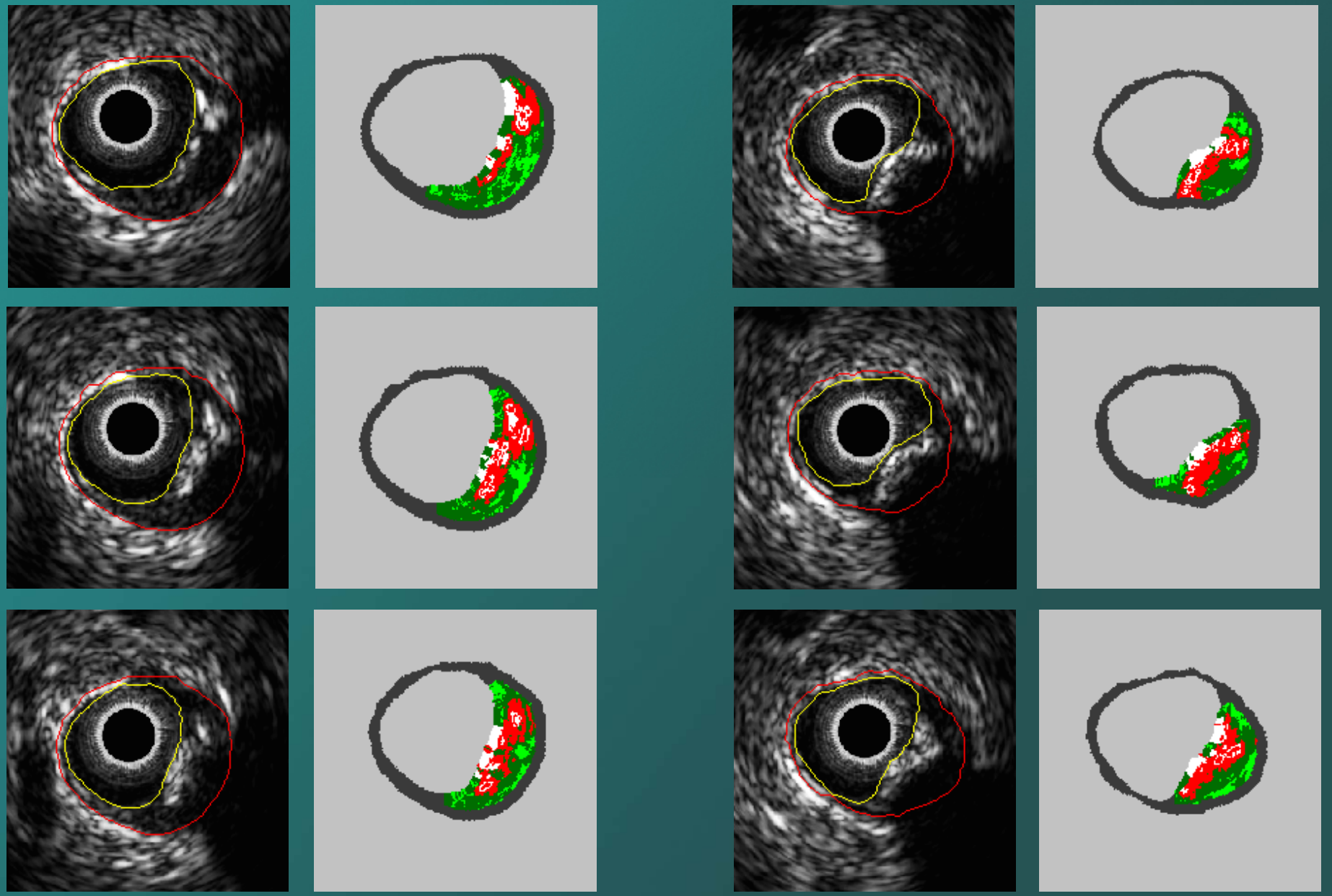
“Vulnerable Plaque” = thrombosis-prone plaque and plaque with a high probability of undergoing rapid progression



70% of ACS culprit lesions

30% of ACS culprit lesions

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



Columbia University Medical Center

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