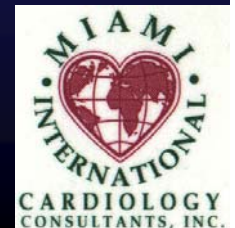


VHTM IVUS to Assess Plaque Progression and Regression

M. Pauliina Margolis, MD PhD & James R. Margolis, MD
Volcano Therapeutics and Miami International Cardiology
Miami, Florida USA



2005

- The incidence of death and MI due to coronary artery disease has declined by an average of 20-30% due to:
 - Life style changes
 - Systemic medication
 - ? PCI and CABG
- Why is Coronary Artery Disease still the #1 killer worldwide?

The “Vulnerable” Coronary Plaque

Thin cap fibroatheroma with necrotic core

Necrotic core

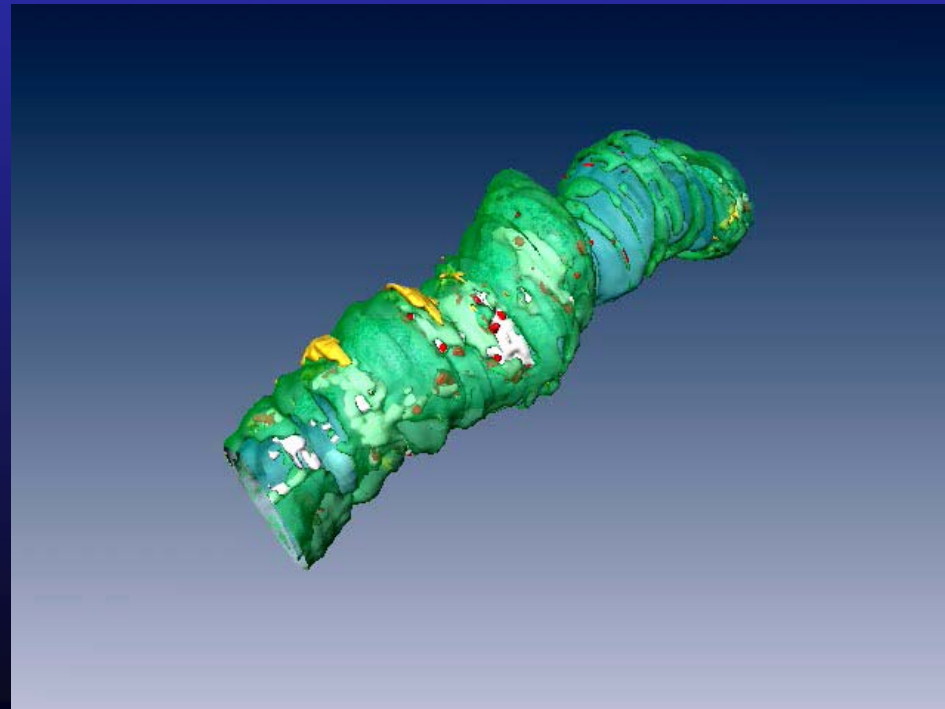
Lumen

Fibrous Cap



Virtual Histology

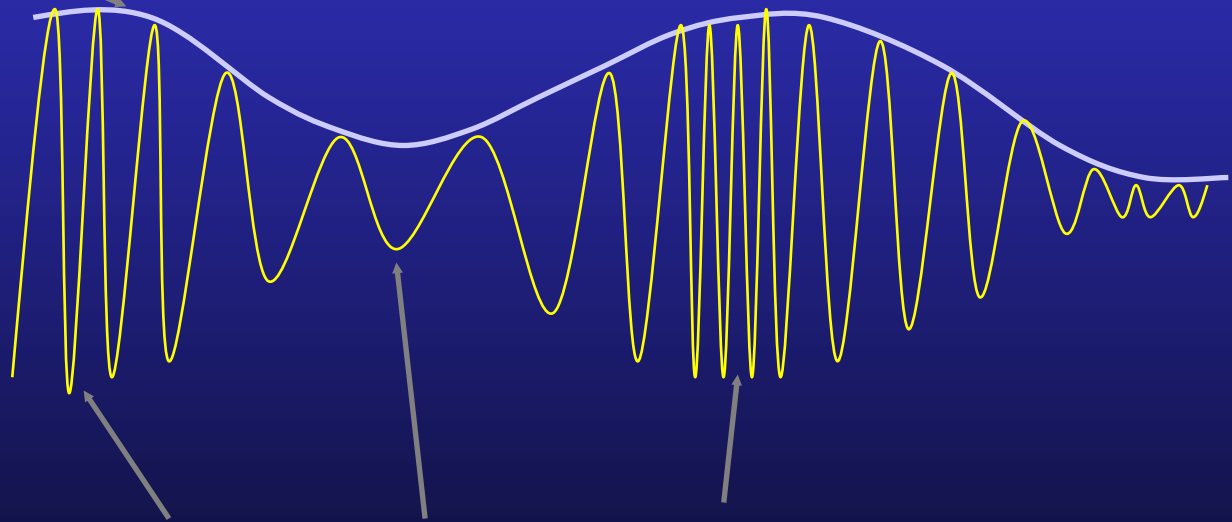
- IVUS-based **tissue characterization** merged with novel **border detection** and analysis software.
- 13 year development effort: Collaboration between The Cleveland Clinic Foundation and Volcano Therapeutics.



Virtual Histology™ IVUS

Gray-scale IVUS uses only the envelope amplitude (echo intensity) in formation of the image

Virtual Histology uses both echo Amplitude AND Frequency

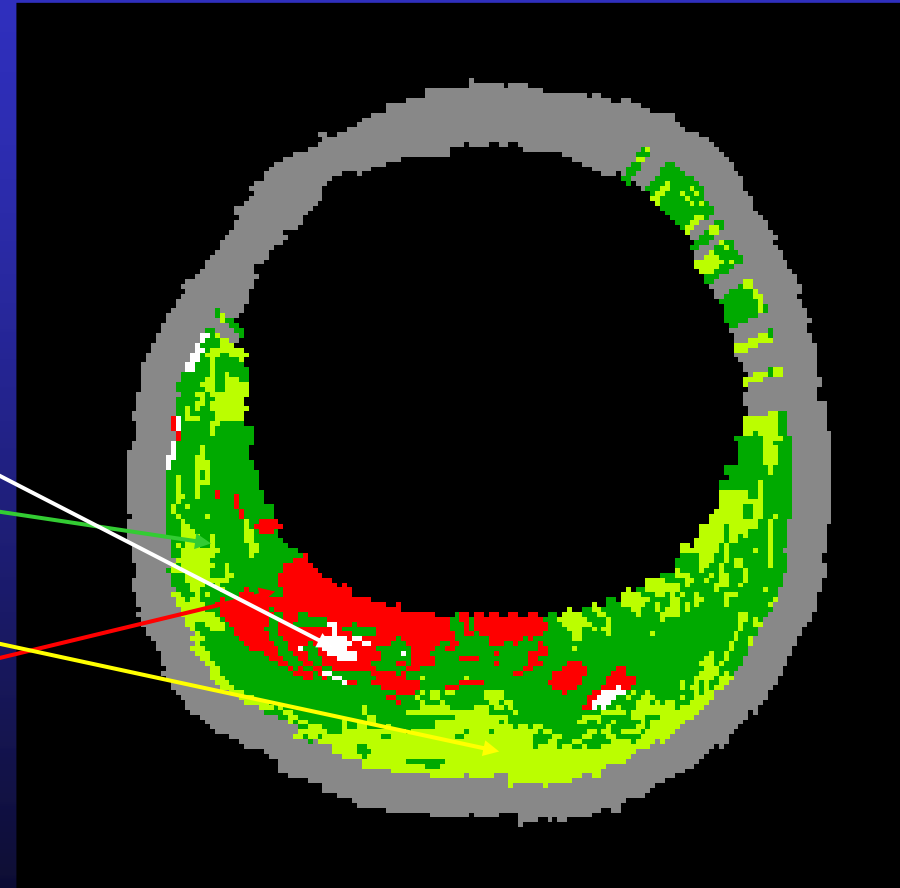


Frequency of echo signal can also vary, depending on the tissue...

Virtual Histology™ IVUS

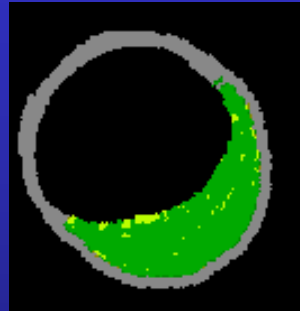
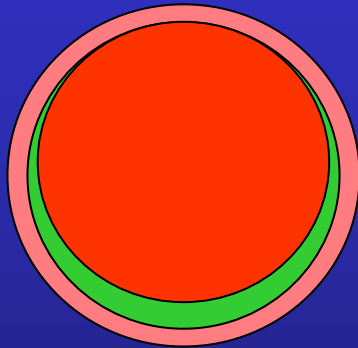
Different frequencies correspond to different types of tissue.

- Dense Calcium
- Fibrous
- Fibro-fatty
- Necrotic Core

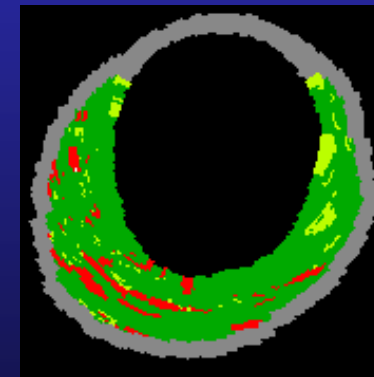
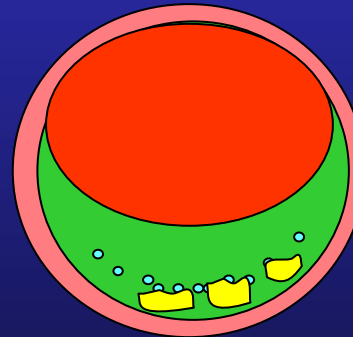


Plaque Classification

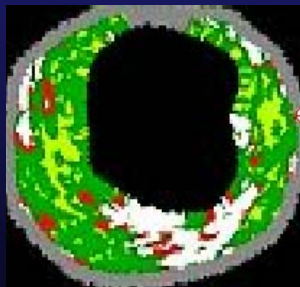
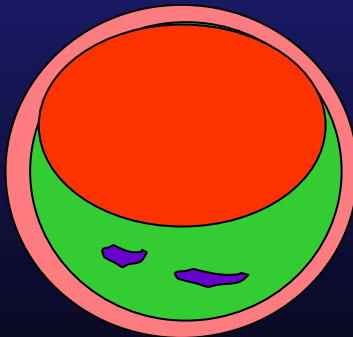
“Fibrous” – Plaque comprised of nearly all fibrous tissue.
Generally not viewed by Dr. Virmani to be acutely dangerous.



“Pathological Intimal Thickening” – Mainly mixture of fibrous, fibrofatty, and some necrotic core (<5%) and calcified tissue

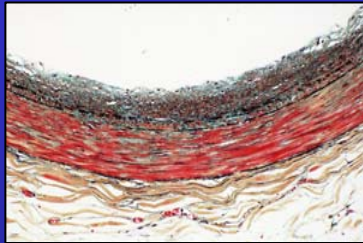


“Fibro-Calcific” – Mainly fibrous plaques, with some Dense Calcium.
Presence of Necrotic Core between 3% and 10% of plaque volume.

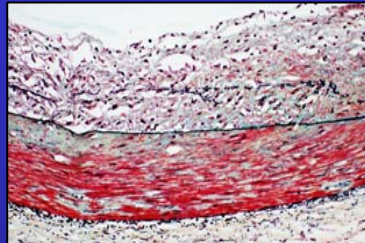


Development of Human Thin Cap Fibroatheroma

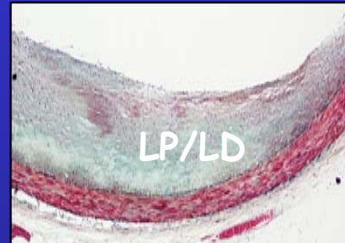
Intimal thickening



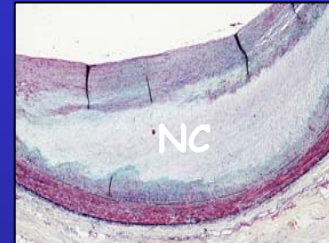
Intimal xanthoma



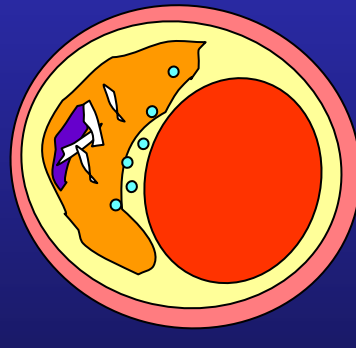
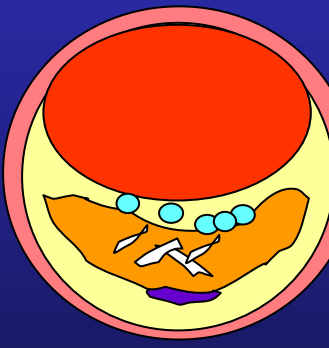
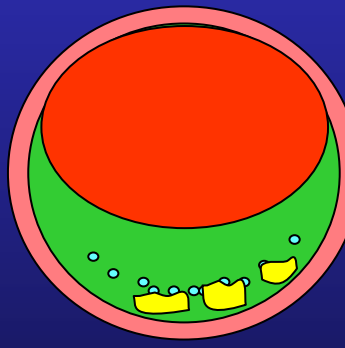
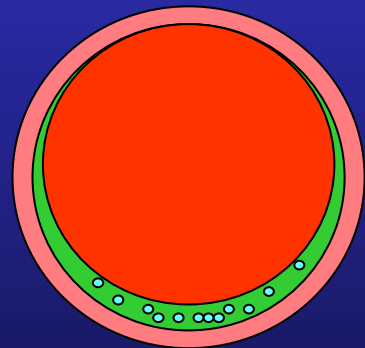
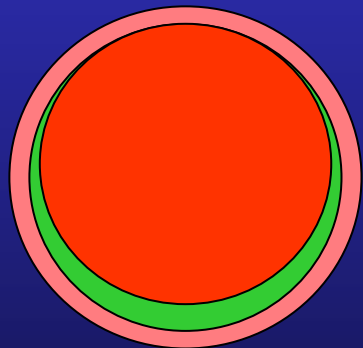
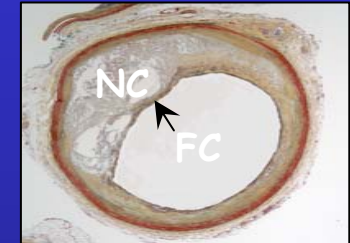
Pathologic intimal thickening



Fibrous cap atheroma



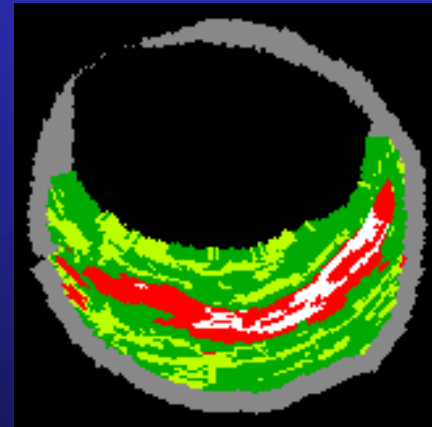
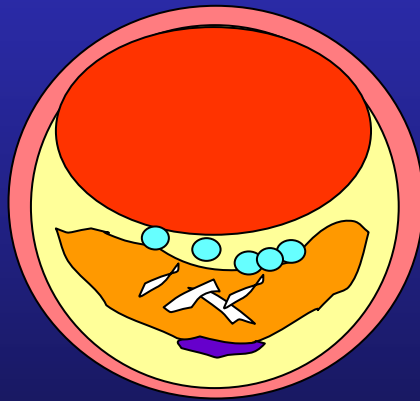
Thin-cap Fibroatheroma



- Smooth muscle cells
- Macrophage foam cells
- Extracellular lipid
- Cholesterol clefts
- Necrotic core
- Calcified plaque
- Hemorrhage
- Thrombus
- Healed thrombus
- Collagen

Plaque Classification

“Fibro-Atheroma” – Fibrous and/or Fibro-Fatty plaques with significant Necrotic Core (NC greater than 10% of total plaque volume).



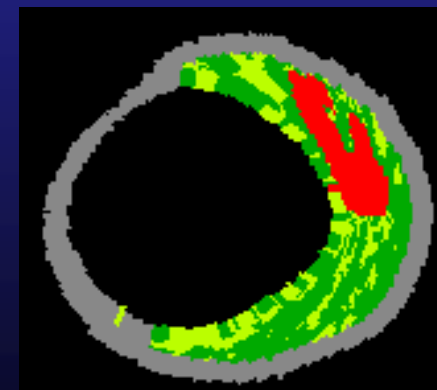
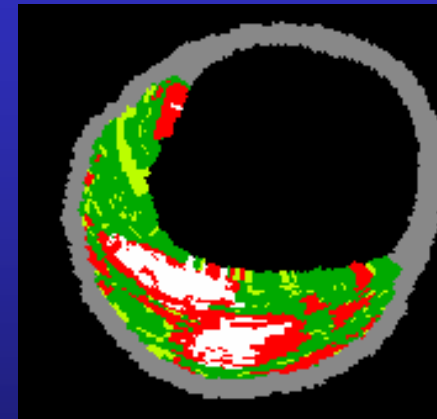
It will very likely be that the most important goal is to differentiate the Fibro-Atheroma plaque type from the other three plaque types during assessments of ambiguous lesions.

Fibro Atheroma

For purposes of risk-assessment, Fibro-Atheroma can be further differentiated into 3 sub-groups:

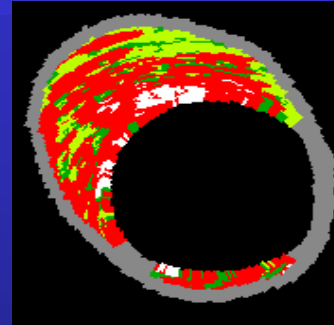
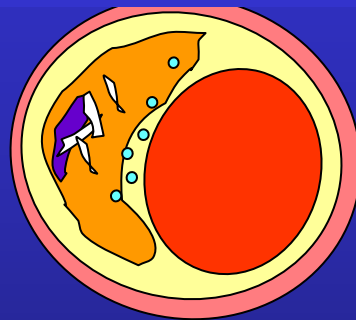
“Fibro-Atheroma with Dense Calcium” –
Fibro-Atheroma with Dense Calcium present in plaque (generally viewed as being more dangerous than FA without DC)

“Fibro-Atheroma without Dense Calcium”
– Fibro-Atheroma without presence of Dense Calcium.



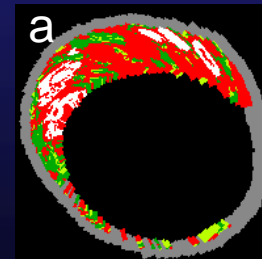
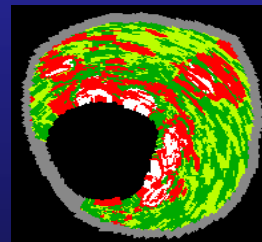
Fibro Atheroma

“Thin Cap Fibro-Atheroma (TICFA)” or “Vulnerable Plaque” -- Necrotic Core is significant (>10% of total plaque volume) *and located on or near the lumen at VH.*



Further sub-classification based on presence of luminal narrowing may be of further prognostic value in assessing TICFA risk.

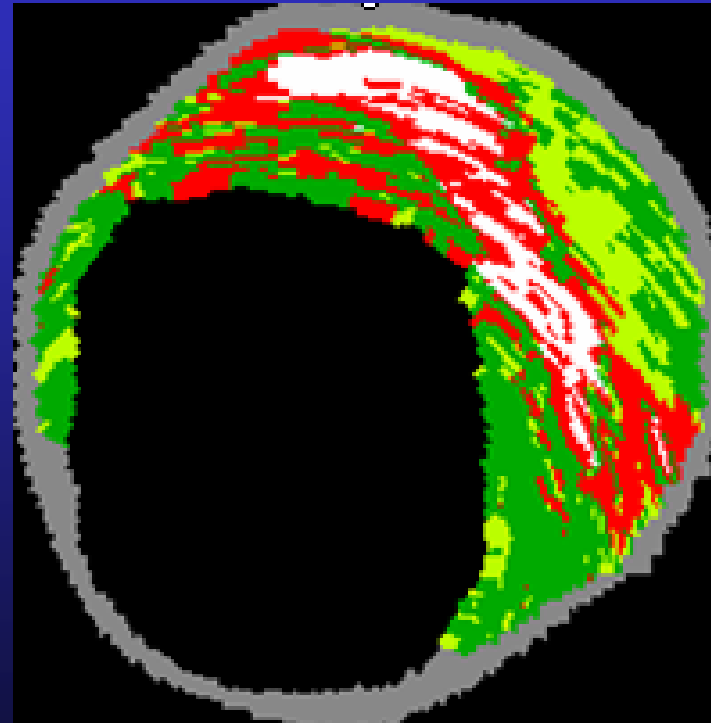
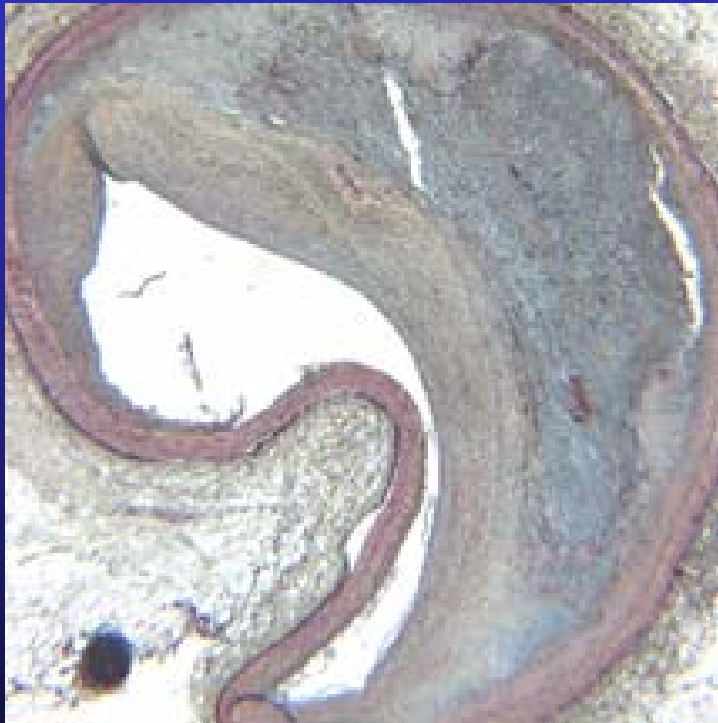
a. “TICFA with significant narrowing”
(significant narrowing defined as greater than 50% reduction in Cross Sectional Area (CSA) on IVUS, or stenosis of 25% or greater on angiogram). Dr. Virmani’s data suggest that TICFA with significant narrowing represents the highest risk of all plaques.



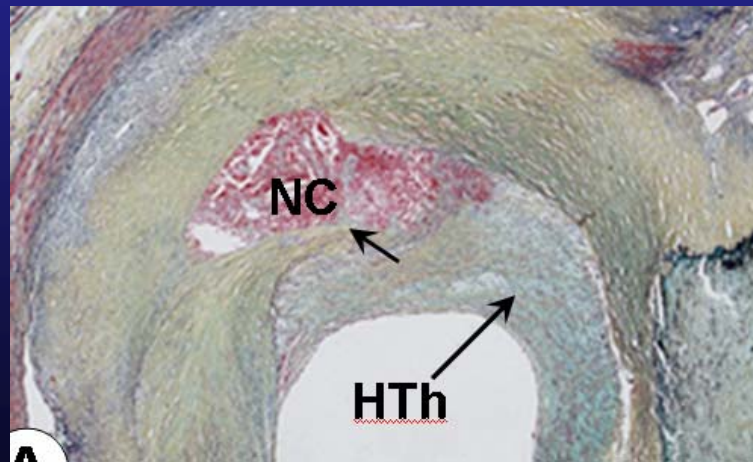
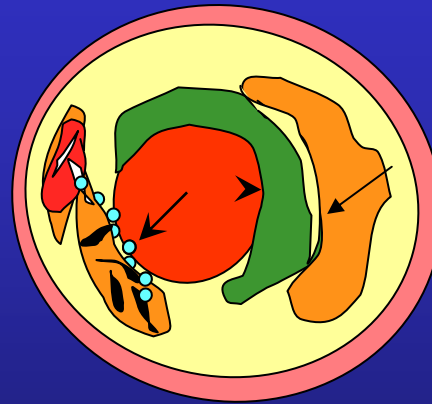
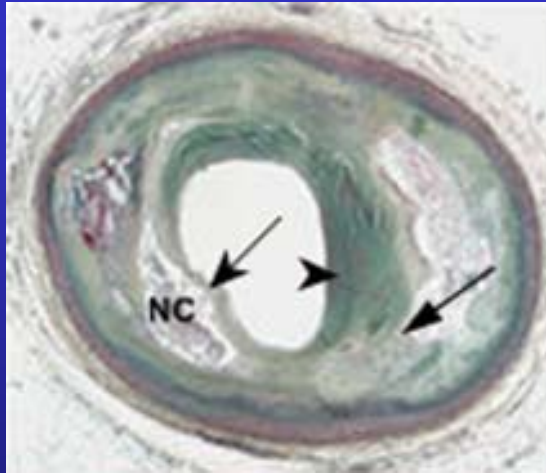
b

b. “TICFA without significant narrowing” (CSA reduction of less than 50% on IVUS, less than 25% narrowing on angiogram). Dr. Virmani’s data suggest that TICFA without significant narrowing purports a considerably lower risk TICFA.

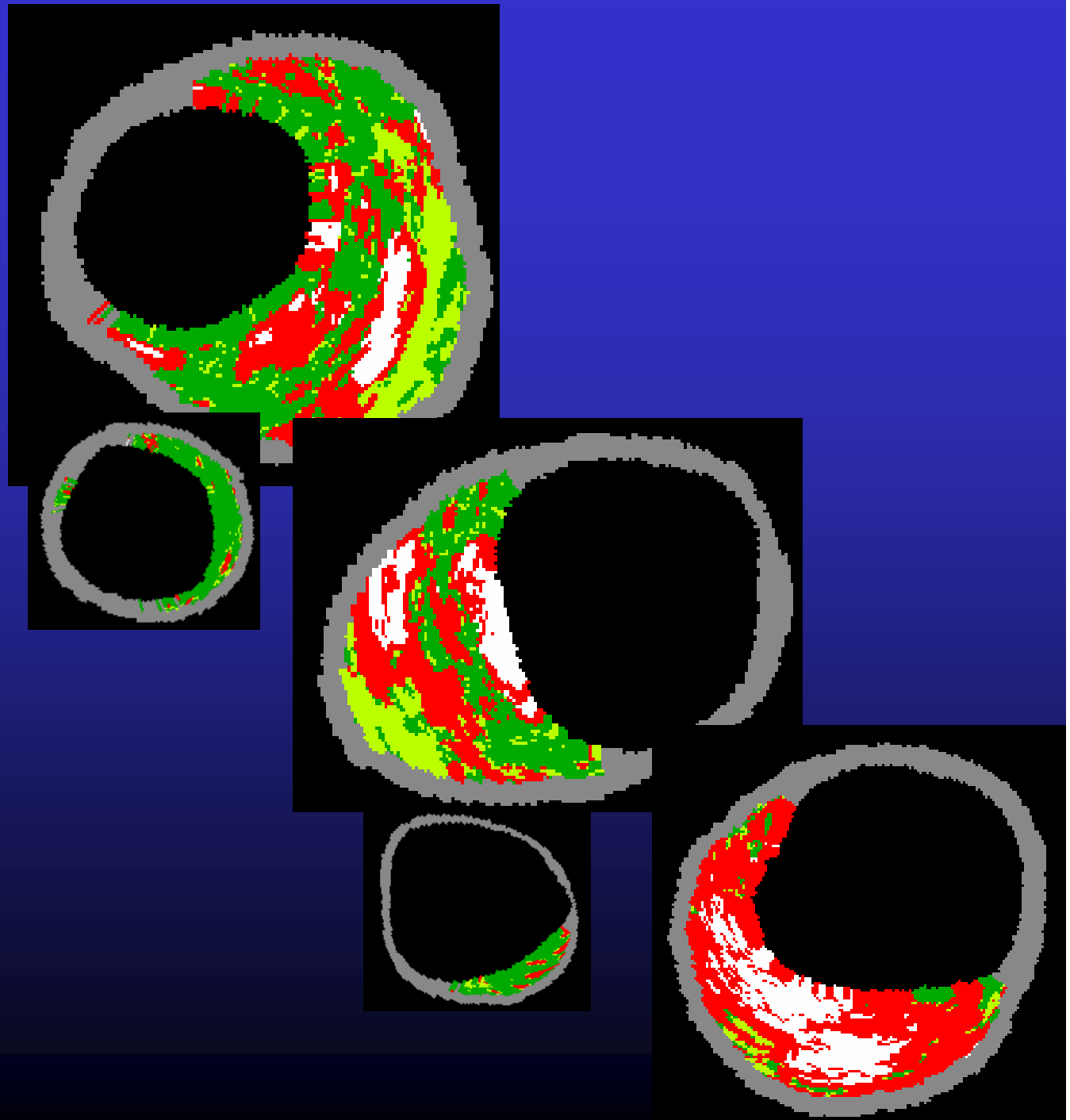
Fibro Atheroma with Fibrous Cap



Multiple Plaque Ruptures and Healed Ruptures



Multiple
Plaque
Ruptures
One patient,
one artery,
different
lesions

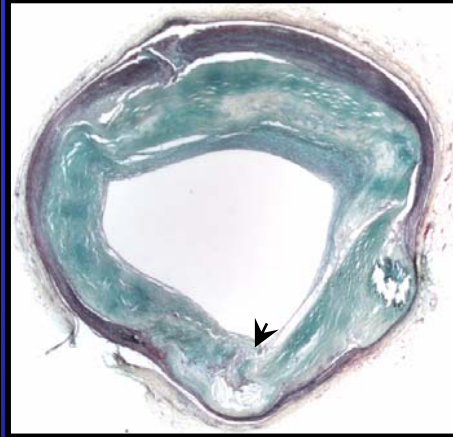


Serial Sections of a Thin-Cap Fibroatheroma

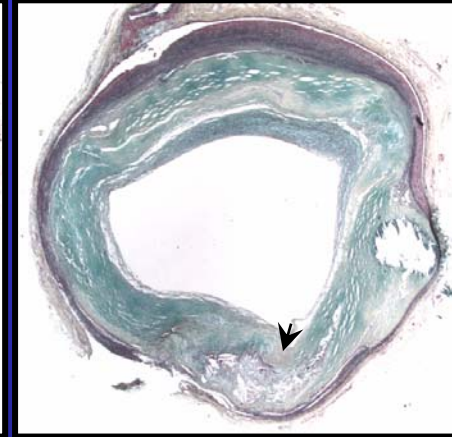
A



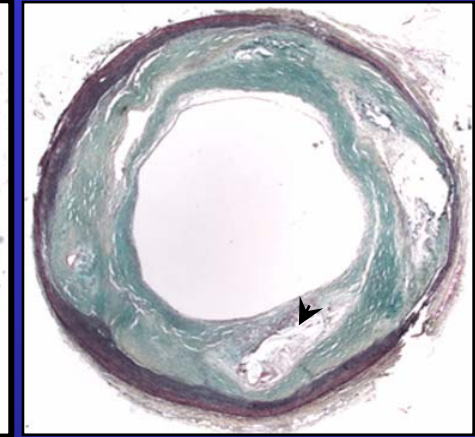
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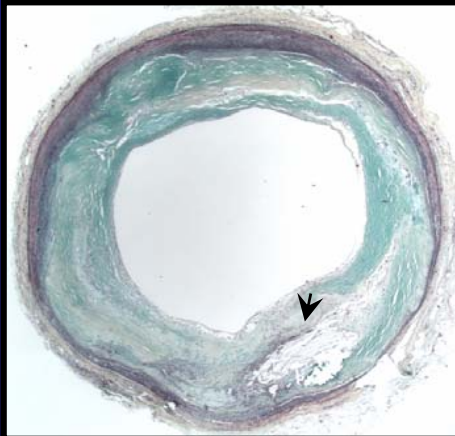
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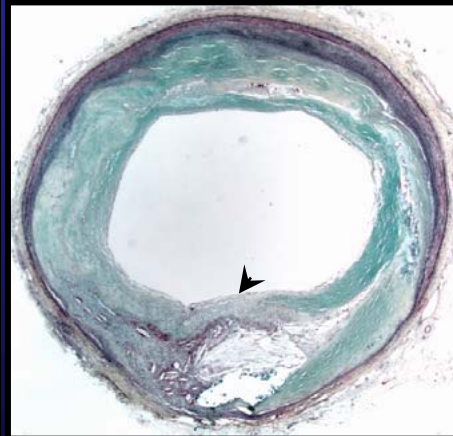
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E



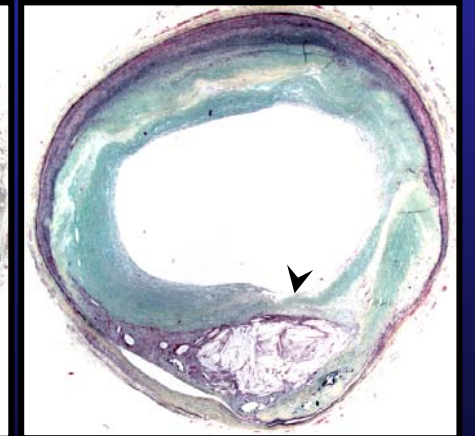
F



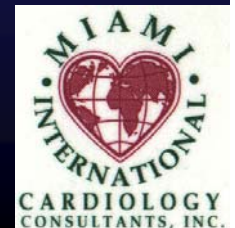
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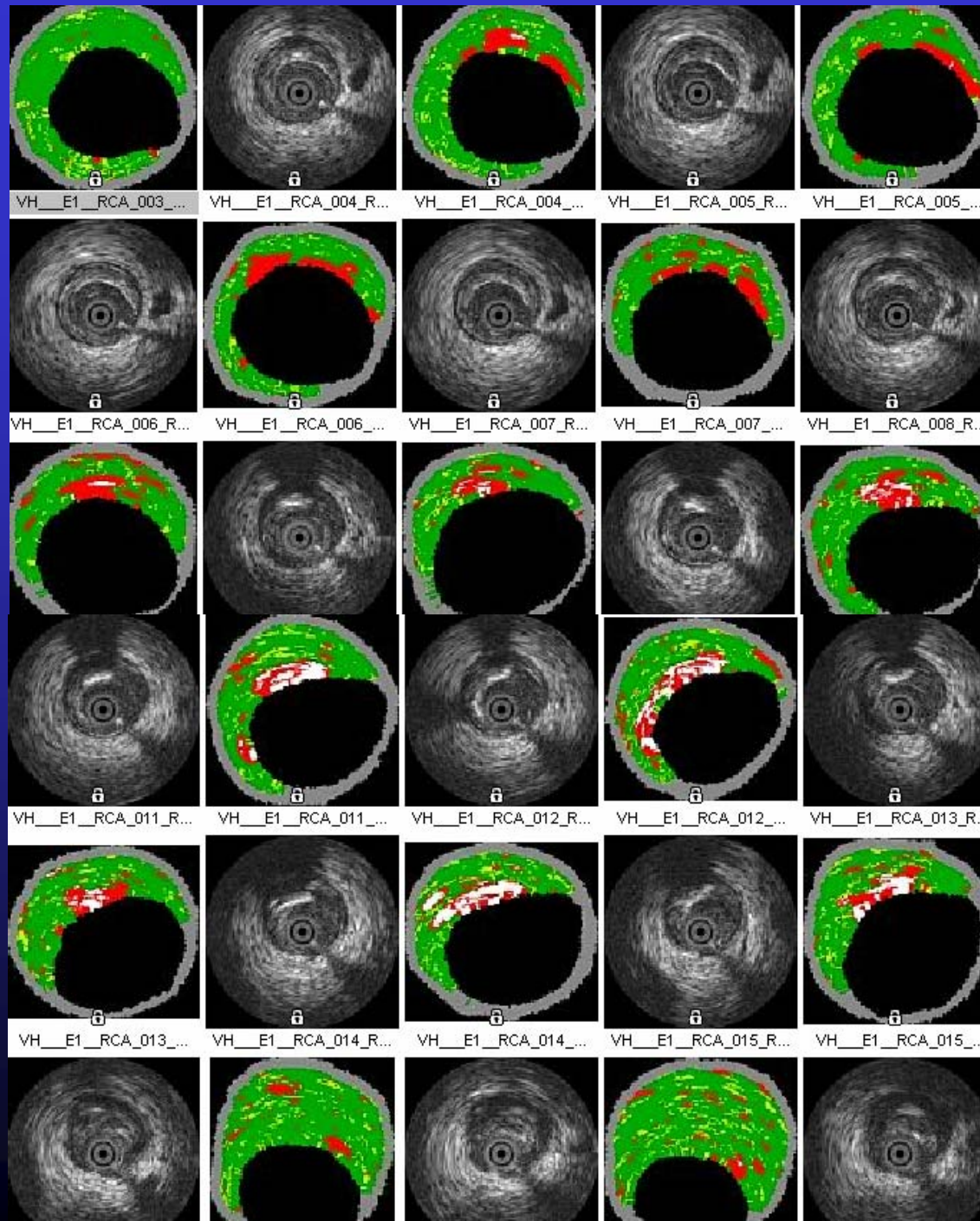
H



Dr R Virmani



Serial images
of plaque
composition
and character
with Volcano
IVUS



VH™ IVUS

Plaque Progression and Regression

- Current and future studies are designed to provide information of the role of VH™ IVUS with regards to the four conundrums of plaque progression:
 - Correlation of clinical indices (risk factors, biomarkers, clinical presentation, MSCT and other technologies) with general plaque composition (FT, FF, NC, DC) at index and follow-up
 - Progression and regression of different plaque types (fibrotic, fibro-calcific, pathological intimal thickening, thick cap FA, and TCFA)
 - Role of thrombus in plaque progression in different clinical presentations (grayscale and VH IVUS)
 - Role of Calcium (fine, dense microcalcification, and calcified aggregates) in plaque stabilization

Plaque Progression/Regression

Expert opinions

Can lipo-necrotic tissue turn into fibrosis or fibro-lipidic tissue?	YES
Can fibrosis turn into fibro-lipidic?	YES/no
Can microcalcification disappear?	YES
Can larger calcified plaques disappear?	NO ?
How much can different plaque types regress?	Can regress lipid, but not fibrosis or large Ca lesions
What is effect of risk factors, medication?	Reduction of plasma lipids leads to lipid mobilization (extracellular versus intracellular lipid), intimal thickening remains

If we have the potential to do so much, why is CAD still number one killer in the world and why has systemic medication failed?

Of the following components of the Atherosclerotic plaque which ones can VH IVUS differentiate?

HISTOLOGY

- Proteoglycans
- Fibrous tissue
- Lipid pool/droplets
- Necrotic core
- Calcium
- Thin fibrous cap
- Hemorrhage
- Thrombus
- Macrophages/inflammation

VIRTUAL HISTOLOGY

- Fibrous tissue
- Fibrous tissue
- Fibrofatty
- Necrotic core
- Calcium
- >110 μm
-
-
- non specific, part of NC

The Role of Plaque Calcification in Plaque Stability

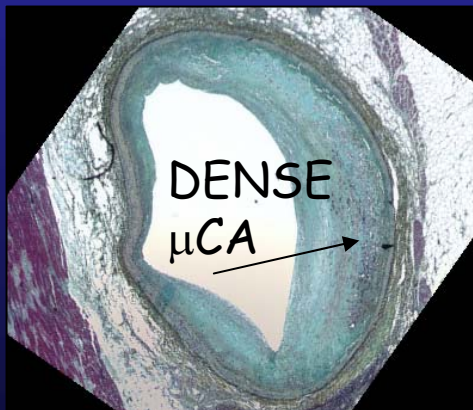
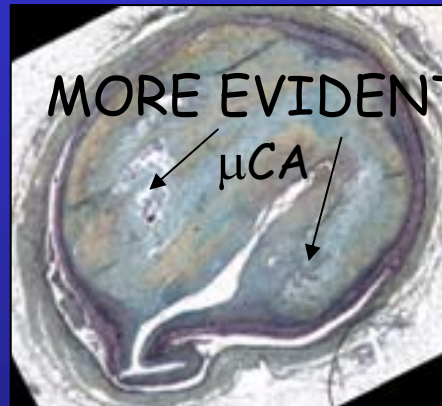
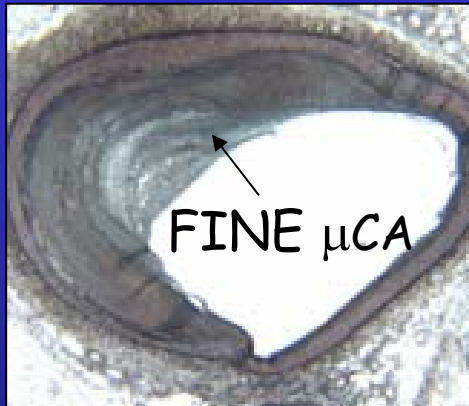
- Coronary calcification correlates highly with plaque burden, but its effect on plaque instability is less obvious.
- Plaque calcification is enhanced significantly due to the presence of inflammation (NC) and intraplaque hemorrhage (plaque rupture, leakage of vasa vasorum)
- Over 50% of TCFA (non-ruptured) show an absence or only speckled calcification. In the remaining segments, Ca is almost equally divided into fragmented or diffuse patterns, suggesting a large variation in the degree of calcification within these lesions.
- In contrast, 65% of acute ruptures show speckled calcification, with the remainder showing a fragmented or diffuse pattern.

The Role of Plaque Calcification in Plaque Stabilization

- Plaque erosions are almost devoid of calcification, or when present it is only speckled.
- Calcified nodules contain massive amounts of calcium relative to plaque area and in some instances even show bone formation.
 - Cause of sudden cardiac death in 5% of the cases.
- The amount of calcification within a coronary artery increases with age; however, women generally show a 10-year lag compared to men with equalization by the 8th decade.

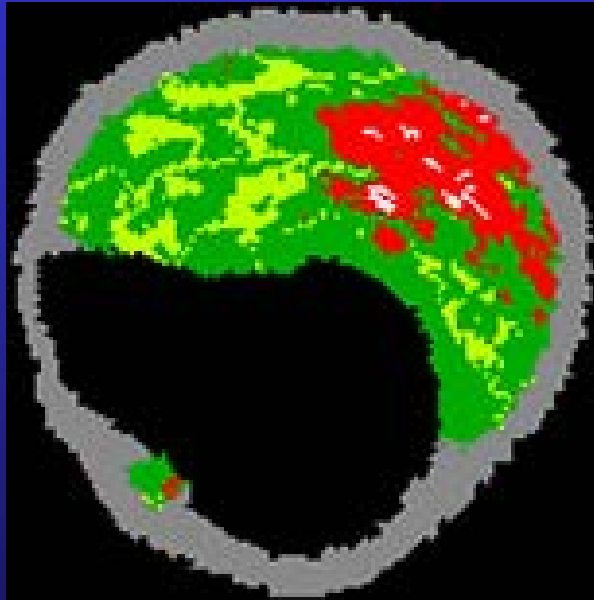
Different Stages of Tissue Calcification

Microcalcification – Red on VH

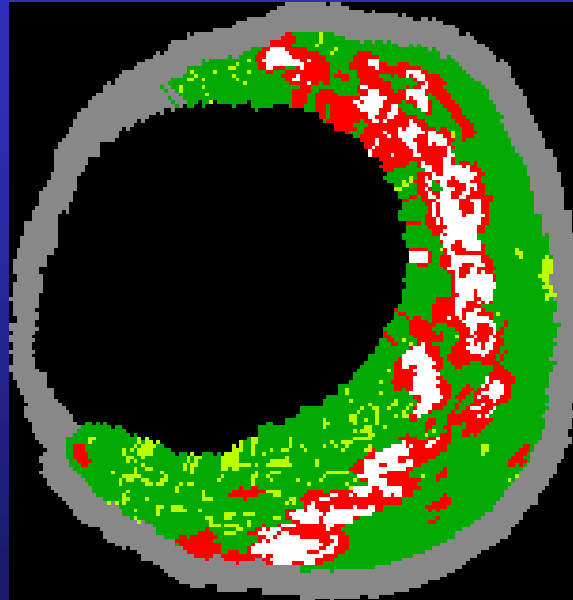


Dense Calcium – White on VH

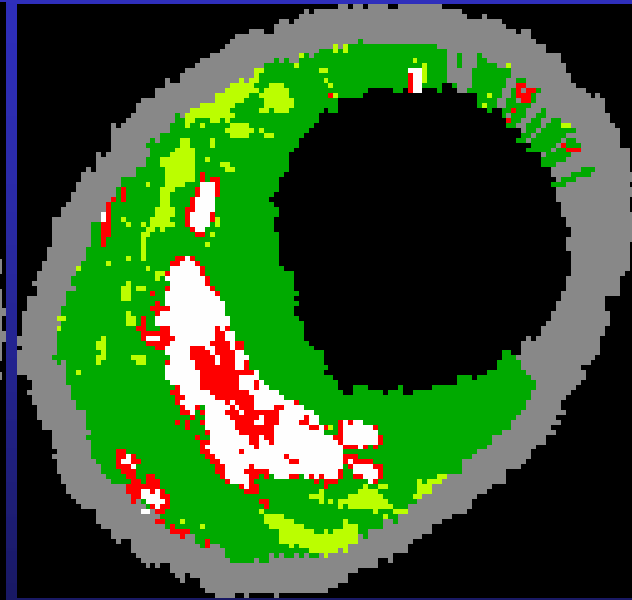
Plaque Calcification with VH IVUS



Fine microcalcification



Dense microcalcification



Aggregate of Ca

Progression Factoids

- Symptomatic CAD takes on average 65 years to develop.
- 18.6% progression of CAD in non-bypassed segment in 5 years (CASS 1980s).
- Of patients waiting for PTCA (Kaski 1995):
 - 24% had angiographic progression of CAD in eight months.
 - 57% had an acute coronary event.
 - 28% of lesions intended for angioplasty progressed.
 - 9% of non-culprit lesions progressed.

Progression Factoids

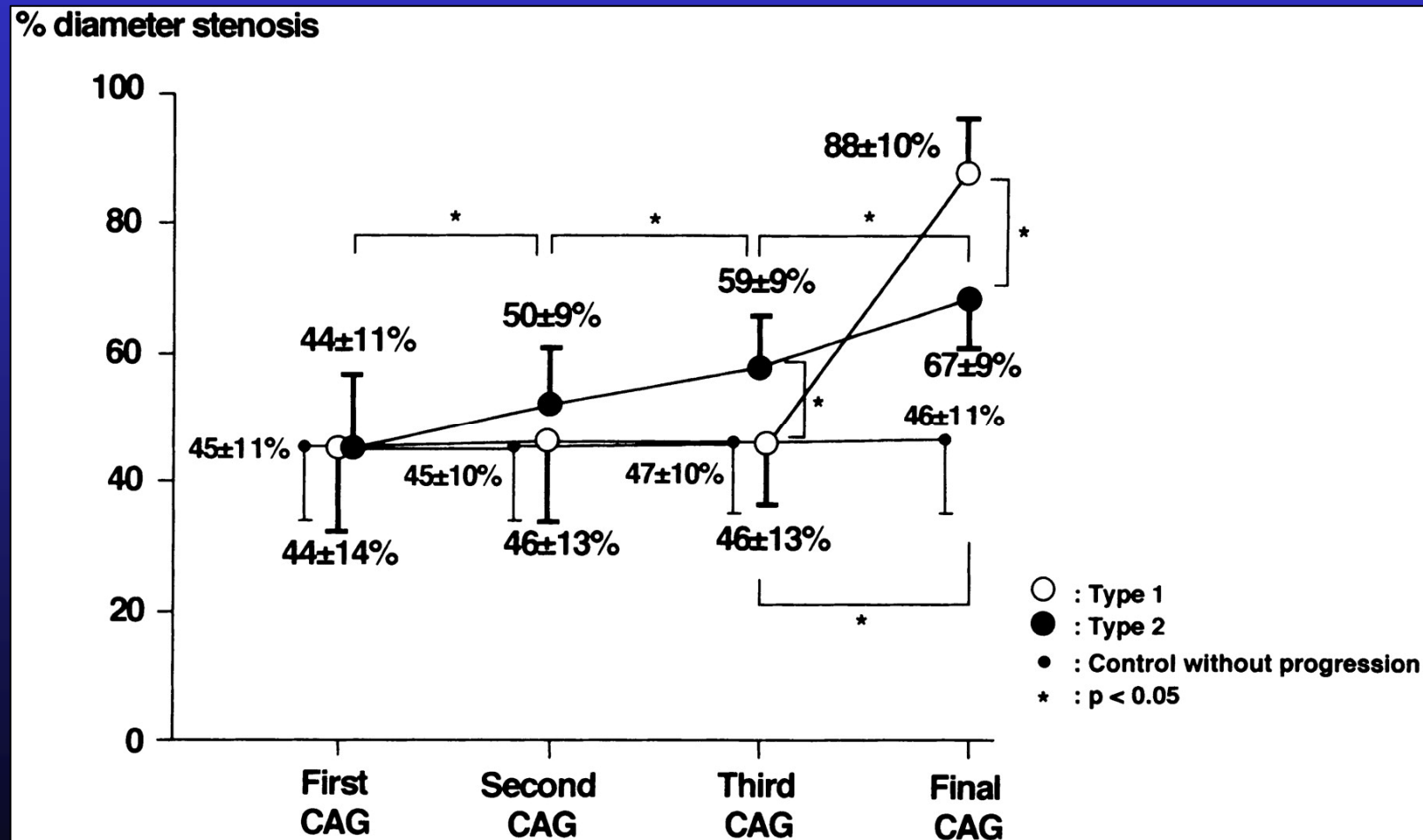
- After PCI, 20% of patients with multiple complex lesions will have an ACS the following year and 6% will die (Goldstein NEJM 2000).
- In a well medicated patient population (e.g. statins 66.3%) incidence of PCI for previously asymptomatic lesion is 5.8-10.8%. (Glaser, et al Circ. 2005)
 - 87% of these lesions are intermediate by angio at index.
 - Mean time for 2nd PCI was 163 ± 99 days.
 - in the non-PCI arm 25% increase in the use of long-acting nitrates.
 - After unstable AP, if 3-VD and prior PTCA, the risk for another event increases by 20% with each risk factor.

Progression Factoids

- Ruptured plaques are associated with positive remodeling.
- ~50% of sudden coronary deaths attributed to plaque rupture occur in lesions with <50% diameter stenosis.
- 75% of plaques which cause a sudden coronary death, have ruptured previously 2-5 times at the same site.
 - Repeated ruptures, which may or may not be silent, are likely responsible for more plaque progression.
- Necrotic core expansion may occur from intraplaque hemorrhage:
 - due to plaque rupture or leaking vasa vasorum.
 - through accumulation of free cholesterol derived from erythrocyte membranes and recruitment of macrophages.

Progression of Coronary Artery Lesions

- n=486 patients with 4 serial angiograms within a year
- One non-intervened major coronary artery was chosen for the follow up
- 7 % (36 arteries), progressed significantly, 13/36 had ACS



Yokoyama, Suzuki et al Circulation 1999



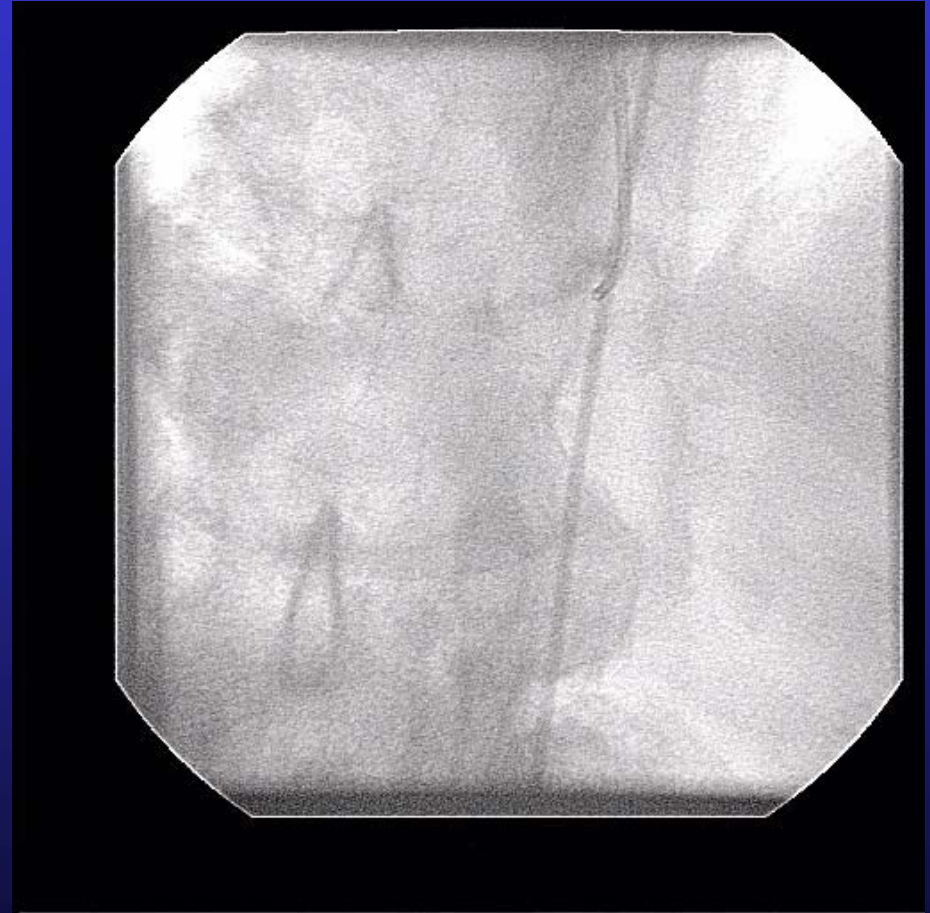
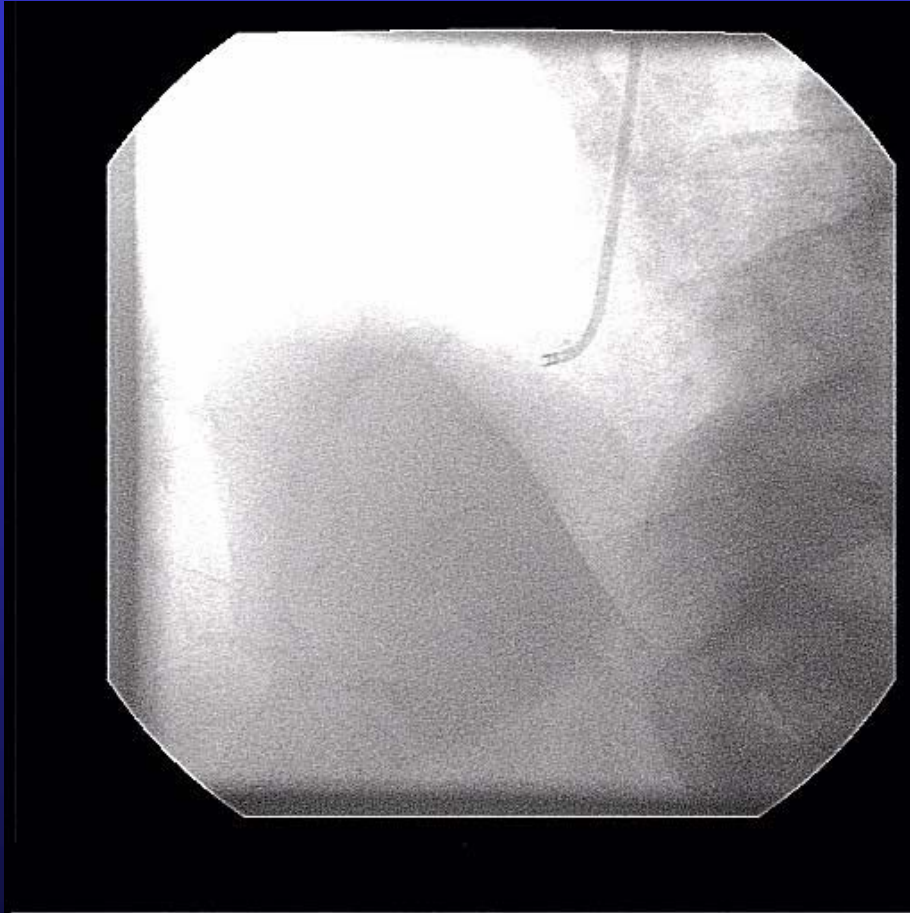
Role of Thrombus in Plaque Progression

- Intramural thrombus serves as a nidus for development of the next thin cap atheroma.
- After a plaque rupture thrombus with its long tail attaches to the vessel wall, organizes within 14 days, and becomes part of the plaque (fast plaque progression).
- Thrombus may not be visible on angio due to compensatory positive remodeling.
- R. Virmani: *lesions with hemorrhage and inflammation, characterized by large necrotic cores, macrophage infiltration and calcification are more likely to exhibit vessel expansion than plaques without these features. In addition, vessel enlargement is also dependent on the plaque morphology related to the underlying luminal thrombus such that plaque rupture is associated with severe IEL expansion.*
- Organized thrombus can increase the risk of the progression/formation of other TCFA.

Case # 3 (SG)

- 65 years old male
- Clinical presentation: MI 6 days earlier
- Risk factors: smoker, alcohol abuse
- Angiogram: hazy, about 90 % lesion in the proximal RCA
- EF: 25 %

Baseline Angio



Baseline IVUS

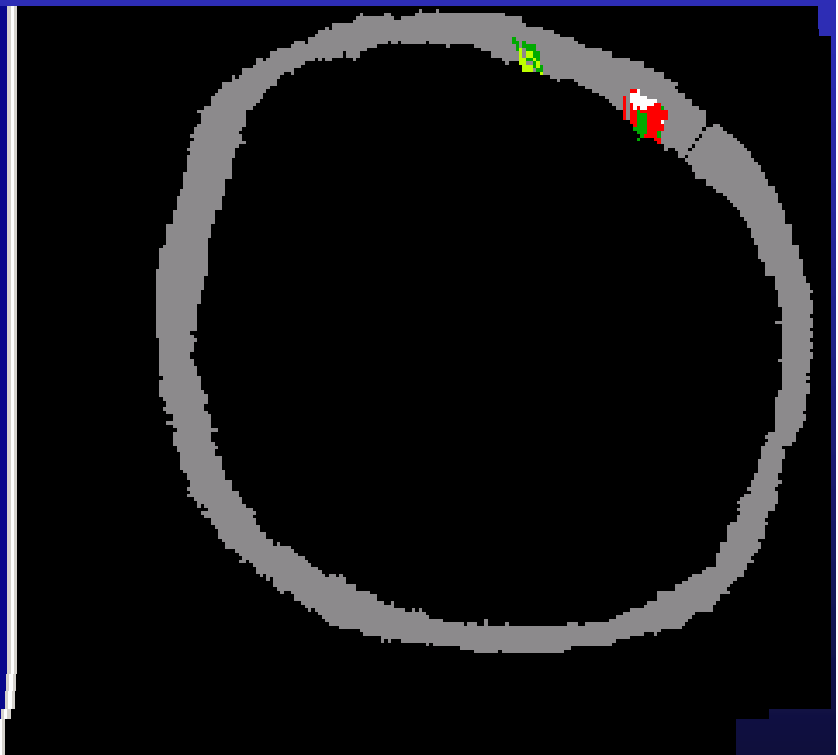
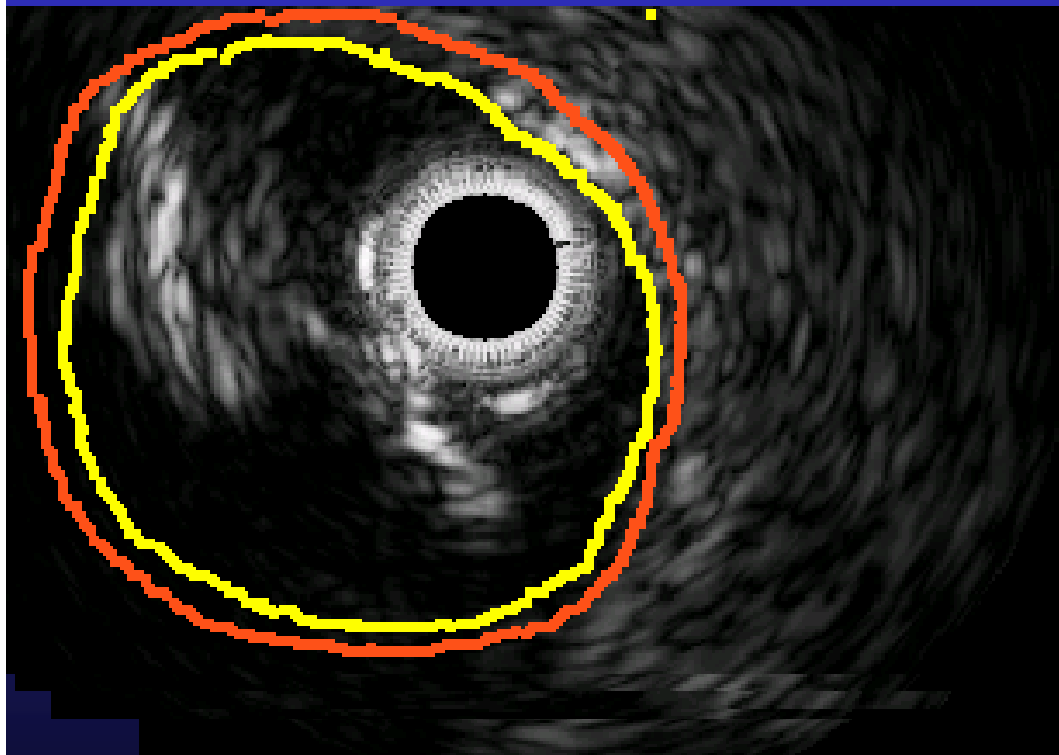
02/08/2005

12:13:15 0003



10 MM

Partly organized 6 Day old Thrombus by grayscale IVUS

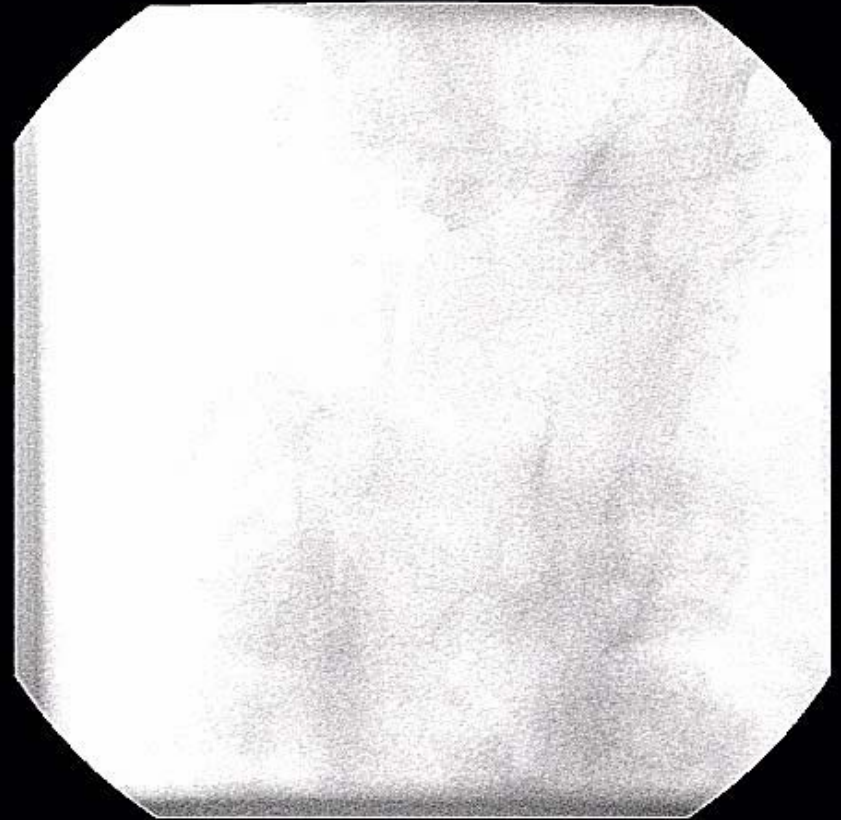
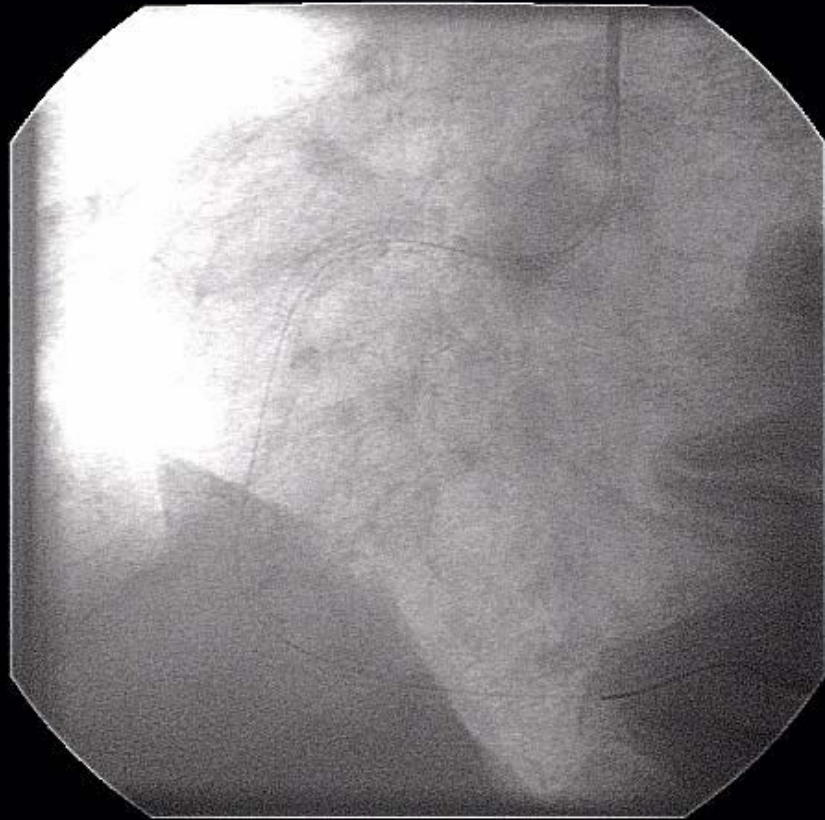


Case # 3 (SG)

Procedural notes

- IVUS VH
- Cutting balloon
- Distal Driver stent
- IVUS VH
- Cutting Balloon
- Mid Driver stent
- IVUS VH
- Proximal Driver stent
- Final IVUS VH

Final Angio



Final Grayscale IVUS

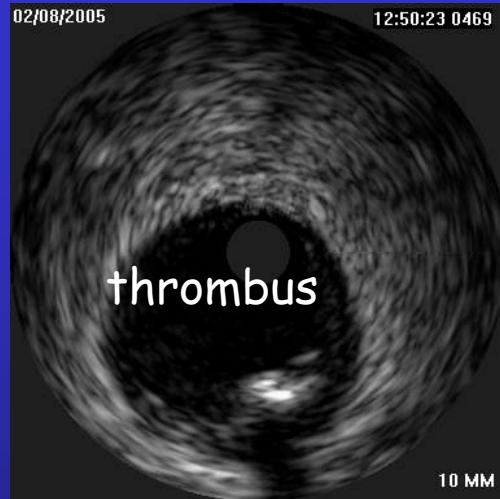
Distal and Mid



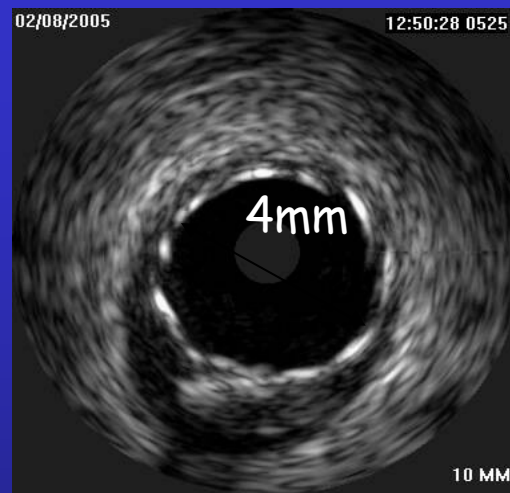
Proximal



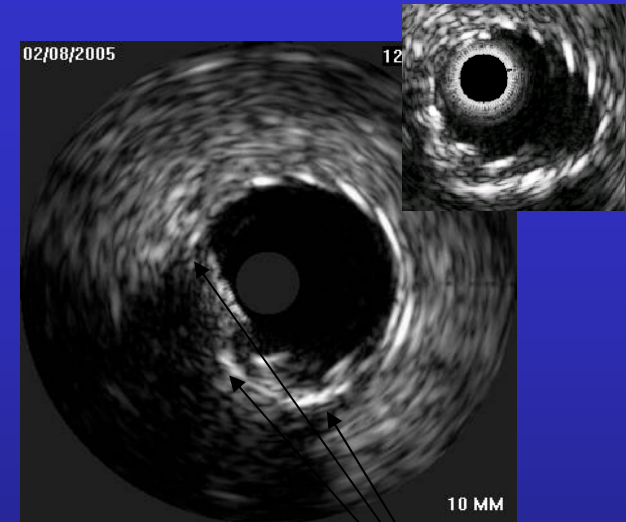
Final IVUS Grayscale pullback Single Frames



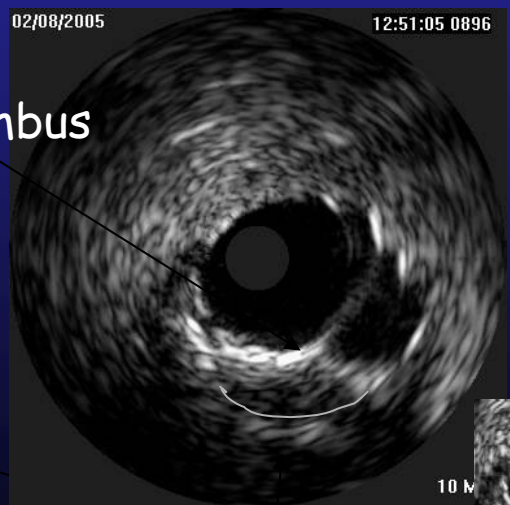
Distal to 3rd stent



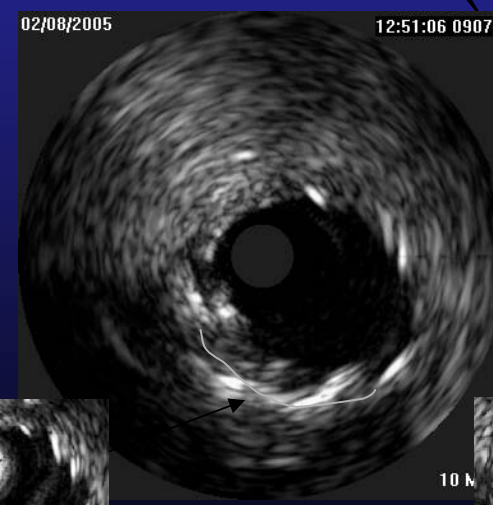
In 3rd stent



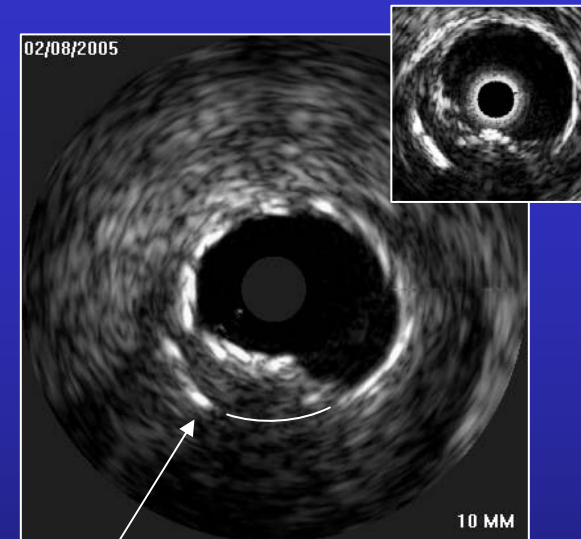
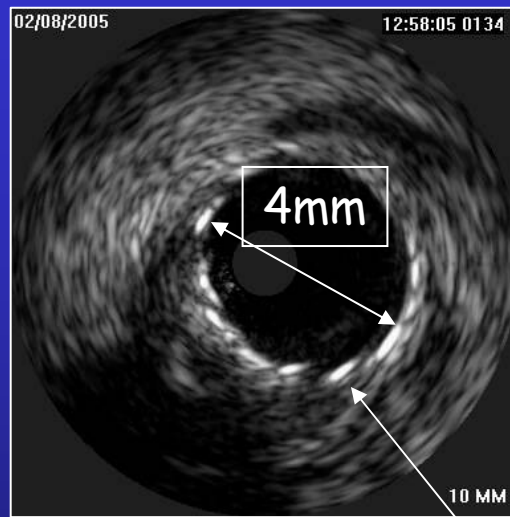
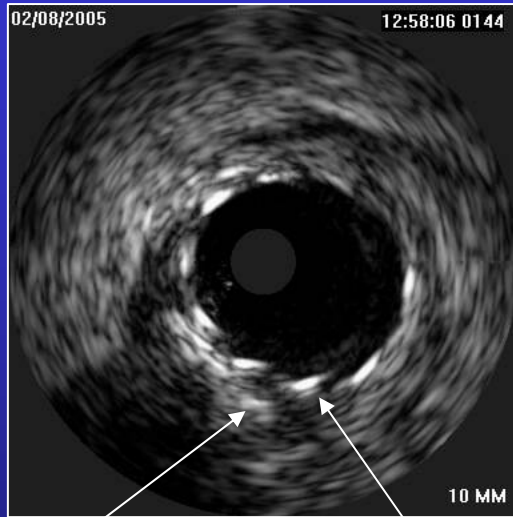
Stent struts



Stent



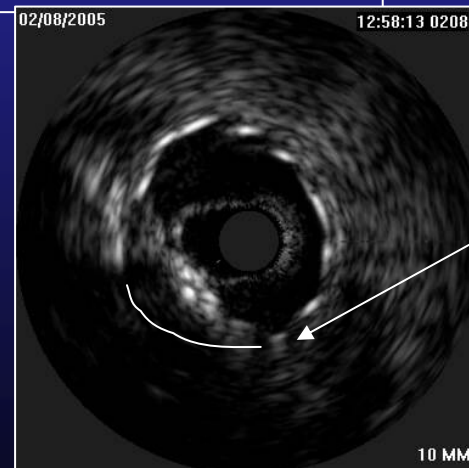
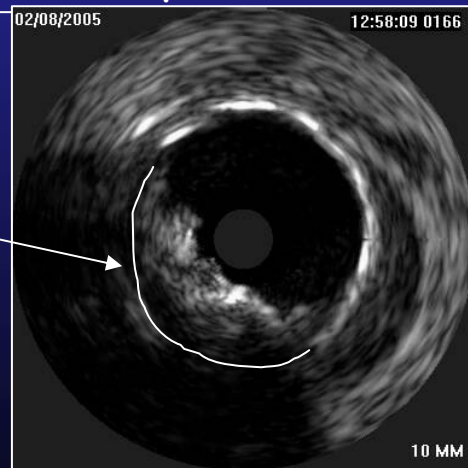
IVUS Grayscale pullback Single Frames



3rd and 2nd stent overlap

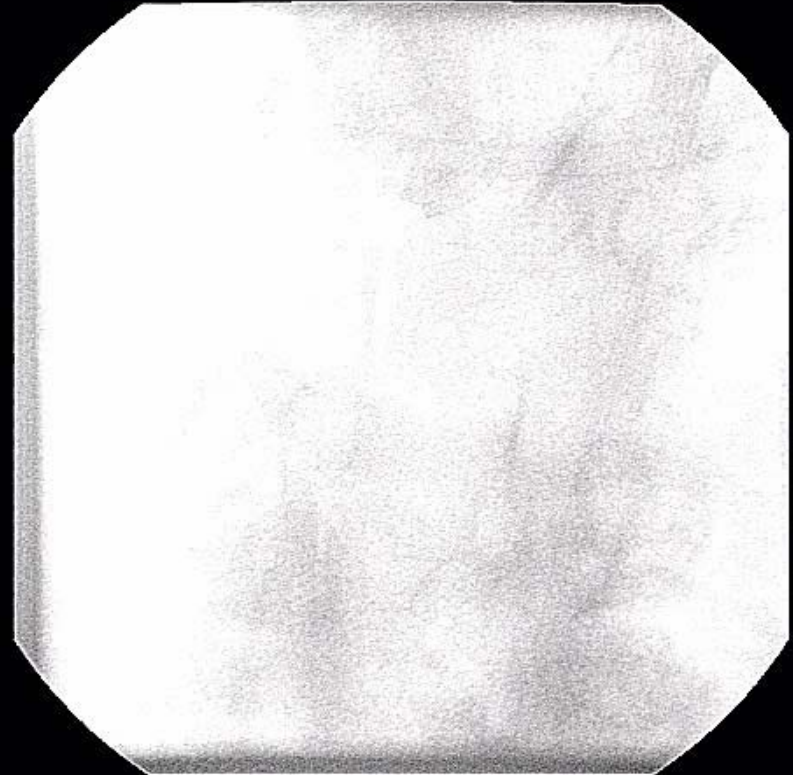
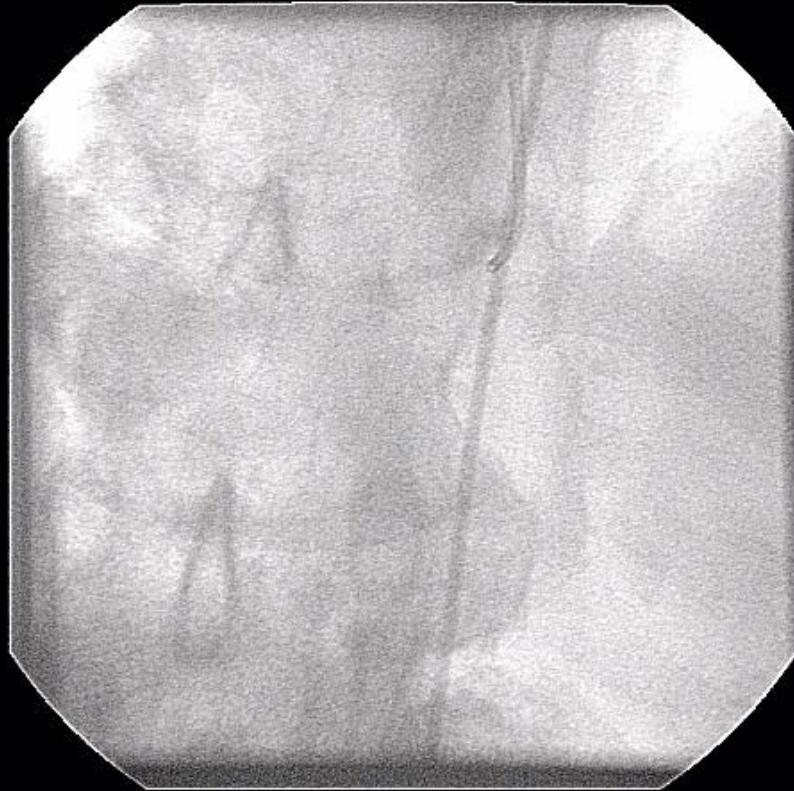
2nd stent

Mid 3rd stent



Proximal 3rd stent

Reduced Myocardial Blush?



Time to Re-focus

- With the advent of DES the risk for non-target lesion intervention has become the same or even higher than the risk for repeat revascularization of the target lesion.
- VH™ IVUS has the potential to assess the:
 - natural history of CAD,
 - role of thrombus on plaque progression,
 - impact of plaque calcification on plaque progression and stabilization,
 - effect of systemic medication on general plaque composition and different plaque types including high risk, vulnerable plaques,
 - effect of regional therapy on high risk lesions,
 - value of VH IVUS itself on the outcome of culprit lesion intervention.