Imaging Overview for Vulnerable Plaque: Data from IVUS Trial and An Introduction to VH-IVUS Imgaging

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- **Today, in reality, almost everything that we currently know about vulnerable plaque has come either from histopathology or from in vivo detection of plaque rupture or study of patients who present with acute coronary syndromes - NOT from prospective correlative studies or prospective identification of vulnerable plaques before they rupture, rapidly progress, or thrombose.**
- **To my knowledge, there are only three, retrospective IVUS studies relating lesion findings to late events – and no trial data**

Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by IVUS before an acute coronary syndrome

- **114 coronary sites from 106 patients**
- **16 pts had an acute event 1-24 months (21.8±6.4months) post index IVUS**
- **12 pts had the event 4.0±3.4 months (range 1 to 8 months) at the same sites where preexisting atherosclerotic disease had been demonstrated by IVUS**

	Sites related to acute events	Sites not related to acute events	p
Plaque burden	67±9%	57±12%	<0.05
Shallow echolucent zones	8/12	4/90	<0.05

(Yamagishi et al. J Am Coll Cardiol 2000;35:106-11)

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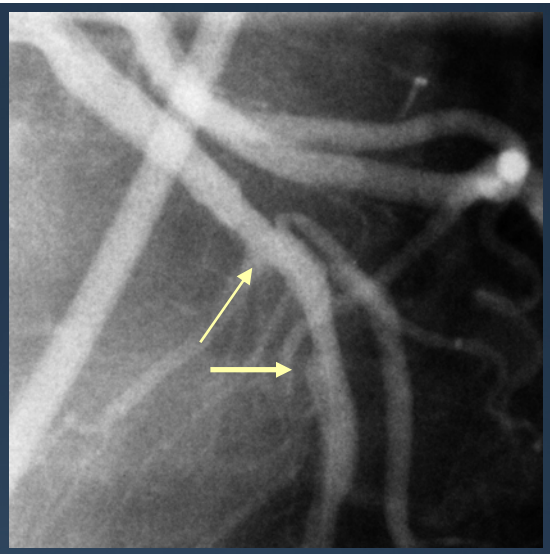
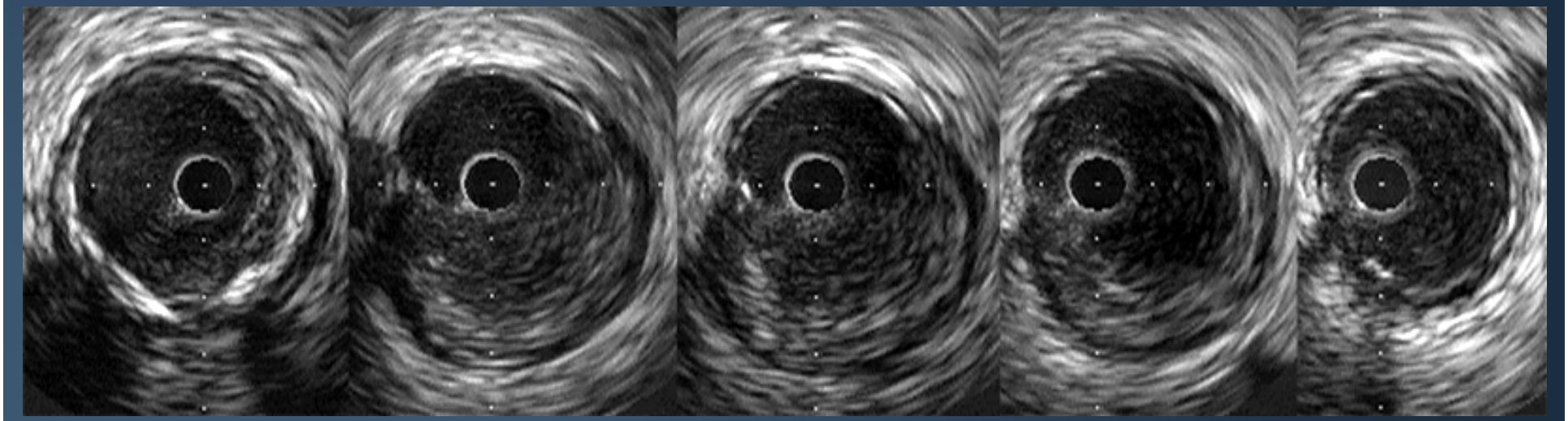


Proximal 0 → 3mm → 12mm



EEM CSA = 21.0mm^2
Lumen CSA = 9.5mm^2
P+M CSA = 11.5mm^2

EEM CSA = 23.5mm^2
Lumen CSA = 5.5mm^2
P+M CSA = 18.0mm^2

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

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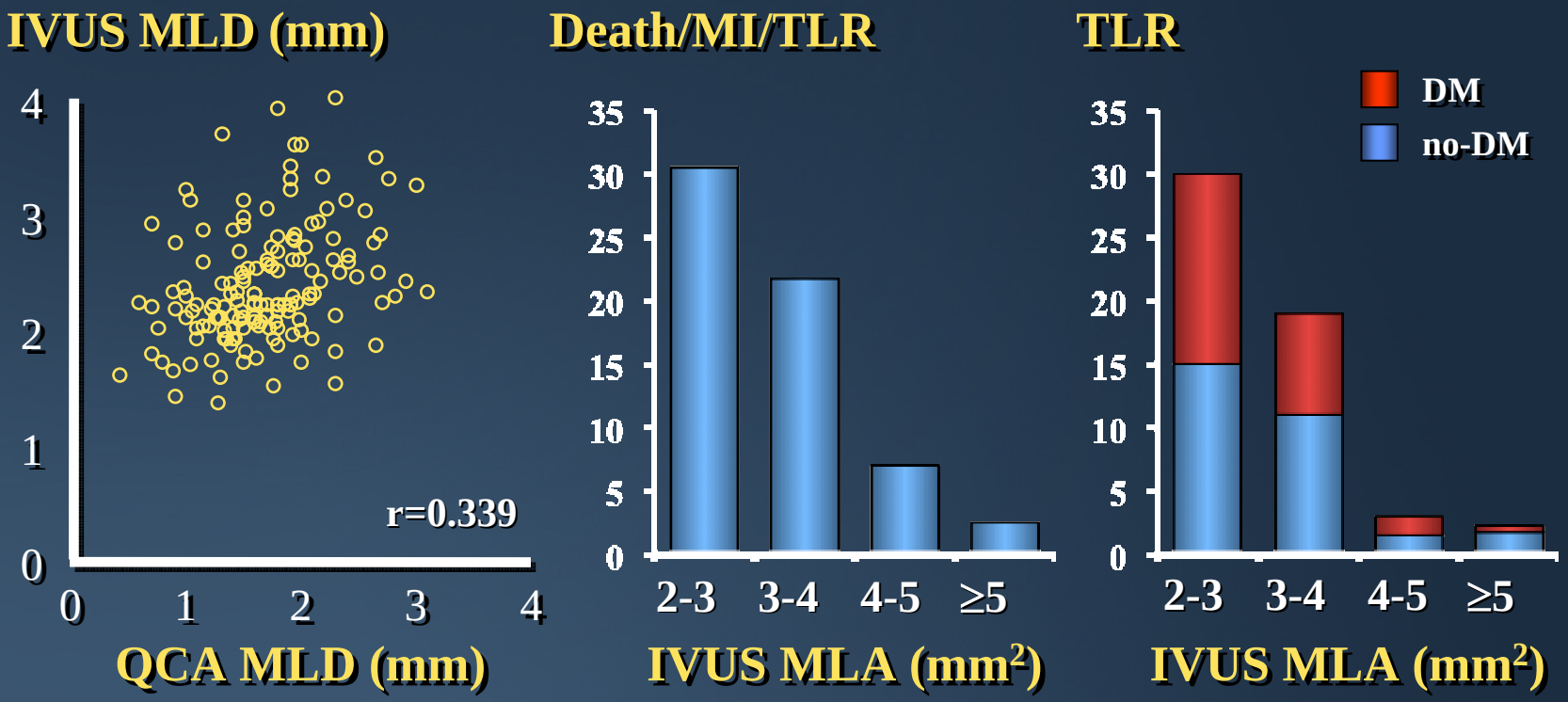
Clinical Follow up in 357 Intermediate Lesions in 300 Pts Deferred Intervention After IVUS Imaging



- Death/MI/TLR @ (mean) 13 mos = 8% overall (2% death/MI and 6% TLR)
- Death/MI/TLR @ (mean) 13 mos = 4.4% in lesions with MLA >4.0mm^2
- Only independent predictor of death/MI/TLR was IVUS MLA (p=0.0041)
- Independent predictors of TLR were DM (p=0.0493) and IVUS MLA (p=0.0042)
- ***Although the number of patients with death/MI was small (n=6), the only independent predictor was IVUS MLD (p=0.0498)***

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(Abizaid, et al. Circulation 1999;100:256-61)

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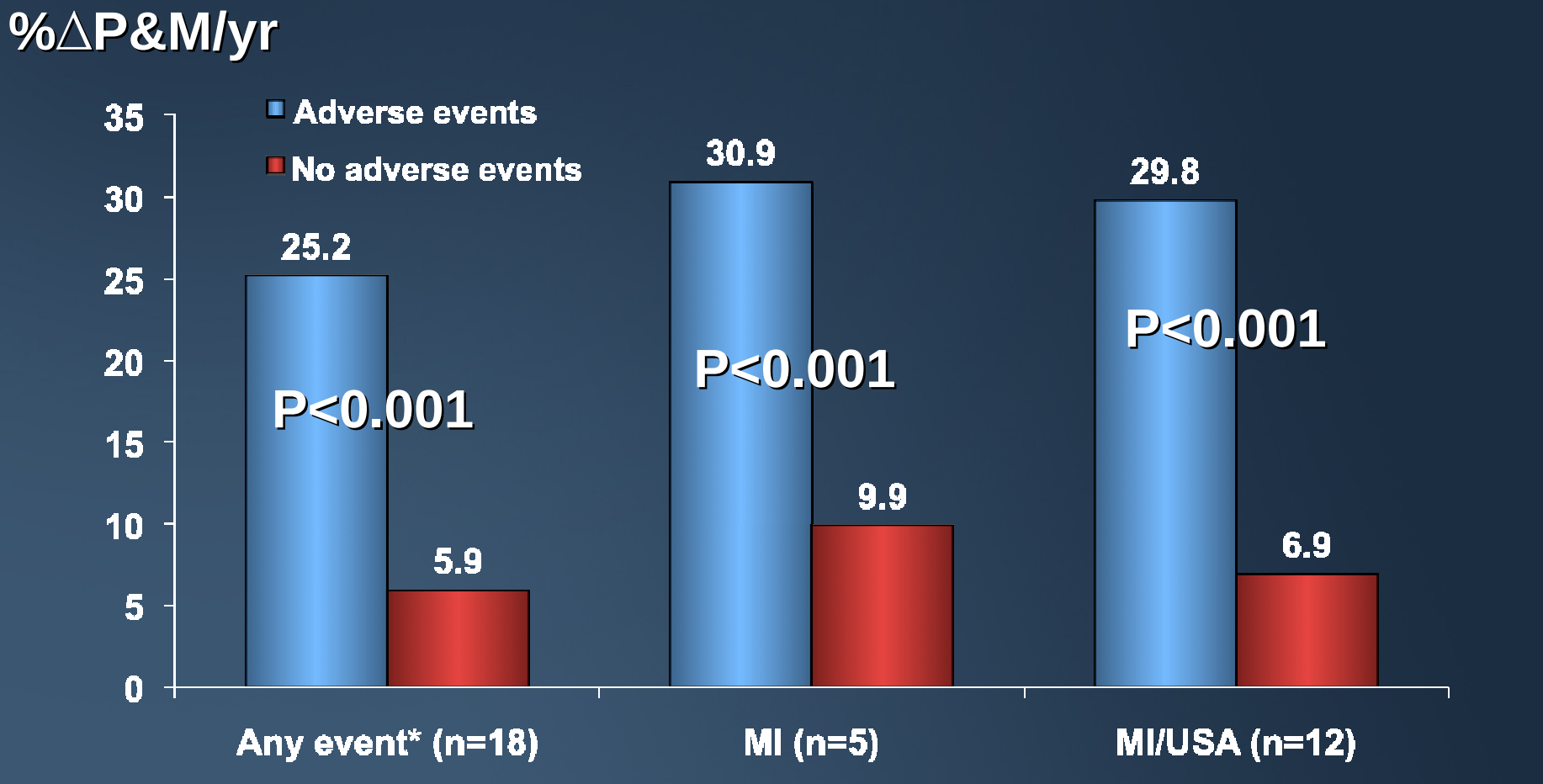
Relationship Between LM Plaque Progression and Non-LM Events



*Death, MI, USA, or PCI or another lesion

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von Birgelen et al. Circulation 2004; 110:1579-85

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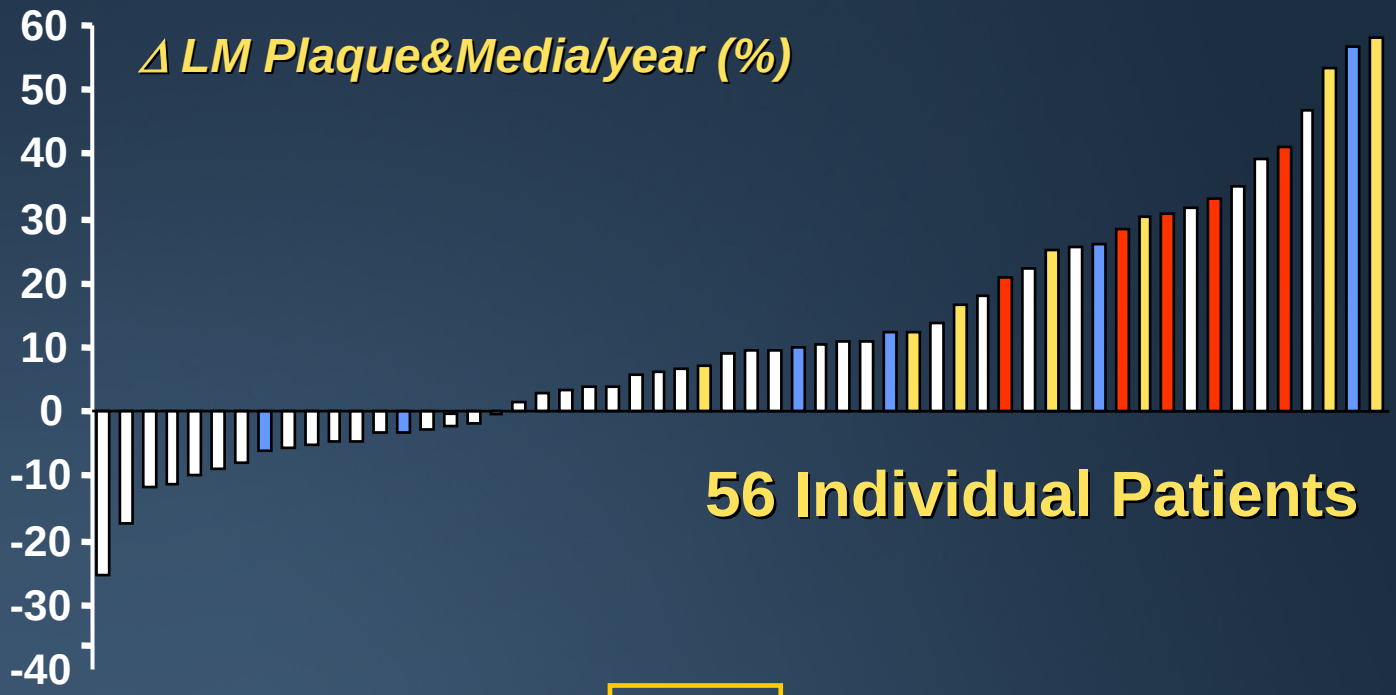
LM Plaque Progression As a Predictor of Non-LM Cardiovascular Events



p<0.001 (vs. no events)

Myocardial infarction (n=5)

Unstable angina (n=7)

PCI of new de-novo lesion (n=6)

No events (n=38)

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von Birgelen et al. Circulation 2004;110:1579-85

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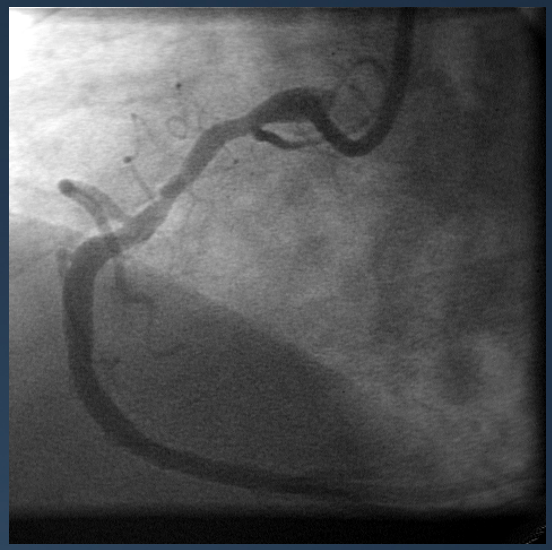
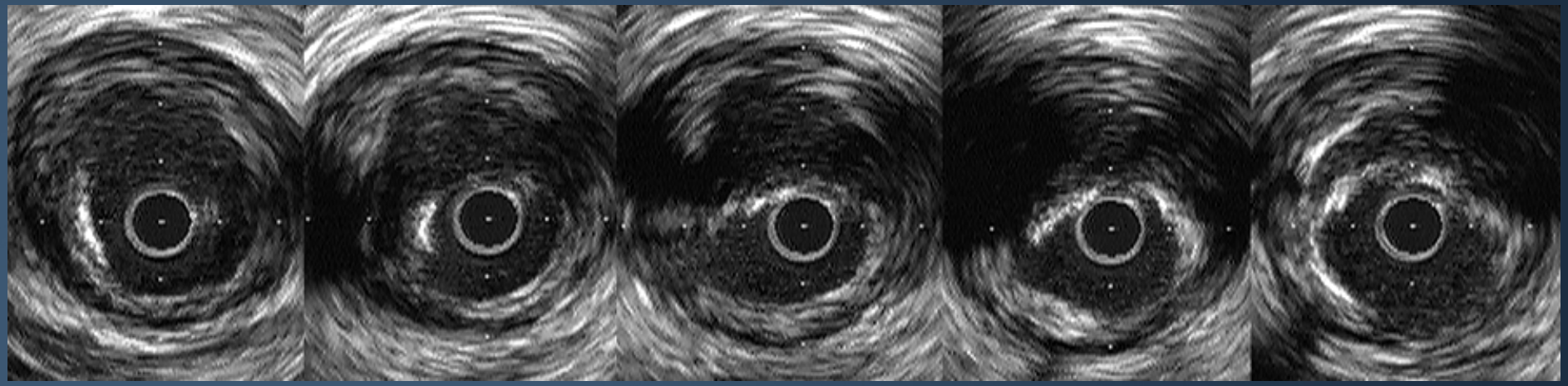


0 → 1mm → 4mm



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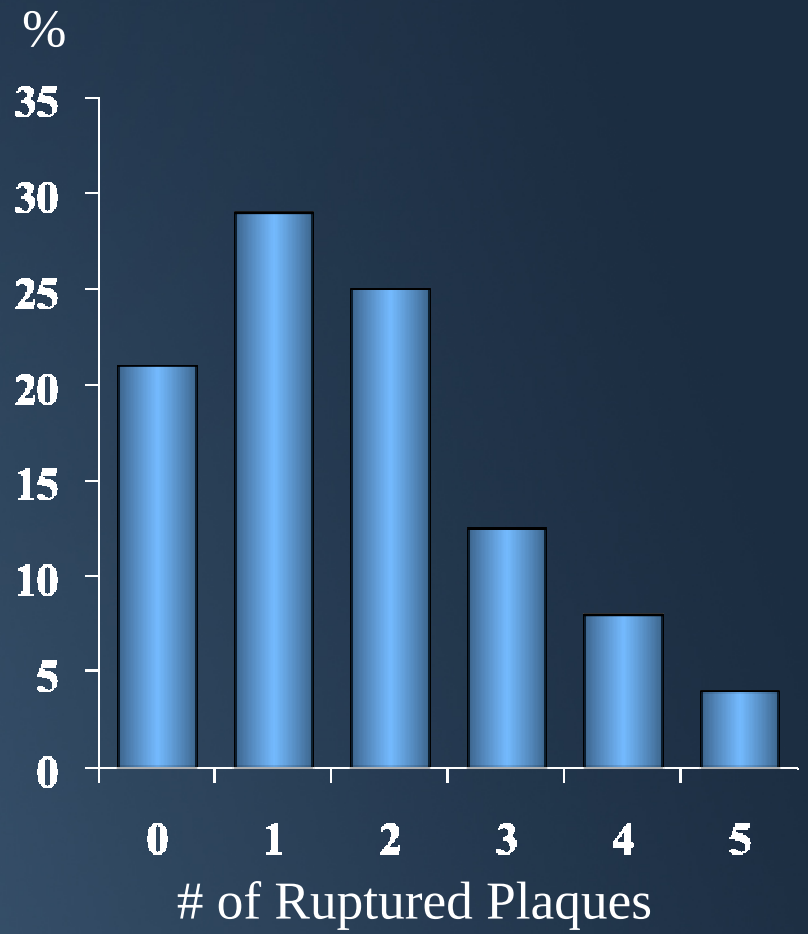
Three Vessel IVUS Imaging in 24 Pts with ACS and Positive Tn

- 50 ruptured plaques
  - 9 culprit lesion
  - 41 nonculprit lesion
- 19 pts had at least 1 nonculprit plaque rupture (79%)
  - 17 pts had 1 plaque rupture in a second artery
  - 3 pts had plaque ruptures in all 3 arteries



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Rioufol et al Circulation 2002;106:804-808

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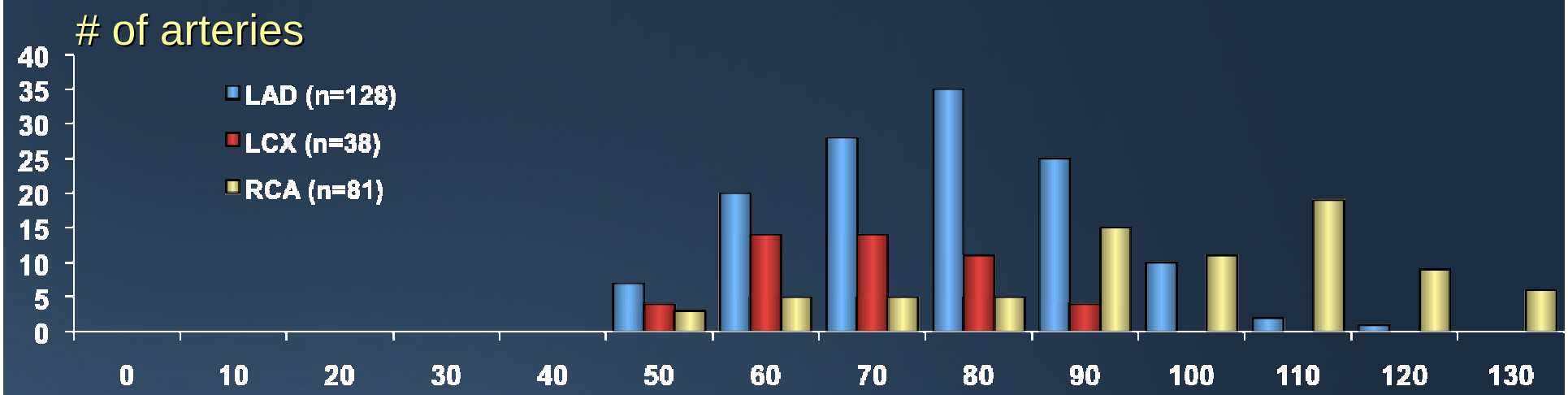
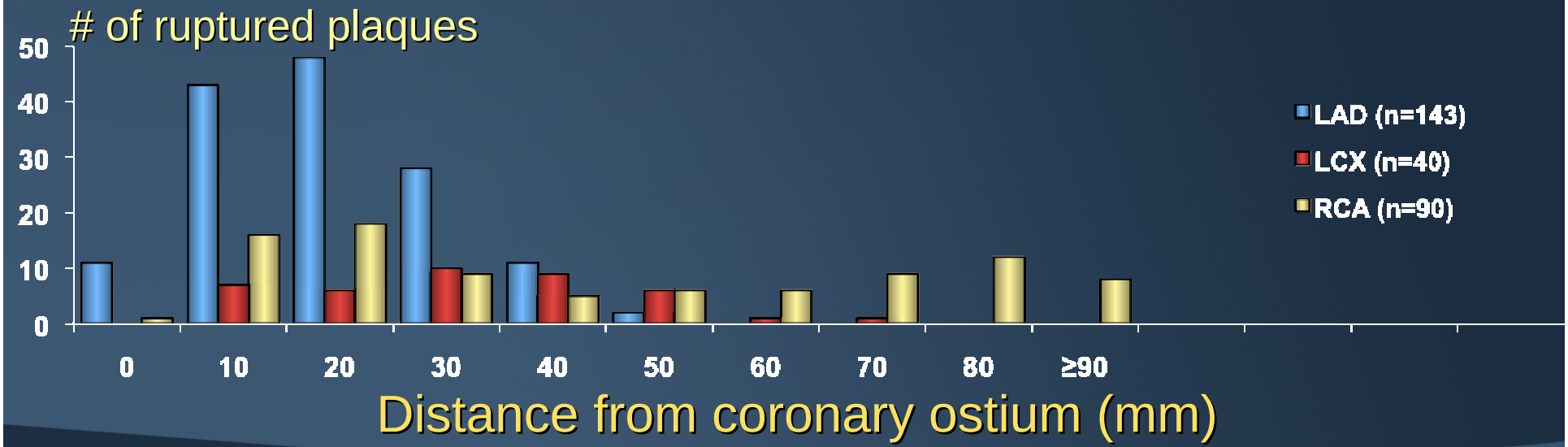
Location of 273 ruptured plaques in 158 patients with ACS and 48 patients with stable angina and three vessel IVUS





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(Hong et al J Am Coll Card 2005;46:261-5)

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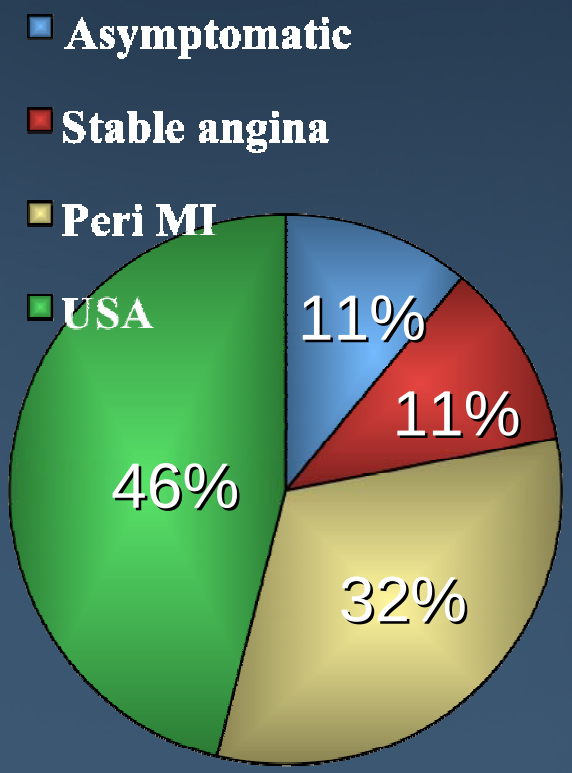
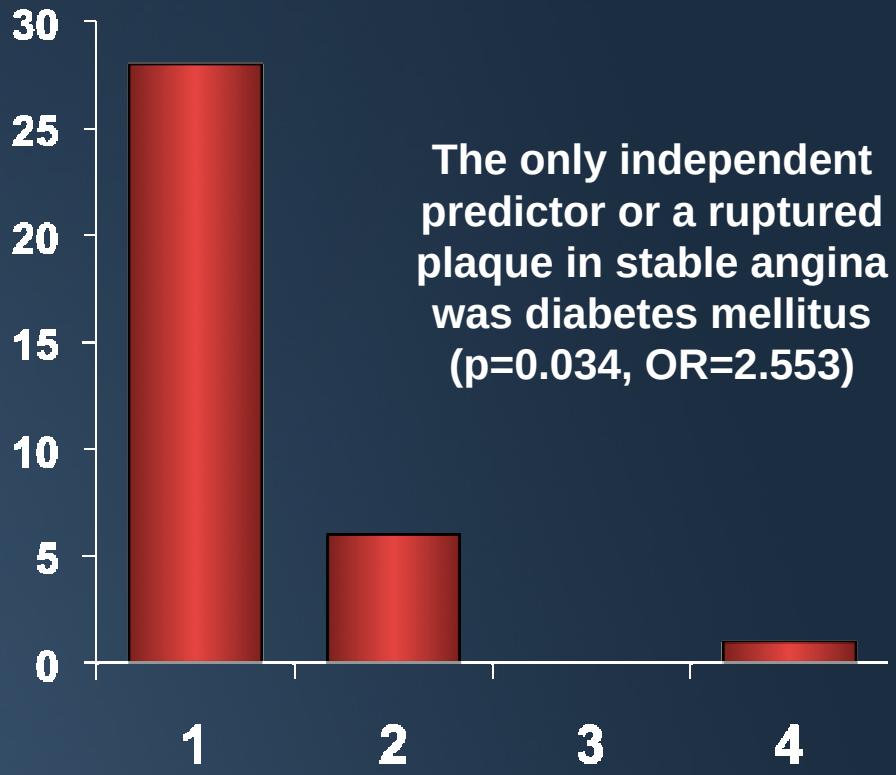
Symptoms in 254 patients with 300 plaque ruptures in 257 arteries



*(Maehara et al
J Am Coll Cardiol 2002;40:904-10)*

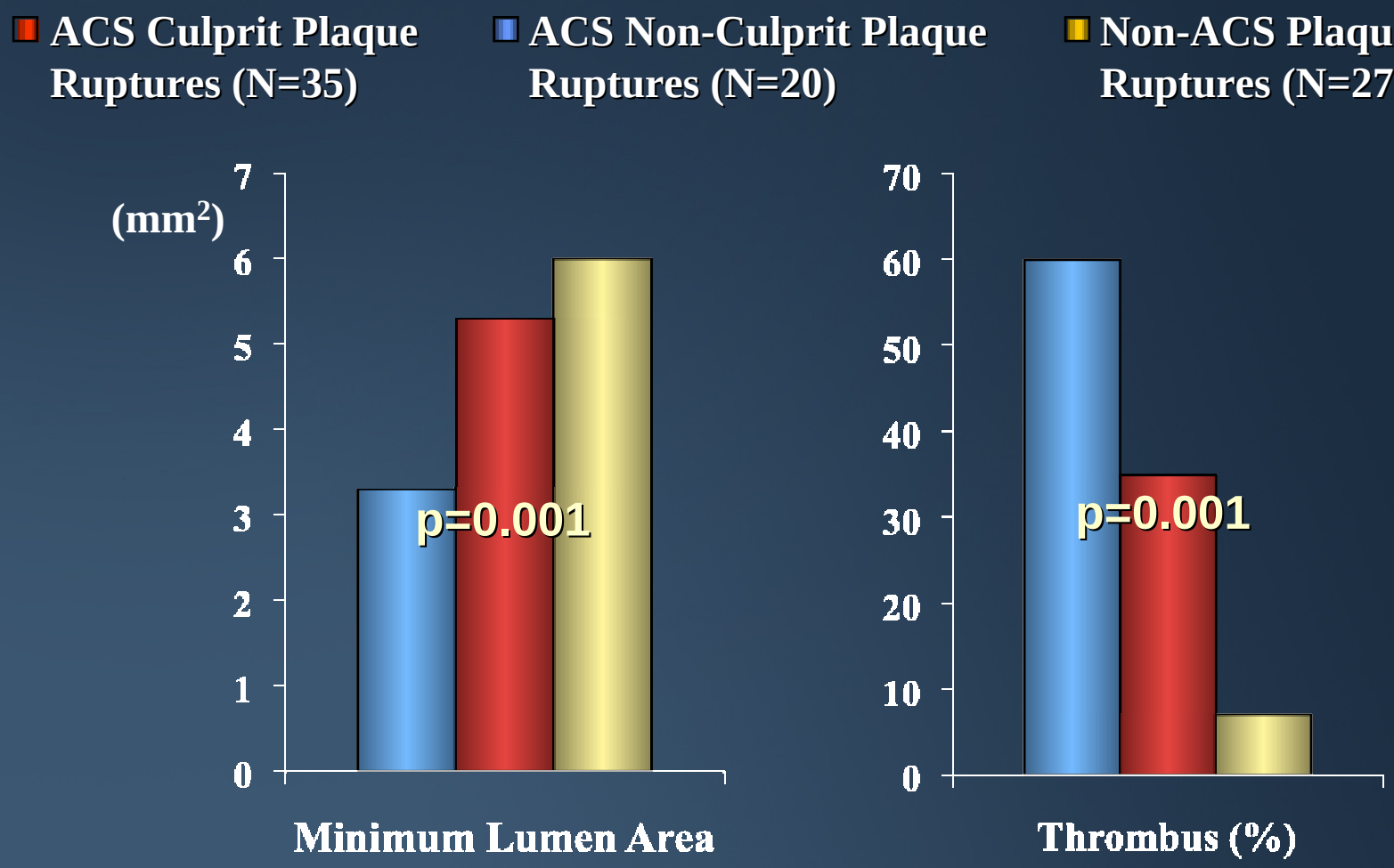
of ruptured plaques per patient with stable angina (n=113)



The only independent predictor or a ruptured plaque in stable angina was diabetes mellitus (p=0.034, OR=2.553)

*(Hong et al
Circulation 2004;110:928-33)*

Comparison of Culprit & Non-Culprit Rupture Sites in ACS Patients and Rupture Sites in Non-ACS Patients



Independent predictors of ACS were MLA and thrombus (both p=0.01)

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Fuji et al. Circulation 2003;108:2473-8

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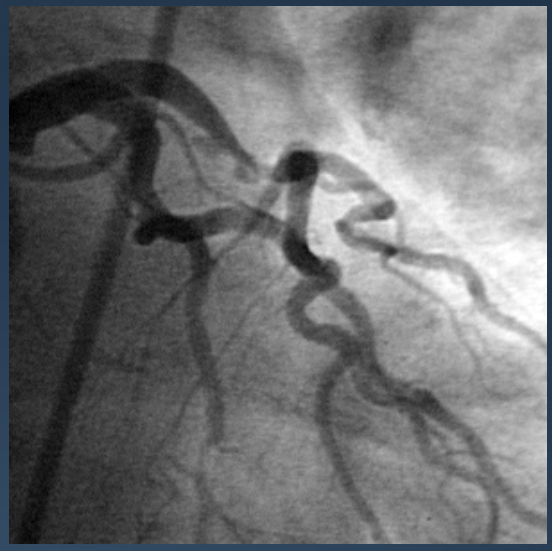
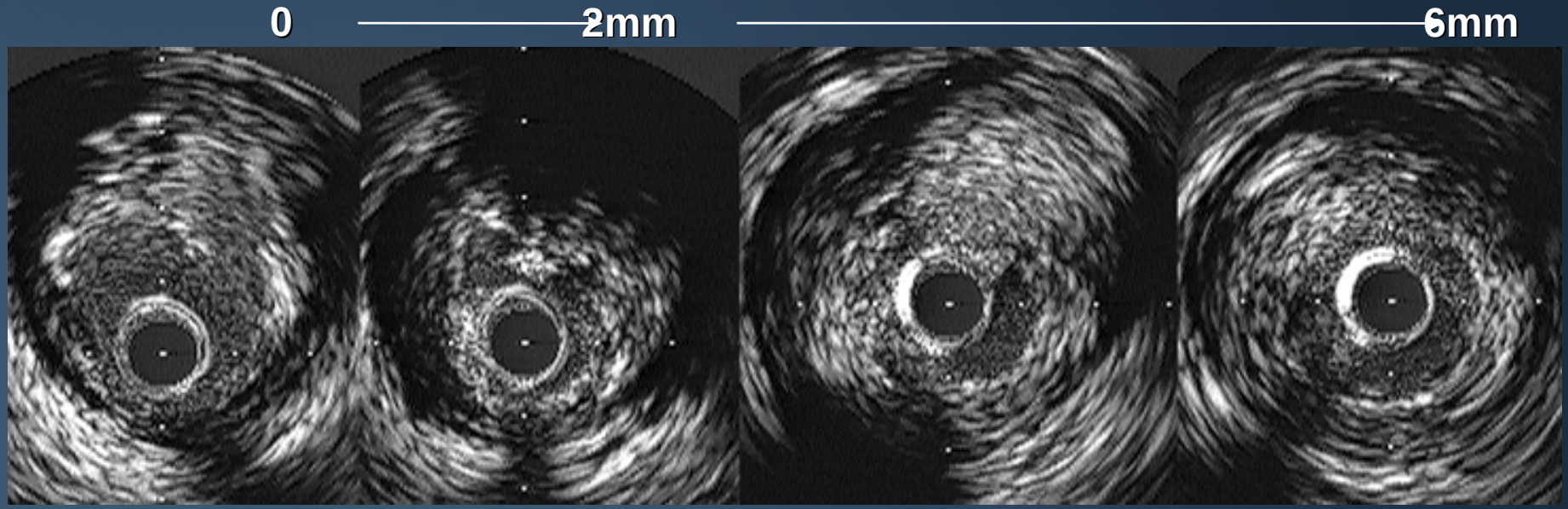
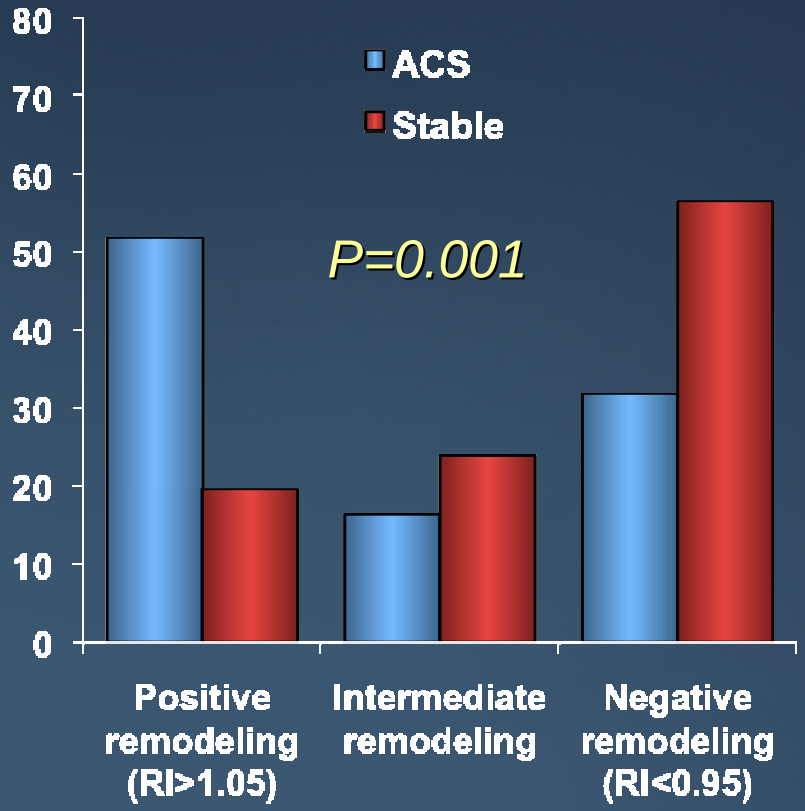
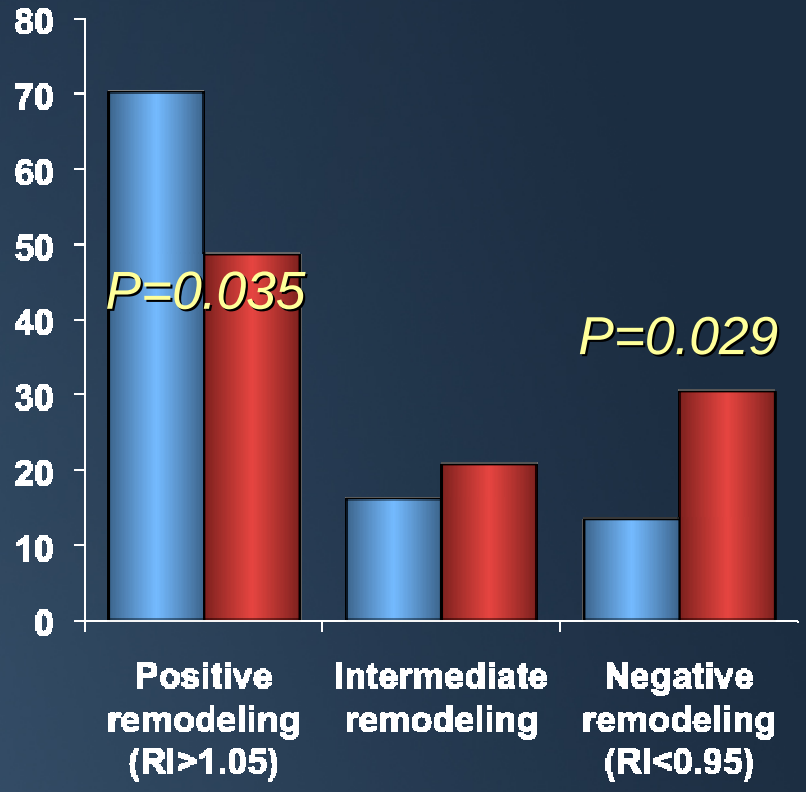



0
2mm
6mm

Association of positive remodeling and ACS





(Schoenhagen et al. Circulation 2000;101:598-603) *(Prati et al. Circulation 2003;107:2320-5)*

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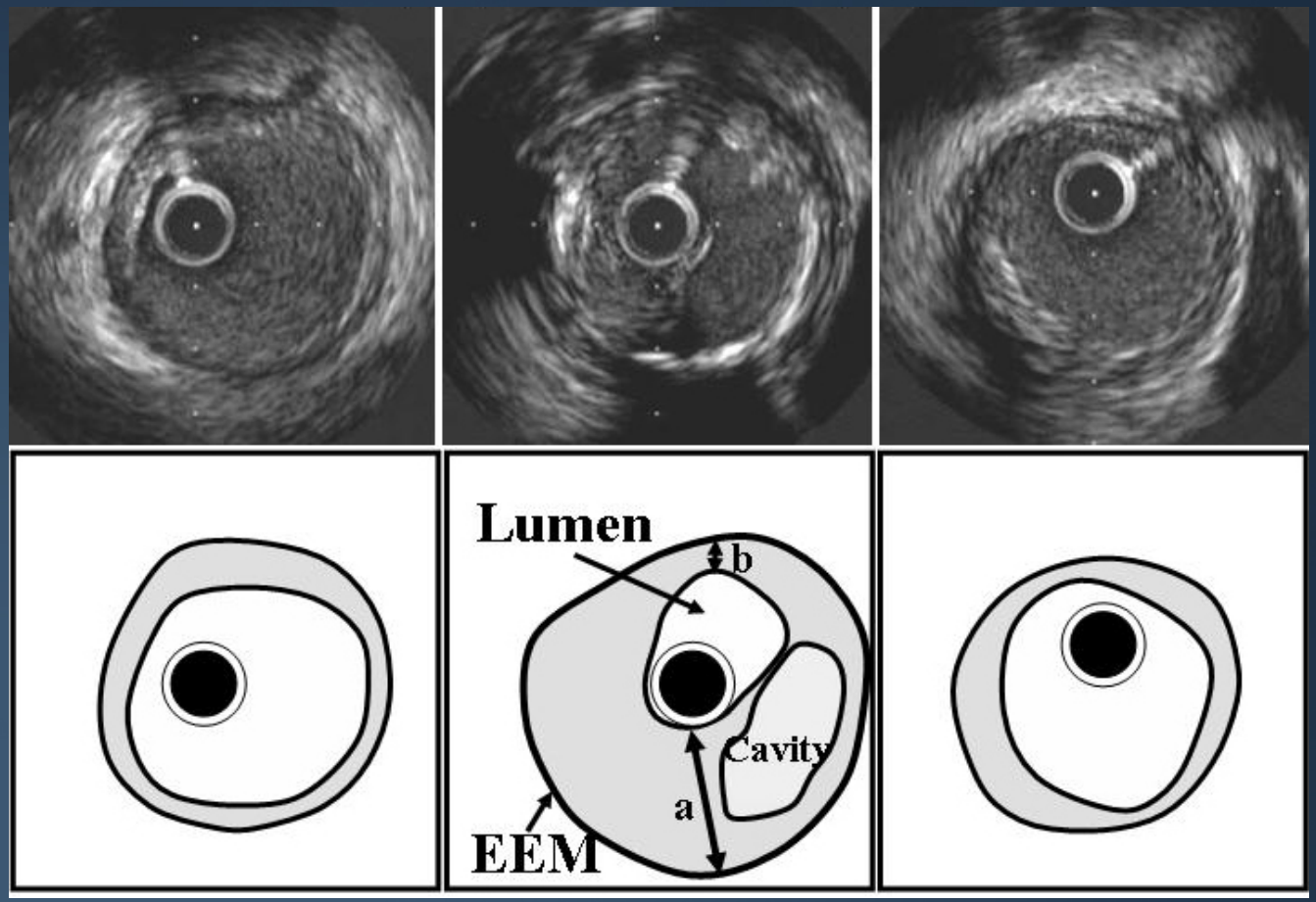
Calcium is less severe and more "spotty" in unstable lesions

	MI (n=61)	Unstable angina (n=70)	Stable angina (n=47)
No calcification	26%	41%	21%
Spotty calcification	51%	40%	30%
Intermediate calcification	15%	16%	11%
Extensive calcification	8%	3%	38%

p<0.0001

(Ehara et al. Circulation 2004;110:3424-9)

IVUS profile of ruptured plaques: Insights into pre-rupture morphology (n=112 culprit ruptured plaques)

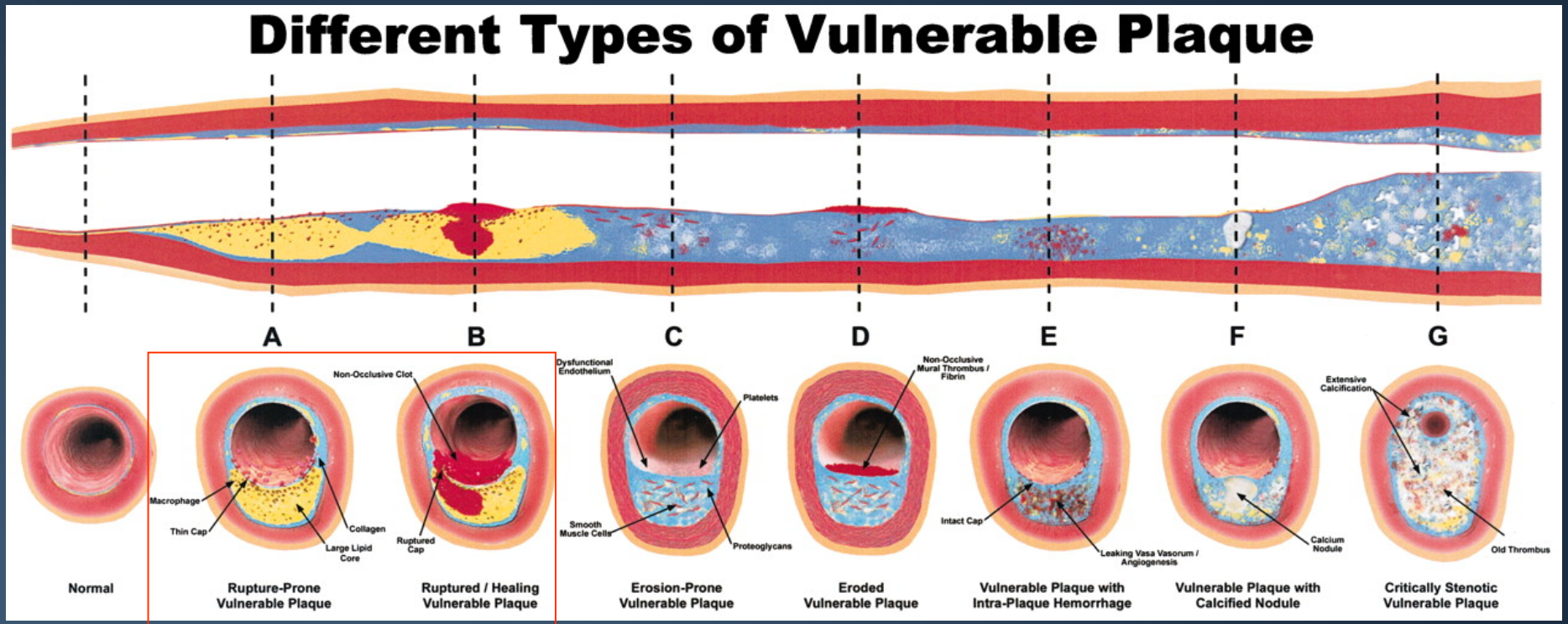


(Fujii et al. Am J Cardiol 2006;98:429-35)

	Mean±1SD	CoV	10th Percentile	90th Percentile
Reference				
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
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
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
Plaque Burden	0.76±0.10	0.12	0.63	0.88
AS	0.57±0.19	0.34	0.28	0.80
RI	1.10±0.20	0.18	0.87	1.38
Arc of Ca^{++}	46.9±51.2	1.09	0	106.7

While the sensitivity of these findings is high, the specificity is low.

Are all vulnerable plaques thin-cap fibroatheromas?



70% of ACS culprit lesions

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

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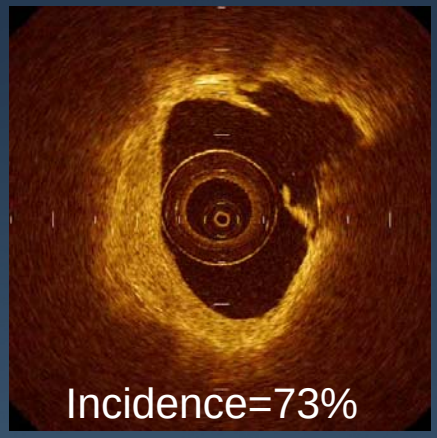
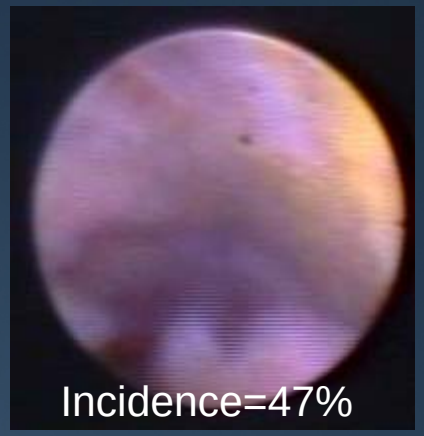
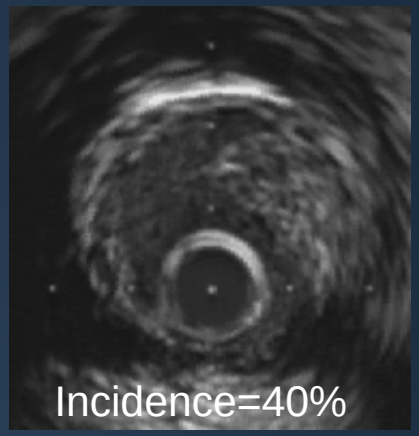
In vivo comparison of OCT and angioscopy in assessing culprit lesions in 30 AMI patients

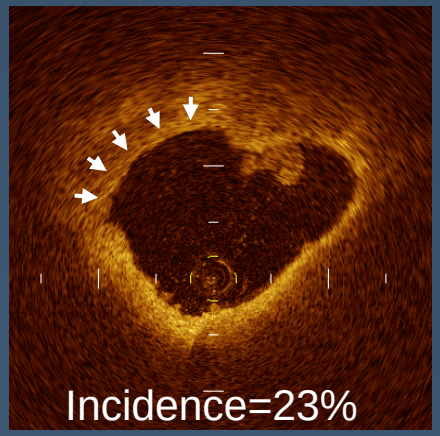
Plaque rupture

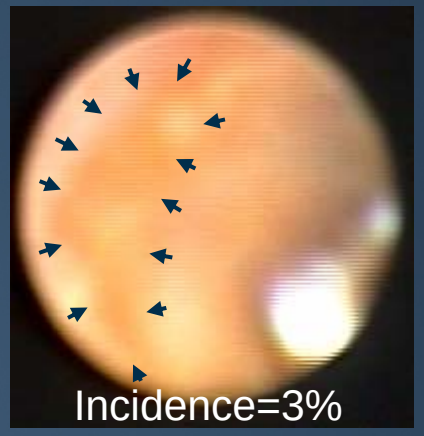


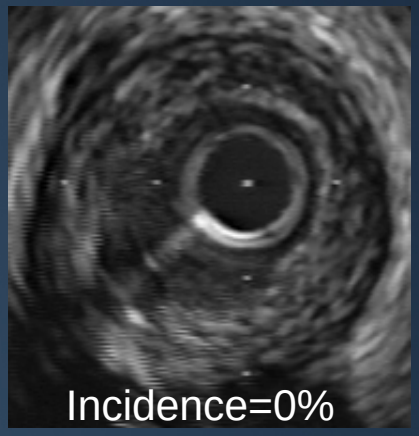




Plaque erosion







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(Kubo et al. J Am Coll Cardiol 2007;50:933-9)

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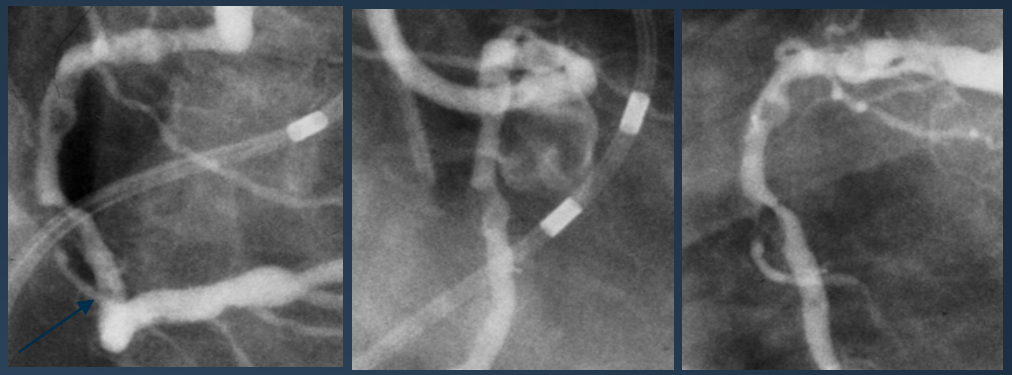

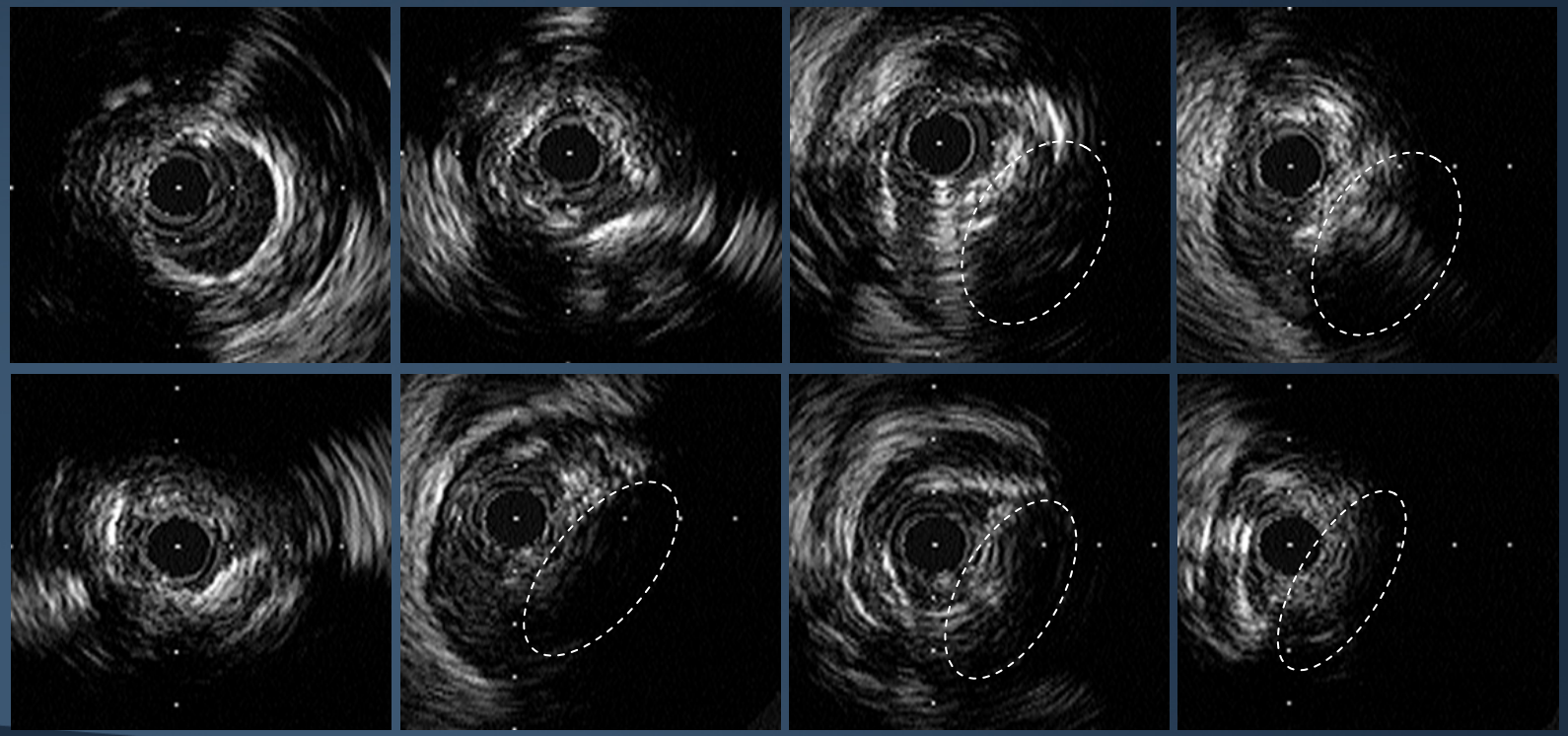

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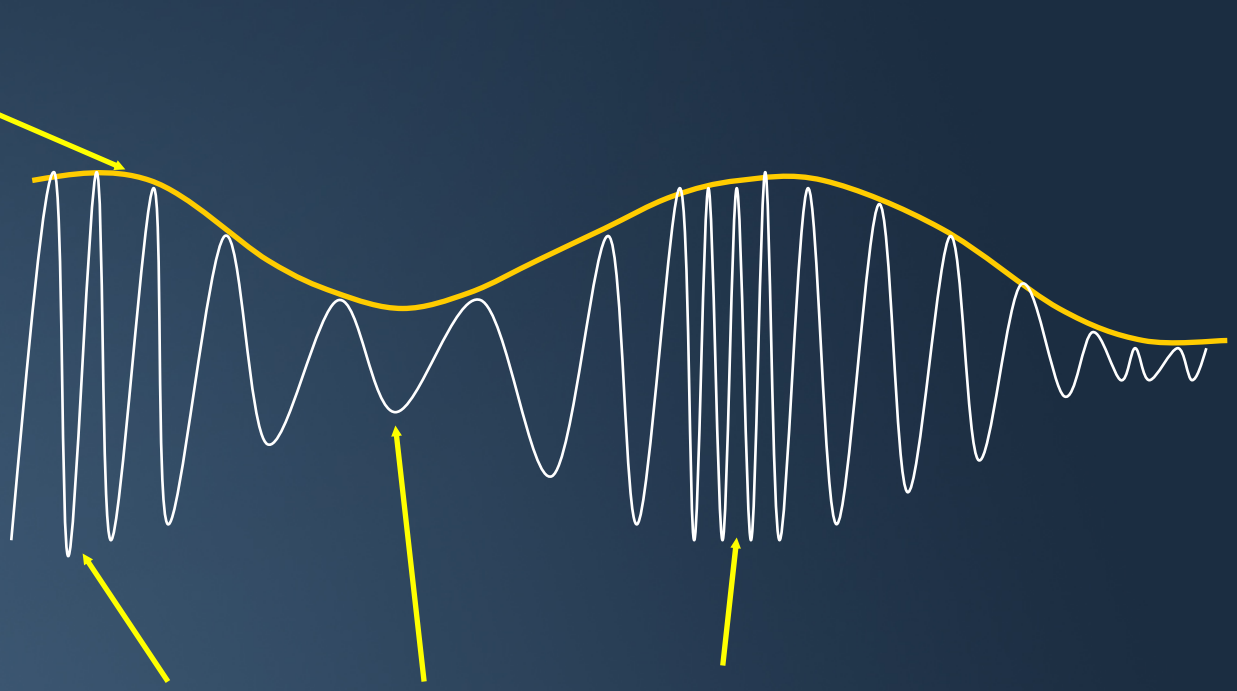
Virtual Histology™ IVUS

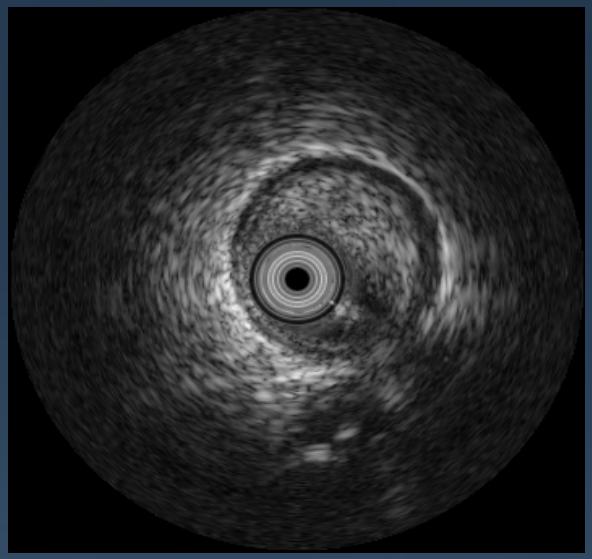
Only the envelope amplitude (echo intensity) is used in formation of the gray-scale IVUS image

Eight amplitude *and* frequency parameters are used in Virtual Histology

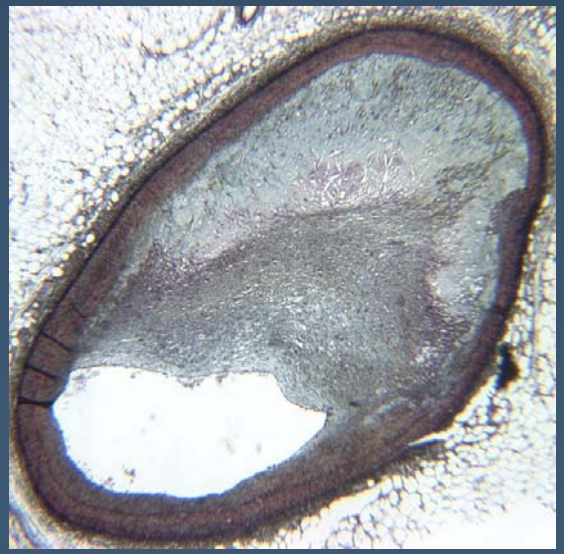


Frequency of echo signal can also vary, depending on the tissue

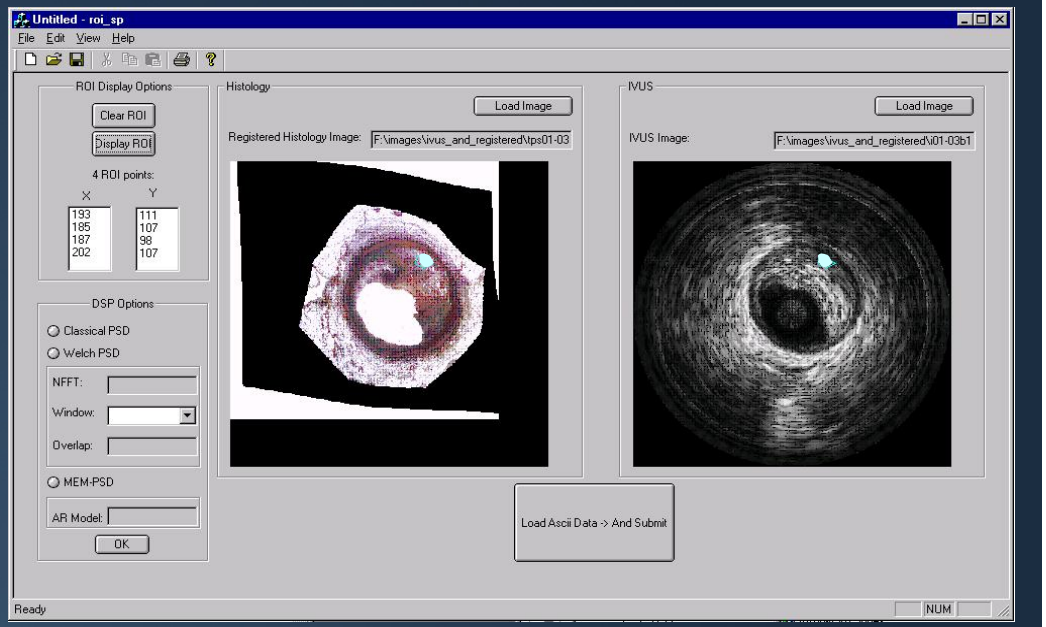
IVUS B scan



Movat pentachrome stain



Thin plate spline morphing after which the computer was taught to recognize four basic tissue types



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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%

Expert review

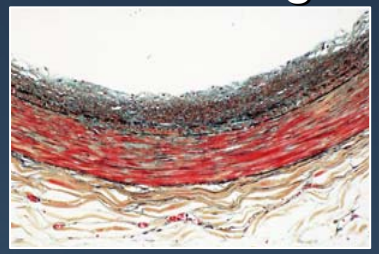
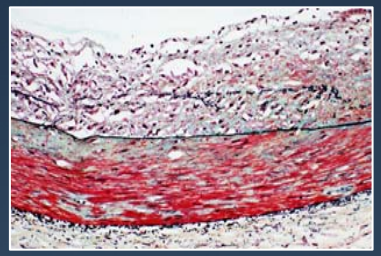
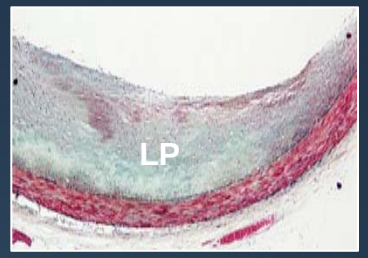
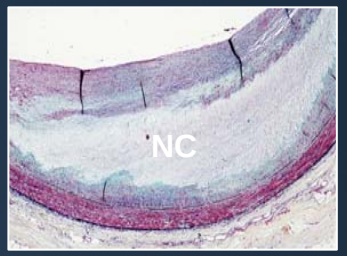
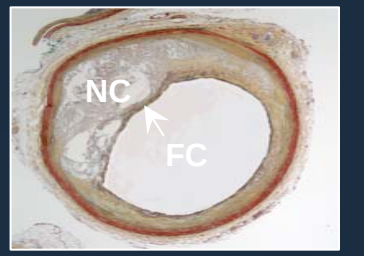
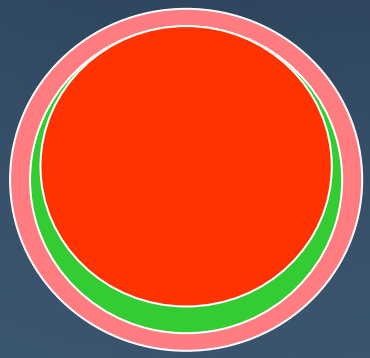
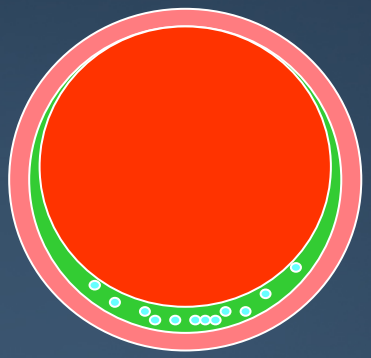
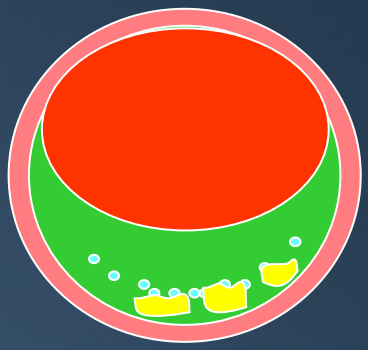
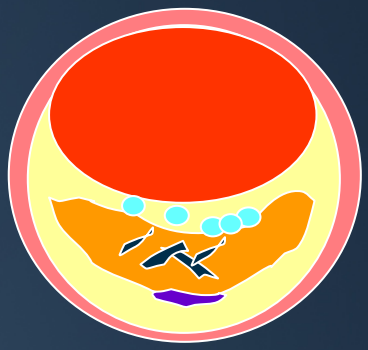
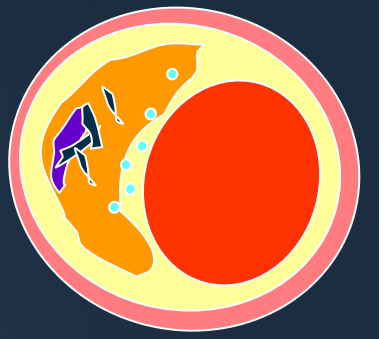
EuroIntervention

Tissue characterisation using intravascular radiofrequency data analysis: recommendations for acquisition, analysis, interpretation and reporting

Héctor M. García-García[1], MD, MSc; Gary S. Mintz[2], MD, FACC; Amir Lerman[3], MD, FACC; D. Geoffrey Vince[4], PhD; M. Pauliina Margolis[4], MD, PhD; Gerrit-Anne van ES[5], PhD; Marie-Angèle M. Morel[5], BSc; Anuja Nair[4], PhD; Renu Virmani[6], MD, FACC; Allen P. Burke[6], MD, FACC; Gregg W. Stone[2], MD, FACC; Patrick W. Serruys[1]*, MD, PhD, FACC, FESC

1. Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands; 2. Cardiovascular Research Foundation, New York, USA; 3. Mayo Clinic, Rochester, Minnesota, USA; 4. Volcano Corporation, Rancho Cordova, California, USA; 5. Cardialysis, BV, Rotterdam, The Netherlands; 6. CVPath Institute, Inc., Gaithersburg, Maryland, USA

Development of Human Coronary Atherosclerosis

Adaptive 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

FC = fibrous cap
LP = lipid pool
NC = necrotic core

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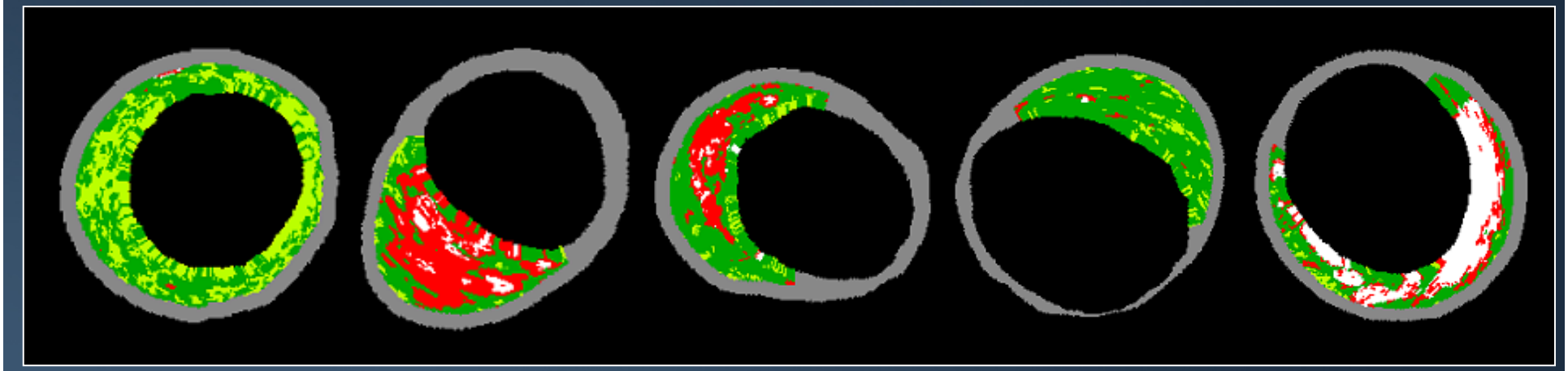

Pathological intimal thickening (PIT)

Thin-cap fibroatheroma (TCFA)

Thick-cap fibroatheroma (ThFA)

Fibrotic

Fibrocalcific

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Morphometry of different plaque types

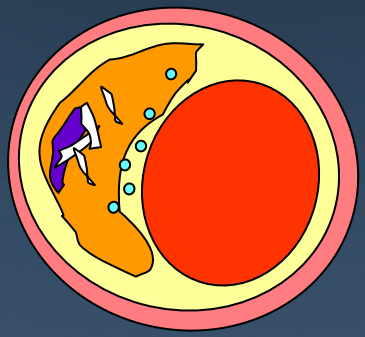
	IEL mm^2	Plaque burden %	Necrotic core %
Pathologic intimal thickening (PIT) (n=125)	6.5	43.0	0.1
Fibroatheroma (n=262)	9.2	64.5	11.2
TCFA (n=46)	12.8	67.0	21.6
Plaque rupture (n=55)	13.2	79.8	29.0

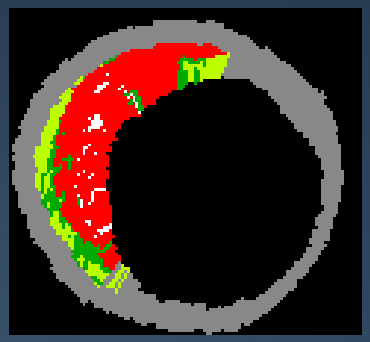
	TCFA (n=64)	Plaque Rupture (n=69)
IEL Area mm^2	11.99	12.63
Plaque Area	8.74	10.35
Plaque burden %	69.2	75.1
% Necrotic core	24.3	32.2
% Calcification	8.95	5.77
% Macrophage	4.56	3.78
Mean cap thickness (μ m)	39	35

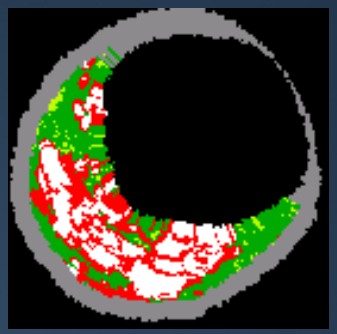
PIT is the likely precursor lesion of fibroatheroma, but the mechanisms responsible for this conversion are poorly understand. . .

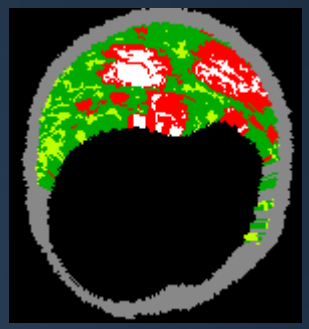
Thin Cap Fibroatheroma (TCFA)

"Thin Cap Fibro-Atheroma (TCFA)" or "Vulnerable Plaque" – Confluent necrotic core >10% of total plaque and located at 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





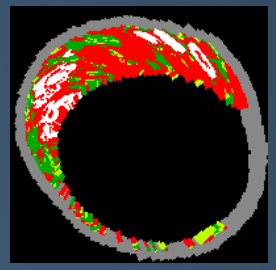


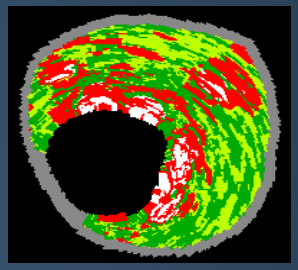


<5% calcium **>5% calcium** **multiple layers**

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)

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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%).

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

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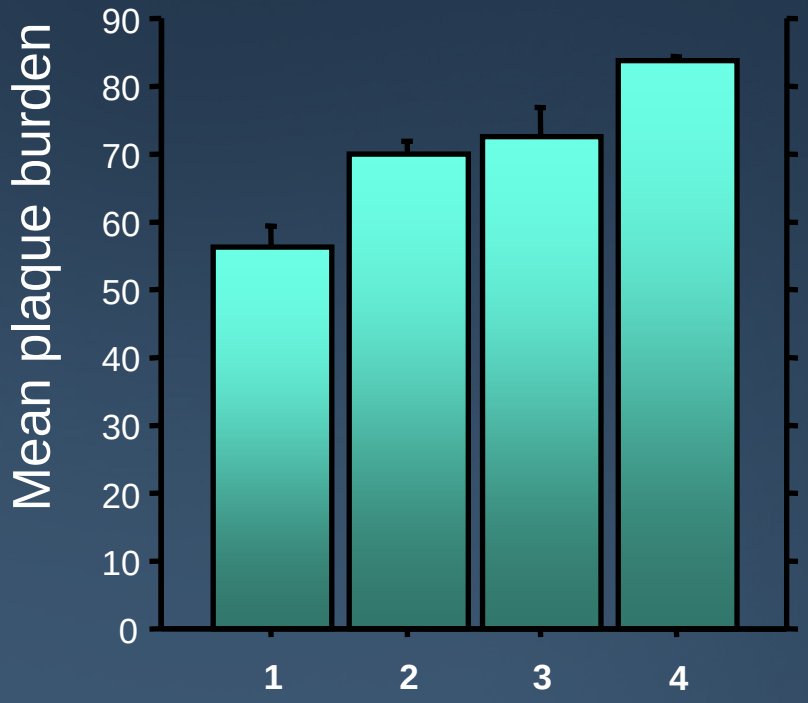
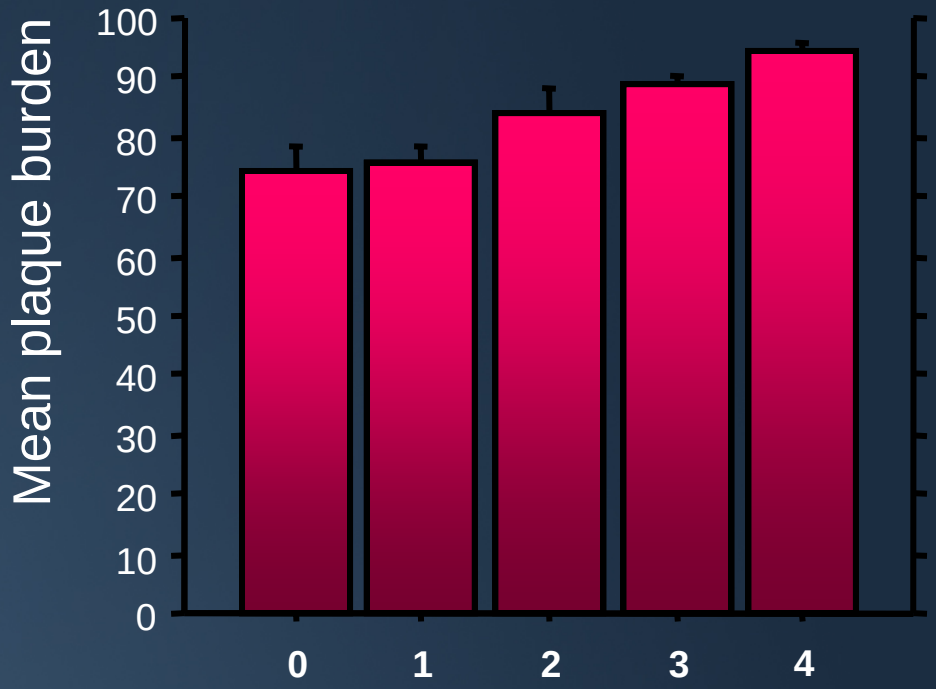
Mean plaque burden increases with number of prior rupture sites



Number of prior ruptures,
healed rupture sites



Number of prior ruptures,
acute rupture sites

11% of plaque ruptures are virgin

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

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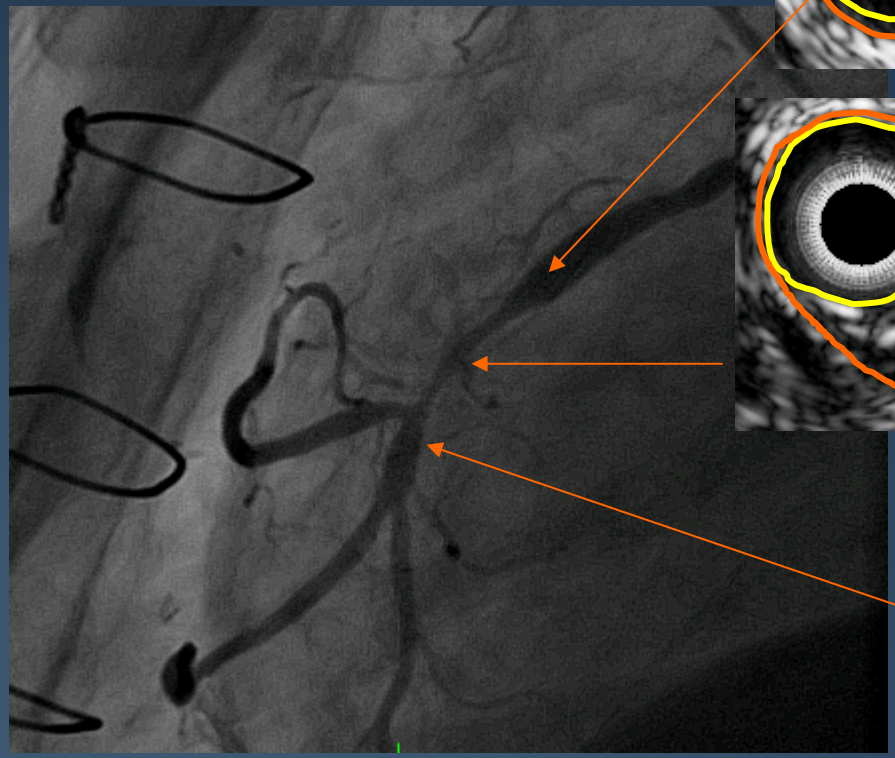
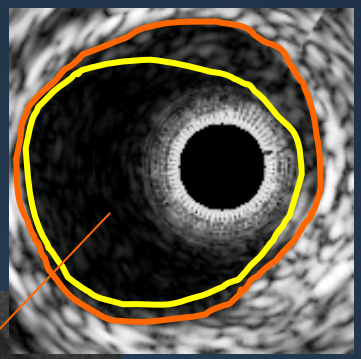
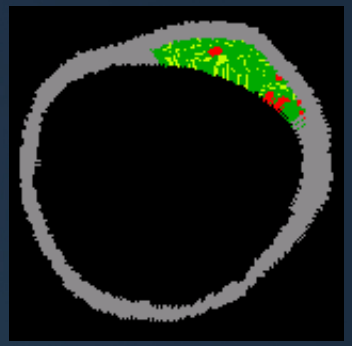
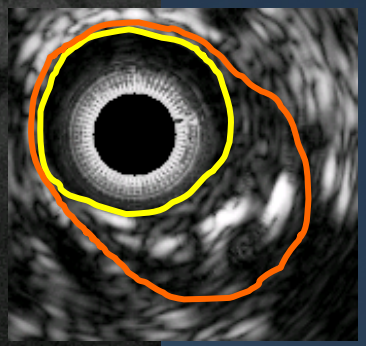
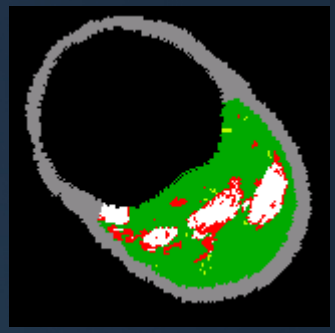
Multiple small calcific deposits by greyscale IVUS, multiple necrotic cores by VH-IVUS

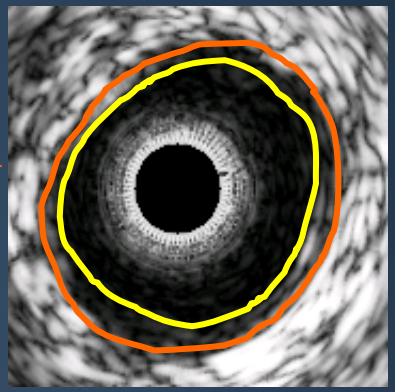


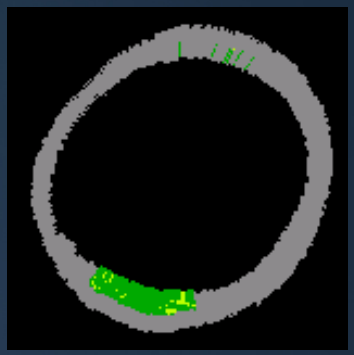












- Greyscale IVUS findings are ubiquitous in diffuse/advanced coronary atherosclerosis and, therefore, of limited ability to predict events.
- VH-IVUS criteria were based on presumptive histologic evidence. But its ability to detect and assess the risk of a specific lesion will depend NOT on correlation with histopathology, but on the ability to predict future events.
- Perhaps PROSPECT will validate these assumptions. Perhaps not.

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