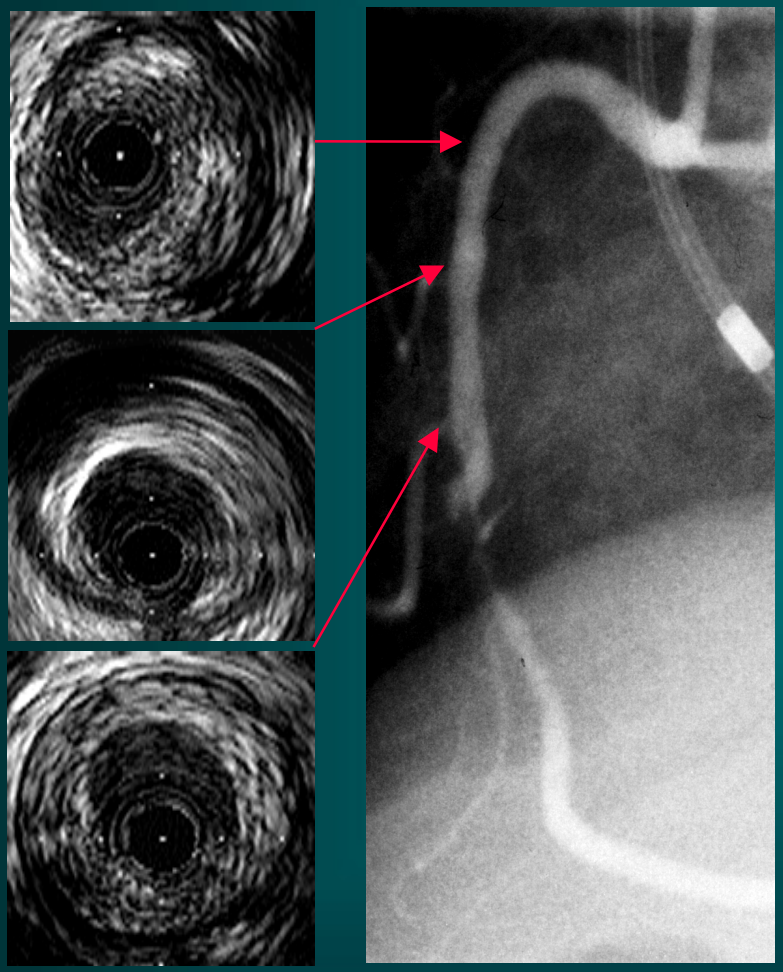
Gary S. Mintz, MD

IVUS Observations in Acute (vs Chronic) Coronary Artery Disease: *Structure vs Function*

Important IVUS Observations: *Remodeling*

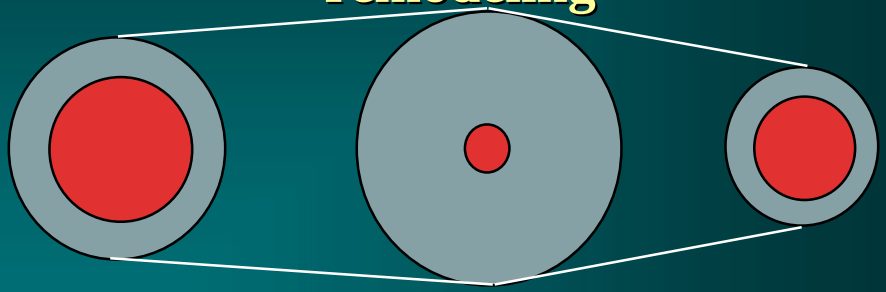
- Originally used (first by Glagov) to explain atherosclerosis in the absence of lumen compromise - mostly in reference segments
- Regardless of the definition, assessing lesion remodeling requires a comparison to the reference segment
  - Positive (outward) remodeling in ACS
  - Negative (constrictive or inward) remodeling in stenosis formation in chronic stable angina

Reference Segments

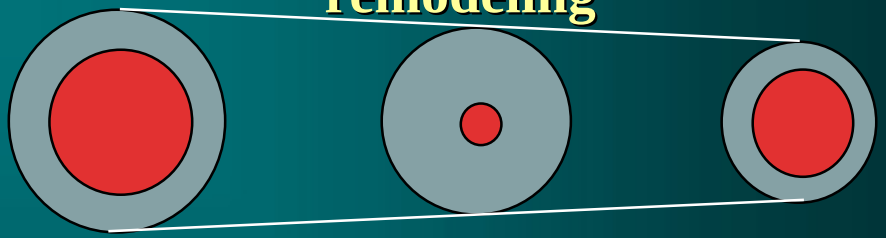


Lesions

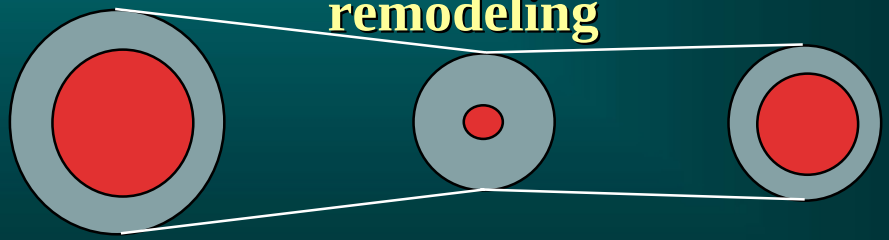
Positive remodeling



Intermediate remodeling



Negative remodeling



Mintz et al, J Am Coll Cardiol 1995;25:1479-85

Nishioka et al. J Am Coll Cardiol 1996; 27:1571-76

+Rem Intermediate -Rem

↑Plaque burden ↓Plaque burden

Reference segment disease (12)
Early atherosclerosis (1)
Soft plaques (9)

Advanced fibrocalcific disease (2,5,9)

Chronic stable angina or old MI (2,3,5,14,17,20)

Acute coronary syndromes (7,8,10,11,16,20)

Advanced age (26)
Smoking (5,14)
Insulin-treated DM (6)

Hypercholesterolemia (5)
High HDL-cholesterol (19)

Increased restenosis and CK-MB post-PCI (13,17,18,23,24)

Vasospastic angina (15)

New stenosis in another location (17)

Transplant atherosclerosis (4,21,22)

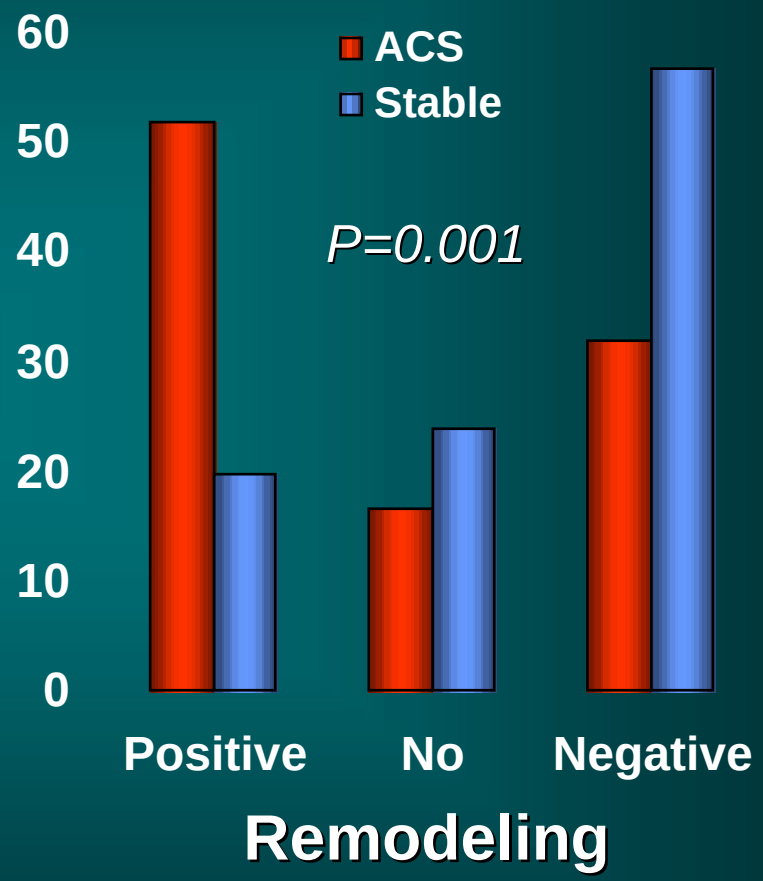
Proximal disease, eccentric lesions surrounded by pericardium (9,25)

Ostial, distal disease, eccentric lesions surrounded by myocardium (9,25,27)

1) Glagov. N Engl J Med 1987;316:1371-5
2) Mintz. Circulation 1997;95:1791-8
3) Nishioka. JACC 1996;27:1571-6
4) Lim. Circulation. 1997;95:855-9
5) Tauth. AJC 1997;80:1352-5
6) Kornowski. AJC 1998; 81:1298-1304
7) Schwarzacher. Circulation 1998;98:I-145
8) Schoenhagen. Circulation 2000;101:598-603
9) Sabate. AJC 1999;84:135-40.
10) von Birgelen. JACC 2001;37:1864-70
11) Kawagoe. Circulation 1998;98:I-368
12) Mintz. JACC 1995;25:1479-85
13) Dangas. Circulation1999;99:3149-54
14) Weissman. AJC 1999;84:37-40
15) Hong. Am Heart J 2000;140:395-401
16) Abizaid. JACC 1999;33:53A
17) Wexberg. JACC 2000;36:1860-9
18) Mehran. Circulation 2000;101:604-10
19) Taylor. JACC 1999;34:760-7
20) Nakamura. JACC 2001;37:63-9
21) Pethig. Am Heart J 1998;135:628-33
22) Kobashigawa. J Heart Lung Transplant 2000;19:546-50
23) Endo. JACC 2001;37:70-5
24) Okura. JACC 2001 (in press)
25) Nishioka. AJC 2001;87:387-91
26) Gyongyosi. Coron Artery Dis 1999;10:211-9
27) Ward. Atherosclerosis 2001;154:179-83

Remodeling in Acute Coronary Syndromes

	ACS	Stable	p
Proximal reference			
EEM CSA (mm^2)	15.2±5,2	14.2±5.2	0.2
Lumen CSA (mm^2)	9.1±3.6	7.9±2.8	0.06
P&M CSA (mm^2)	6.1±2.6	6.2±3.5	0.9
Lesion			
EEM CSA (mm^2)	16.1±6.2	13.0±4.8	0.004
Lumen CSA (mm^2)	2.3±1.1	1.9±0.4	0.3
P&M CSA (mm^2)	13.9±5.5	11.1±4.8	0.005
Remodeling Index	1.06±0.2	0.94±0.2	0.008



Schoenhagen et al. Circulation 2000;101:598-603

Diabetes Modulates Remodeling in ACS and Stable Angina (n=927)

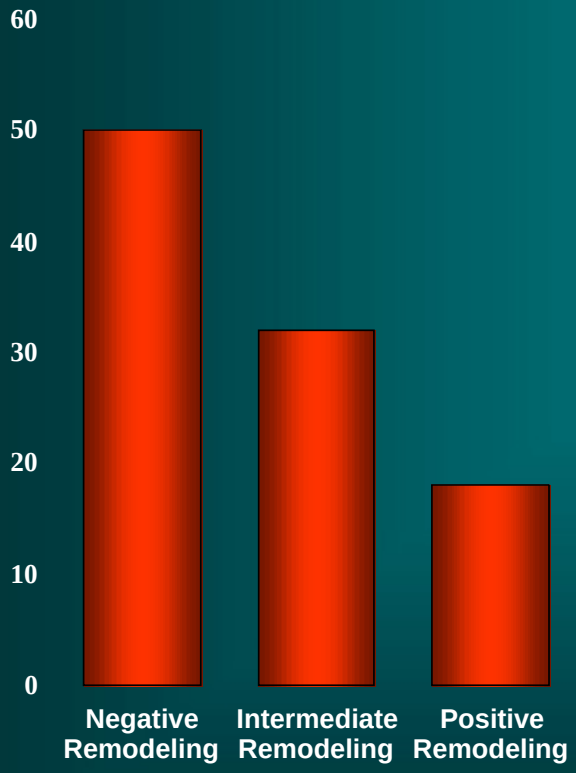
Frequency of Positive Remodeling

	DM	No DM
Acute Coronary Syndrome	59/183 (32.0%)	225/469 (48.0%)
Stable Angina	17/88 (19.6%)	42/187 (22.3%)

Abizaid, unpublished observations

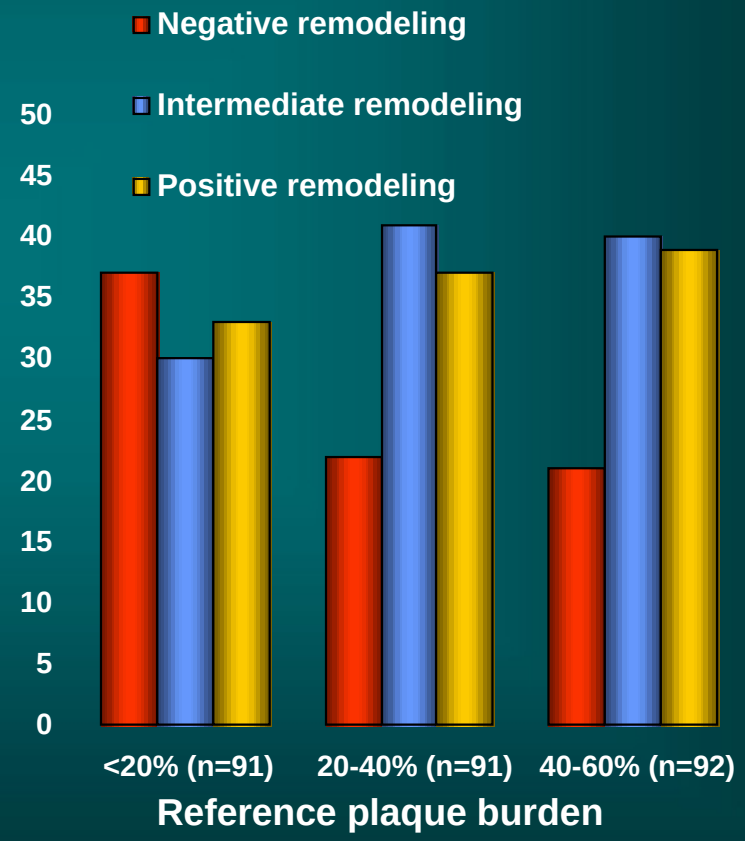
In Some Patients with Chronic Stable Angina Negative Remodeling Appears to Occur Early During Stenosis Formation

104 intermediate stenoses (QCA DS<60%)



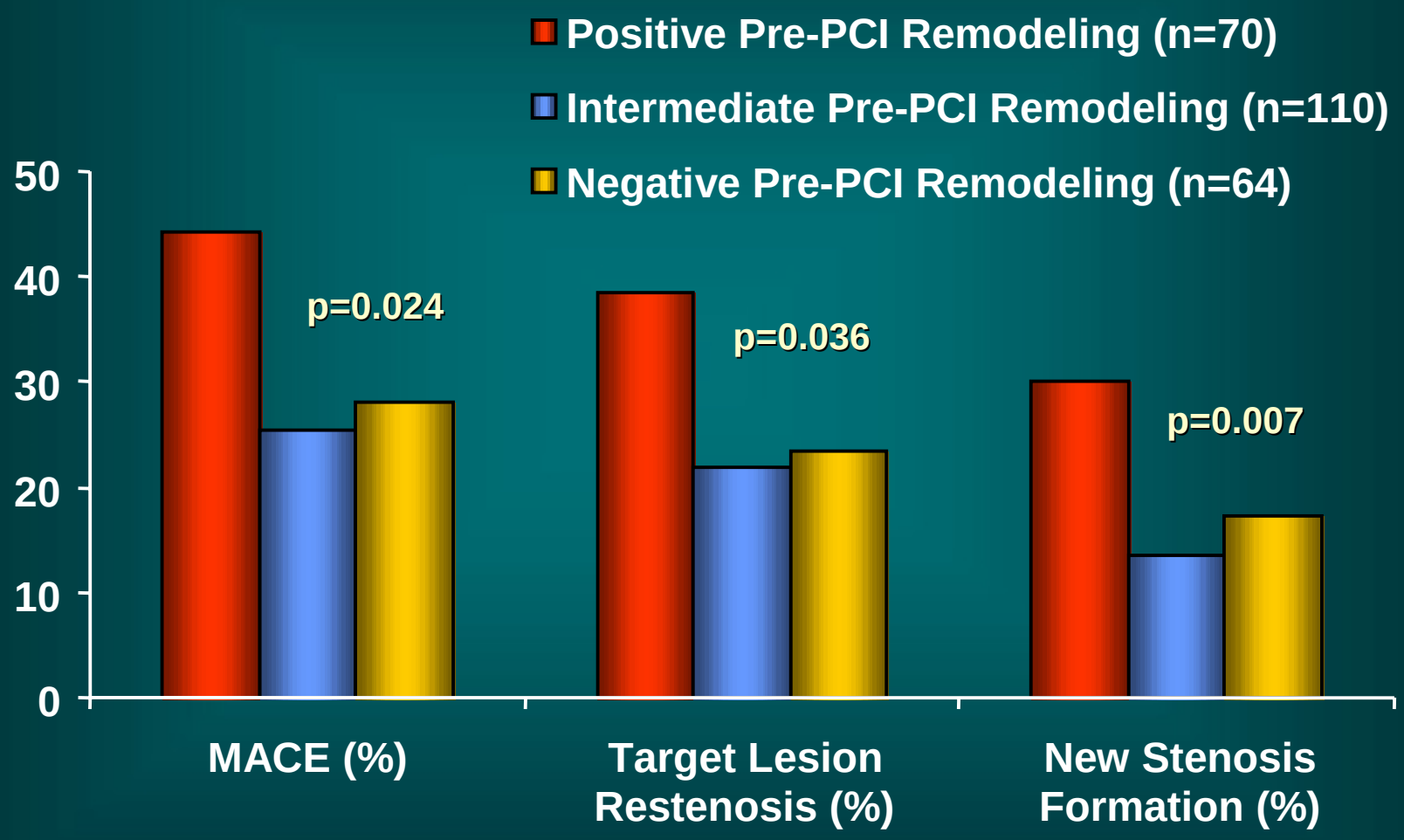
Hirose M, AJC in press

274 RCA stenoses, stratified according to reference disease



Hong M-K, JACC in press

244 Patients with Stable Angina and Single Vessel Intervention

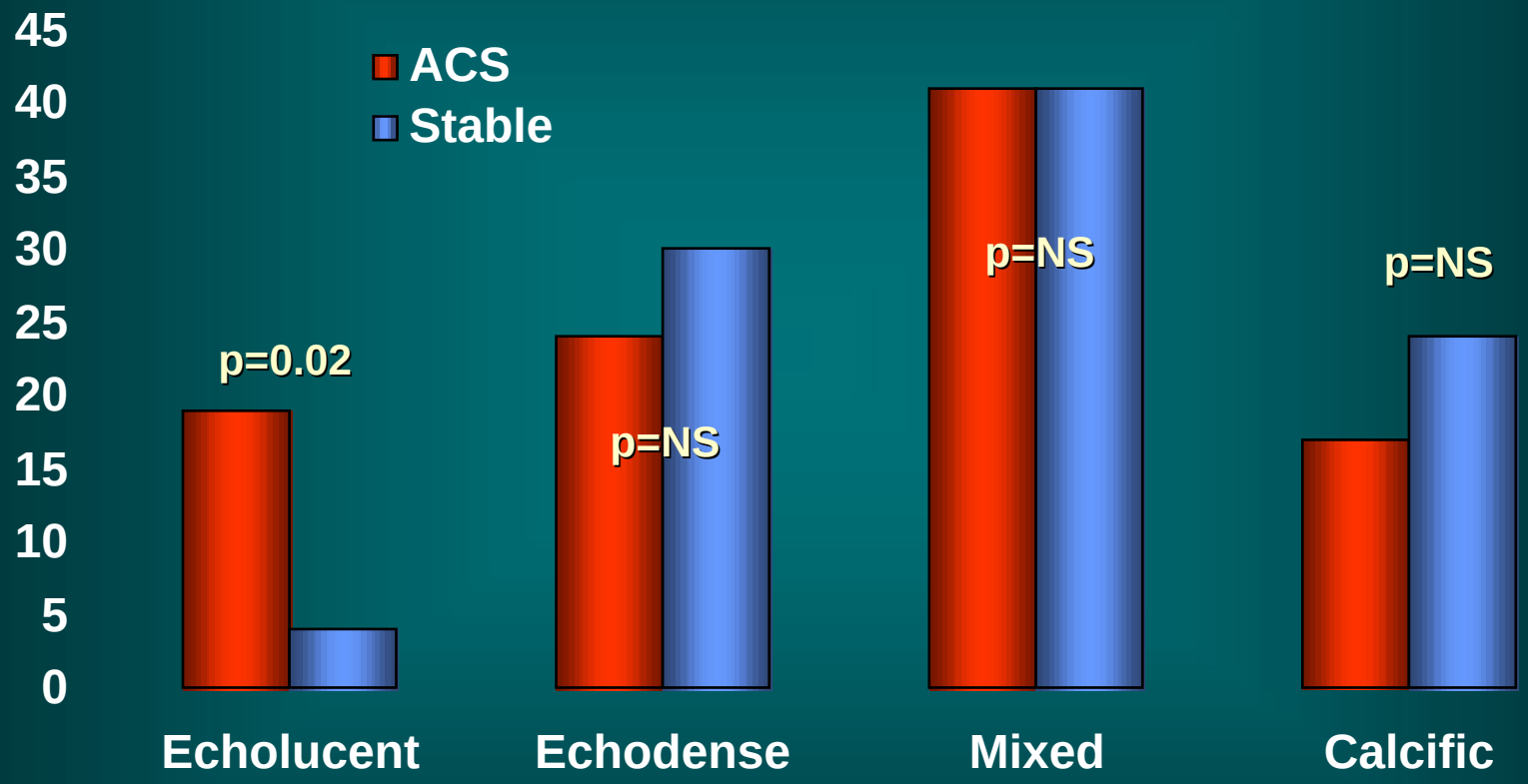


Wexberg et al. J Am Coll Cardiol 2000;36:1860-9

Important IVUS Observations: *Lesion Morphology*

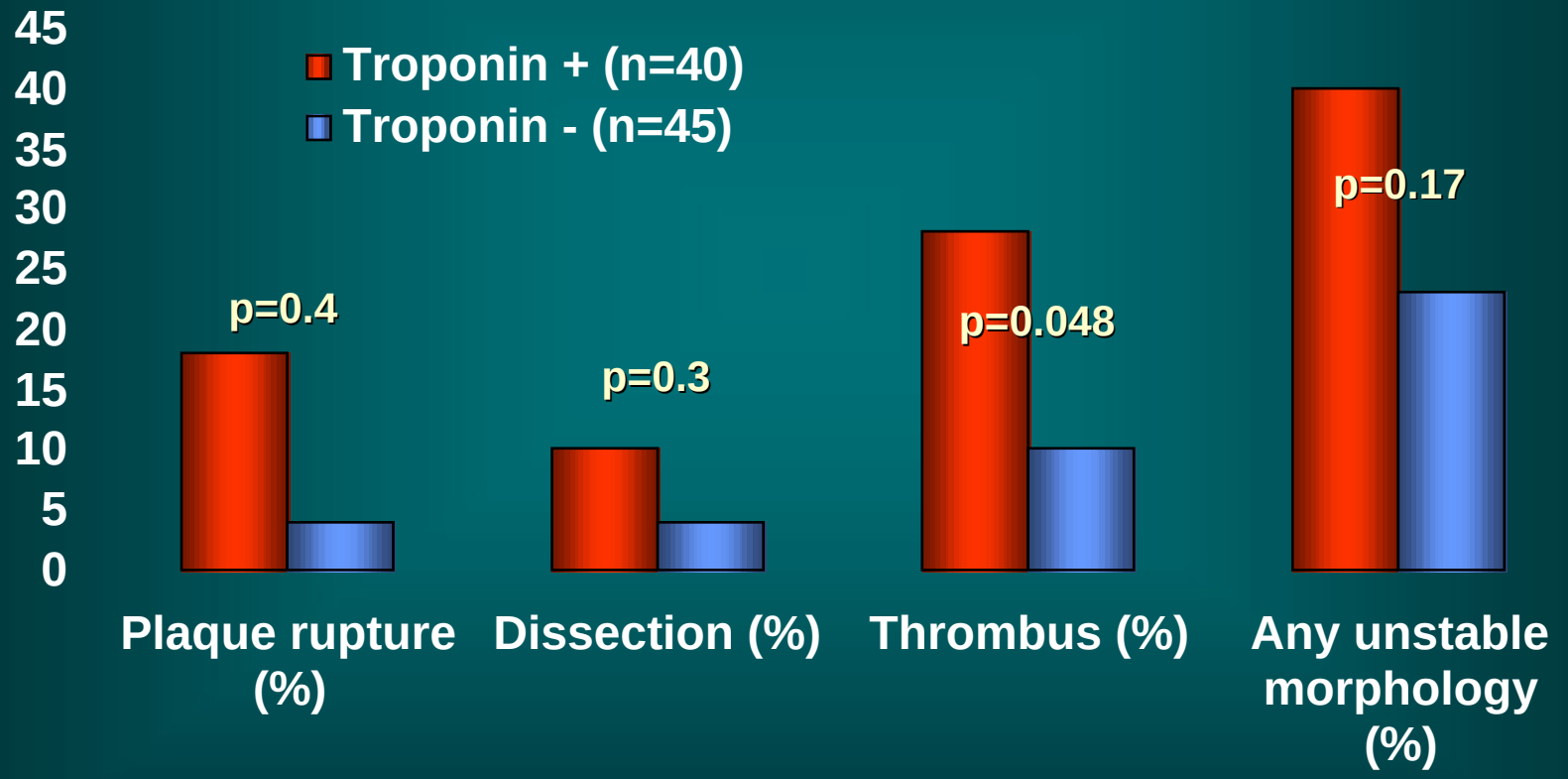
- Acute coronary syndromes
  - Hypoechoic plaque
  - Eccentric lesions
  - Ruptured plaques
  - Thrombus-containing plaques in ACS
- Fibrocalcific plaque in chronic stable angina in association with negative remodeling
- Positive remodeling and unstable lesion morphologies - i.e., ruptured and thrombus-containing plaques - tend to occur together in ACS

Plaque Composition in Acute Coronary Syndromes



Schoenhagen et al. Circulation 2000;101:598-603

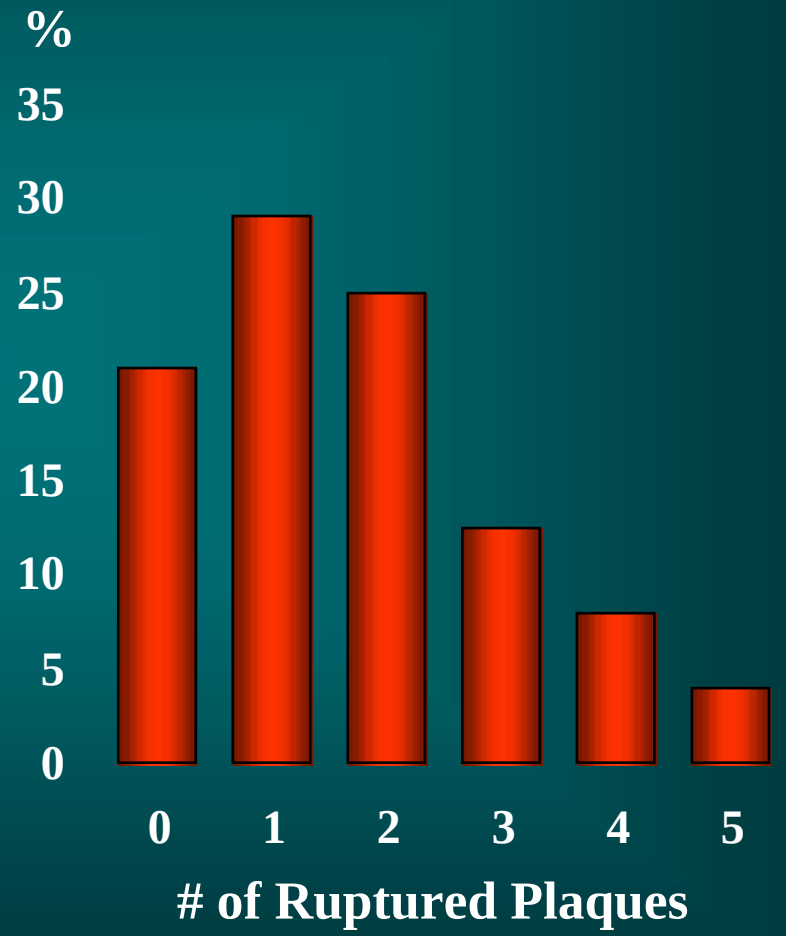
Comparison of Patients with ACS, no MI within 3 weeks, Single *de novo* Culprit Lesion Troponin (+) vs Troponin (-)



Fuchs et al. Am J Cardiol 2002;89:1111-3

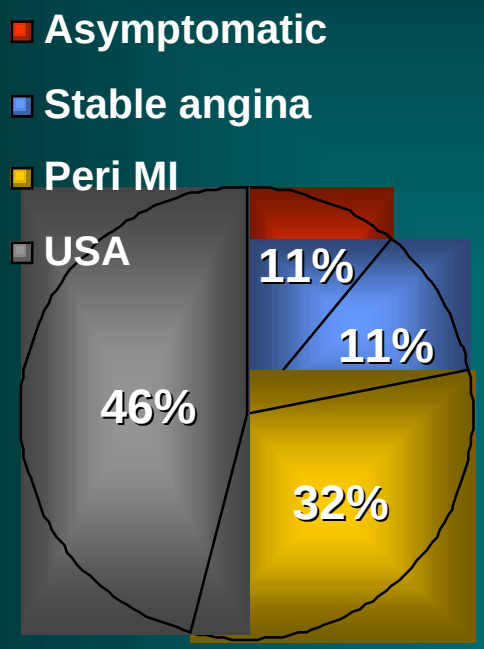
Three Vessel IVUS Imaging in 24 Pts with ACS and Positive Tn

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



Rioufol et al Circulation 2002;106:804-808

300 plaque ruptures in 257 arteries of 254 pts



The frequency of stable angina or no symptoms in patients with plaque rupture suggests that asymptomatic rupture and healing are common and may be one of the mechanisms of progression of CAD

- *Thrombus in 46%*
  - *more frequent in pts with USA or peri-MI, p=0.02*
  - *more frequent in arteries with multiple rupture sites, p=0.04*
- **Ca^{++} in 55%,**
  - **arc=36±47°**
  - **located at the base of the rupture in 86%**
- **Tear in fibrous cap identified in 59%,**
  - **at shoulder of plaque in 68% in center of plaque in 32%**
- ***Multiple rupture sites in 14% of ACS patients***

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

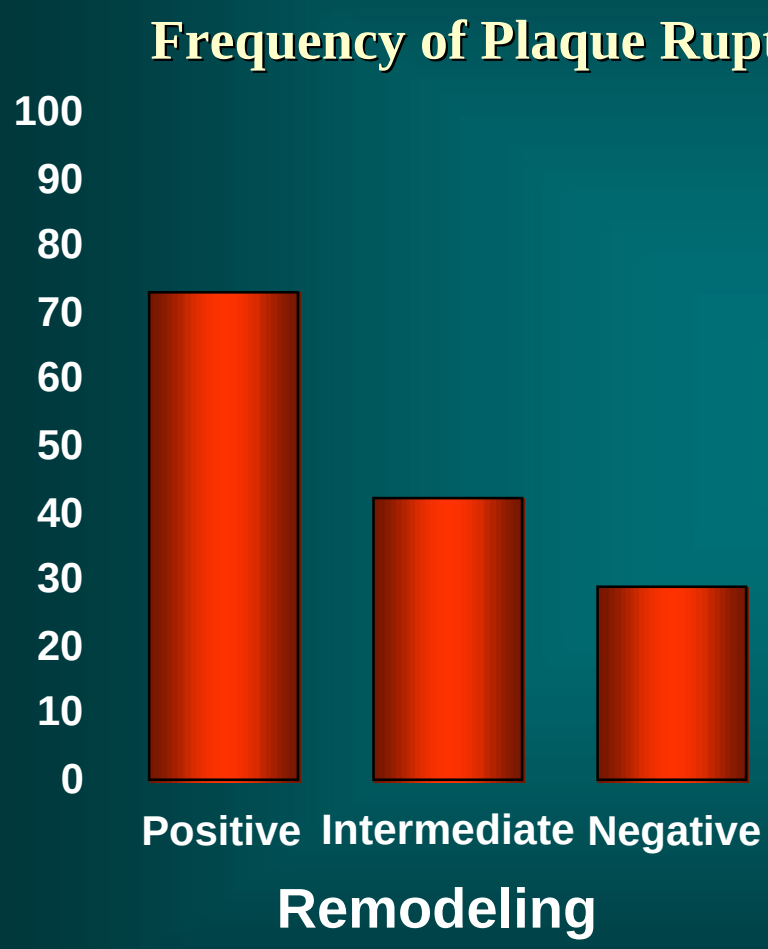
22 patients with single de novo lesions studied using angioscopy and IVUS showed a relationship between thrombus and remodeling

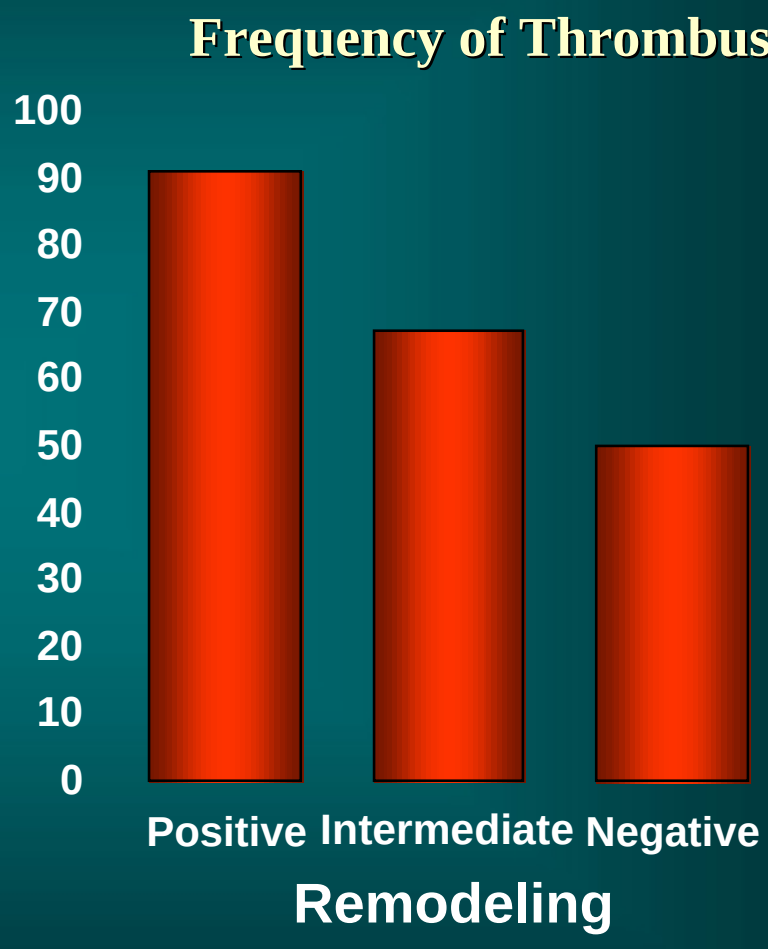
	Positive Remodeling (Lesion EEM>1.05 Reference)	Negative Remodeling (Lesion EEM<0.95 Reference)
Complex lesions (irregular surface ±thrombus)	8	2
Simple lesions (smooth surface w/o thrombus)	1	5

p=0.035

Smits et al. Cardiovasc Res 1999;41:458-464

Culprit Lesion Morphology vs Remodeling in 60 Patients with Unstable Angina

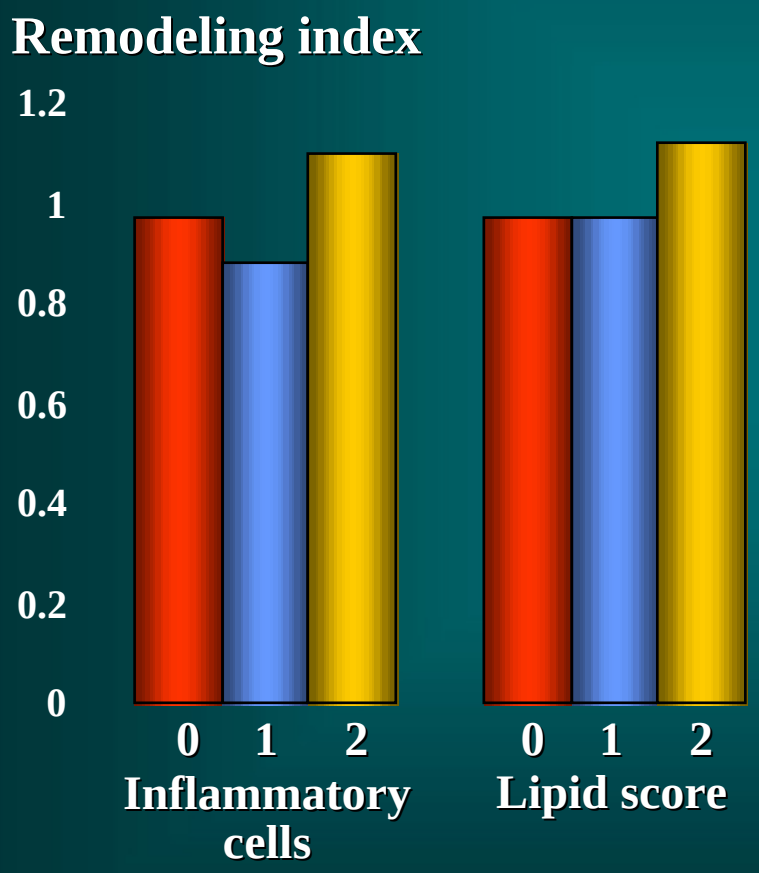




Gyongyosi et al. Heart 1999;82:68-74

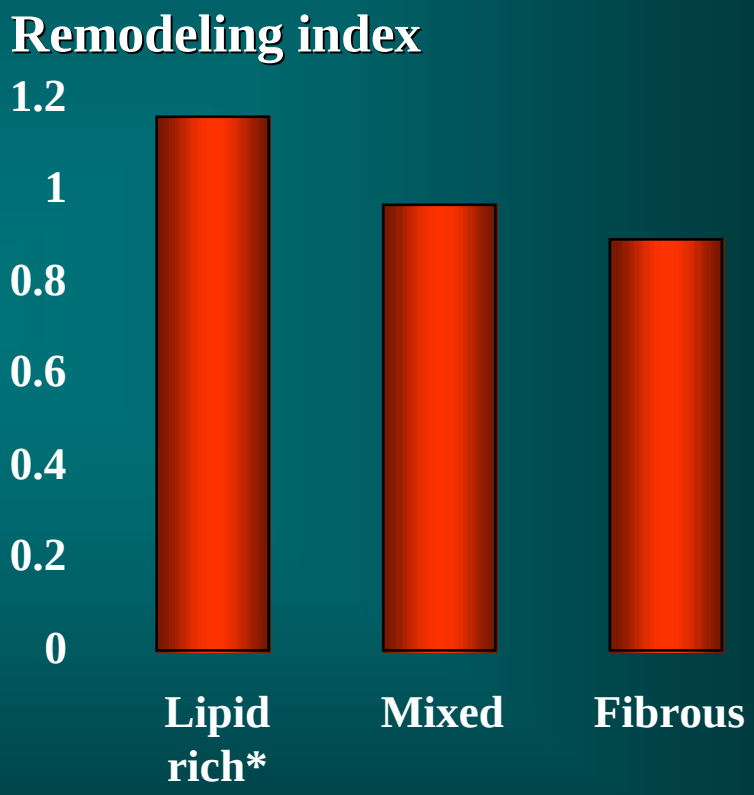
Remodeling vs plaque composition

IVUS & histology in 29 patients (17 stable angina, 12 ACS) treated with DCA



Uemura et al. ACC 2003

IVUS & OCT in 82 lesions in 50 patients

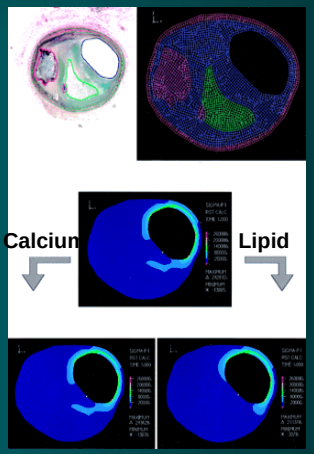


***Remodeling also correlated with quadrants of lipid (p=0.001)**

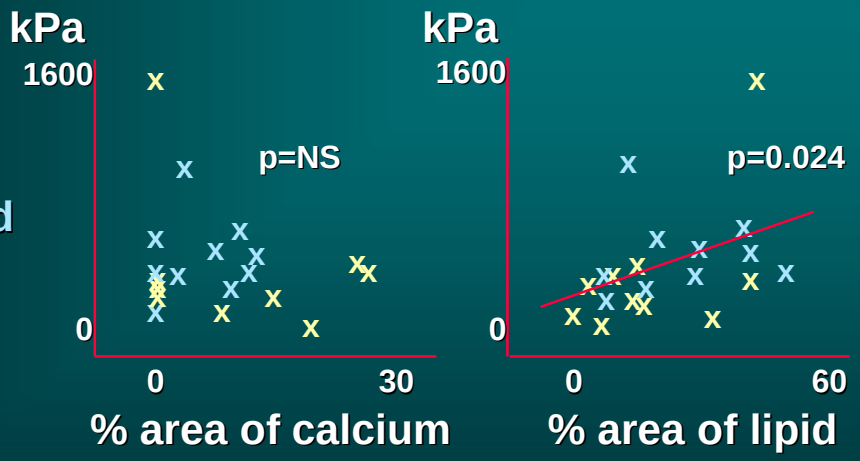
Mac Neill et al. ACC 2003

Calcium Does Not Increase the Biomechanical Instability of Atherosclerotic Plaques!

	Stable (n=10)	Ruptured (n=10)	p
Ca^{++} CSA (%)	4.1	5.4	0.4
Lipid CSA (%)	14.1	2.8	0.3
Maximal stress (kPa)	286	458	0.038



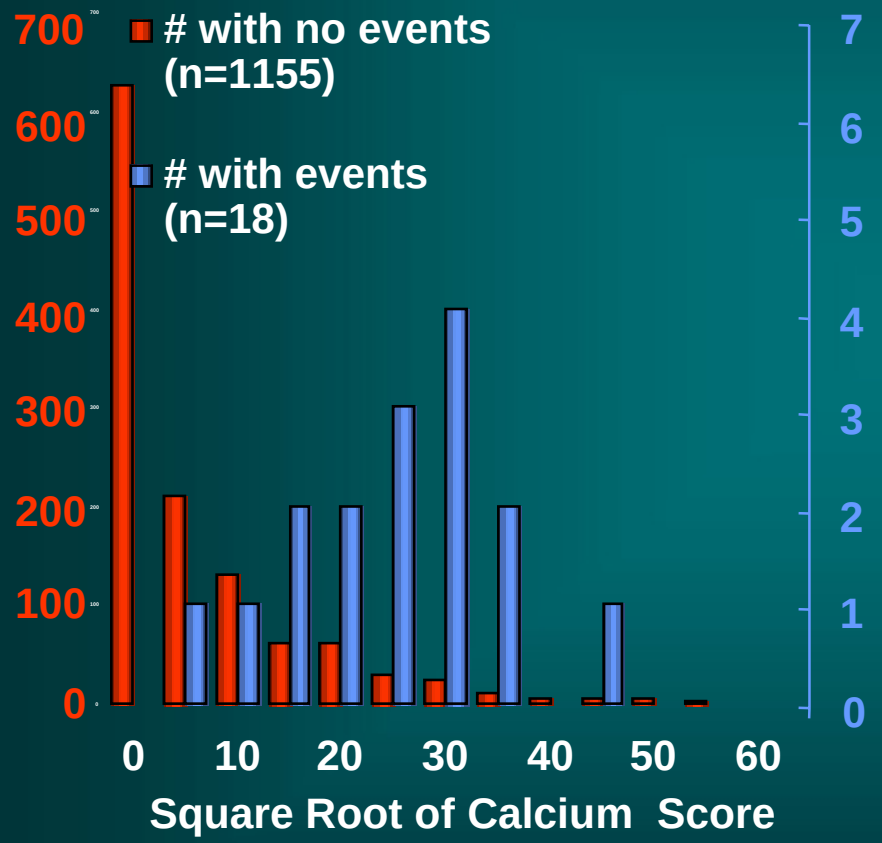
x=stable
x=ruptured



When fibrous plaque was replaced with calcium, stress changed insignificantly (p=0.85). In contrast, stress decreased by 26% (p=0.02) when lipid was replaced with fibrous plaque.

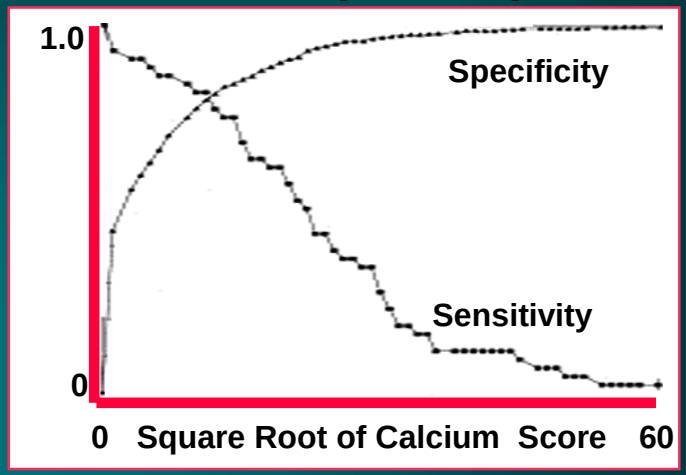
Huang. Circulation 2001;103:1051-6

Multiple studies have shown that EBCT calcium score predicts acute coronary events at 1 year follow-up

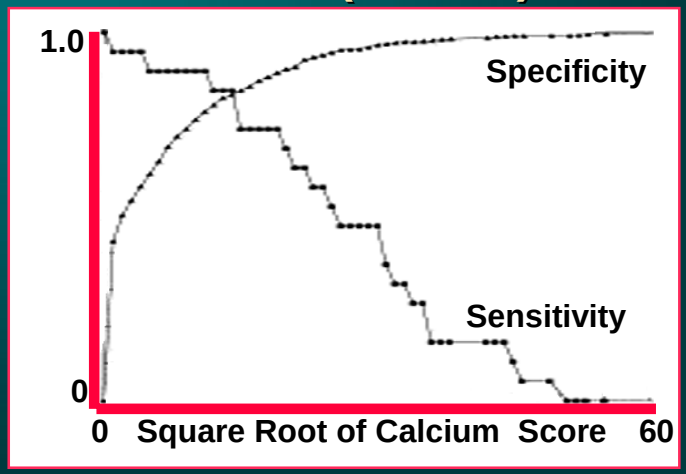


Arad et al. Circulation 1996;93:1951-3

MACE (n=1172)



Death/MI (n=1172)



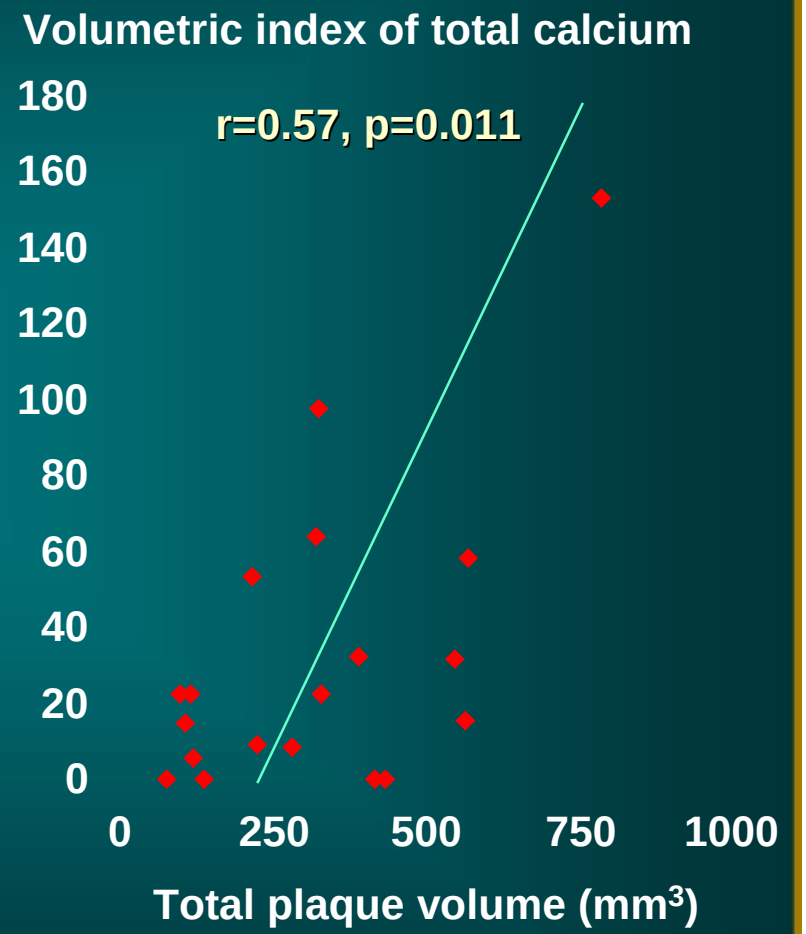
Arad et al. J Am Coll Cardiol 2000;36:1253-60

Important IVUS Observations: *Calcium*

- If calcium is uncommon in ACS lesions and if calcium does not affect plaque vulnerability and instability, why does the EBCT calcium score predict acute events?

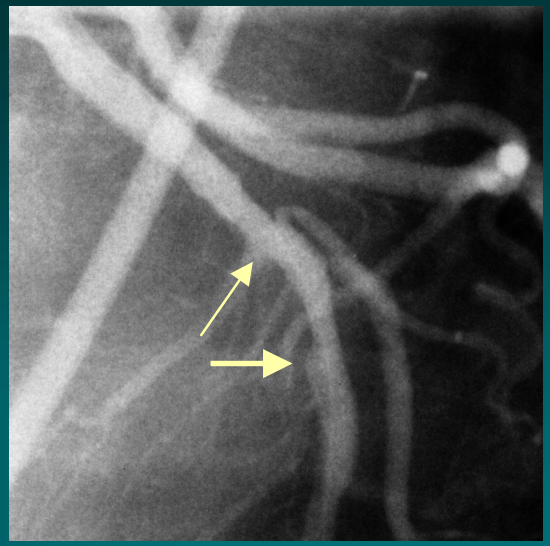
Volumetric IVUS analysis of 19 RCA's with 1 or 2 focal de novo stenoses

	Lesion	Non-Stenotic Segment	p
EEM vol (mm^3)	119 ±111	459 ±283	<0.0001
Lumen vol (mm^3)	29 ±30	228 ±156	<0.0001
P&M vol (mm^3)	90 ±86	231 ±140	<0.0001
Length (mm)	9.4 ±7.6	33.4 ±13.5	<0.0001

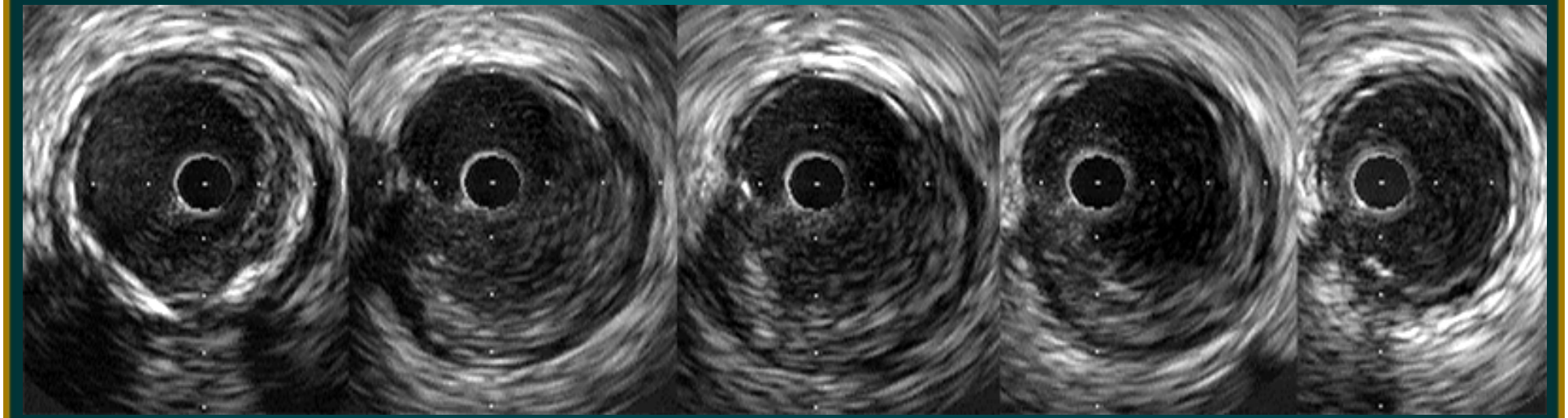


72 ±12% of the plaque volume (range 46-86%) is in nonstenotic segments. Plaque volume

Tinana et al. Am J Cardiol 2002;89:757-60



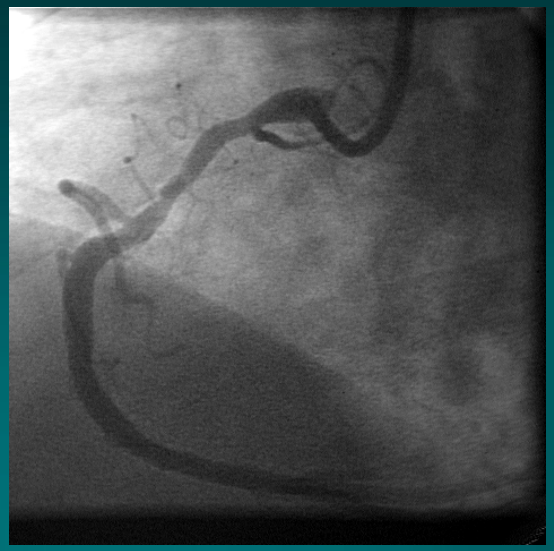
Proximal 0 → 3mm → 12mm



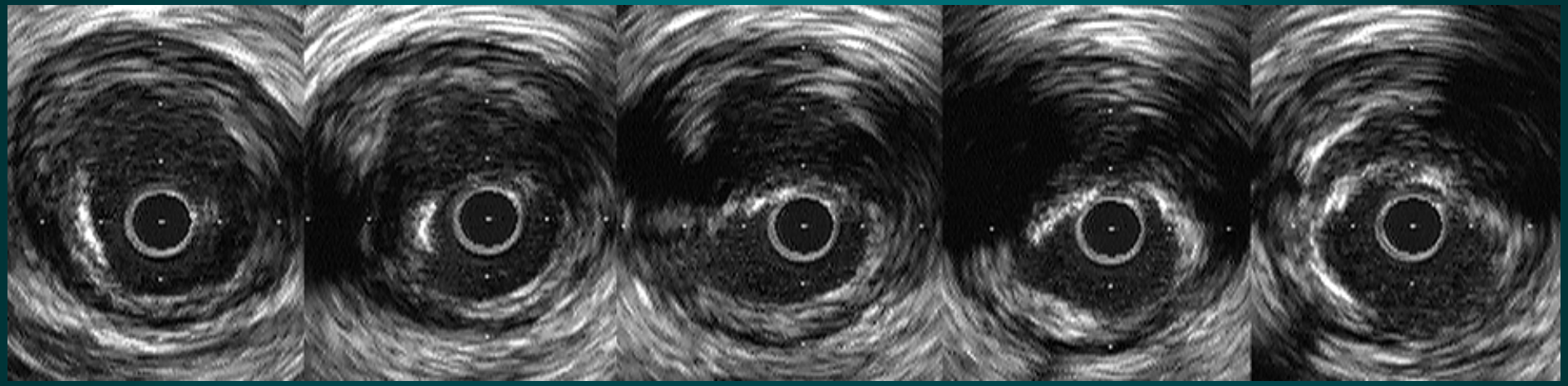
EEM CSA = 21.0mm^2
Lumen CSA = 9.5mm^2
P+M CSA = 11.5mm^2

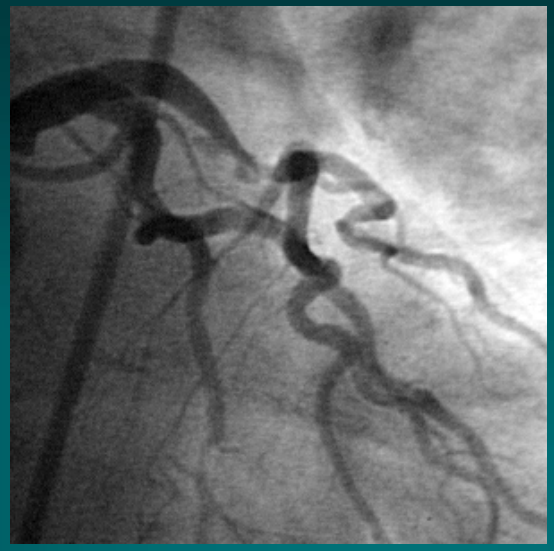
EEM CSA = 23.5mm^2
Lumen CSA = 5.5mm^2
P+M CSA = 18.0mm^2

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

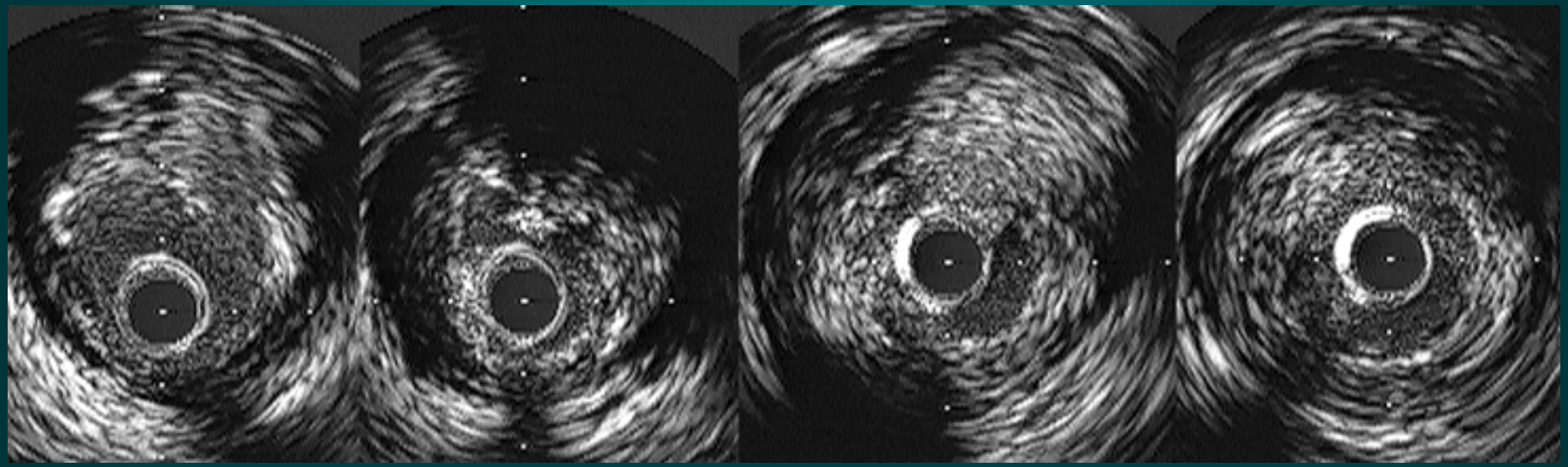


0 → 1mm → 4mm





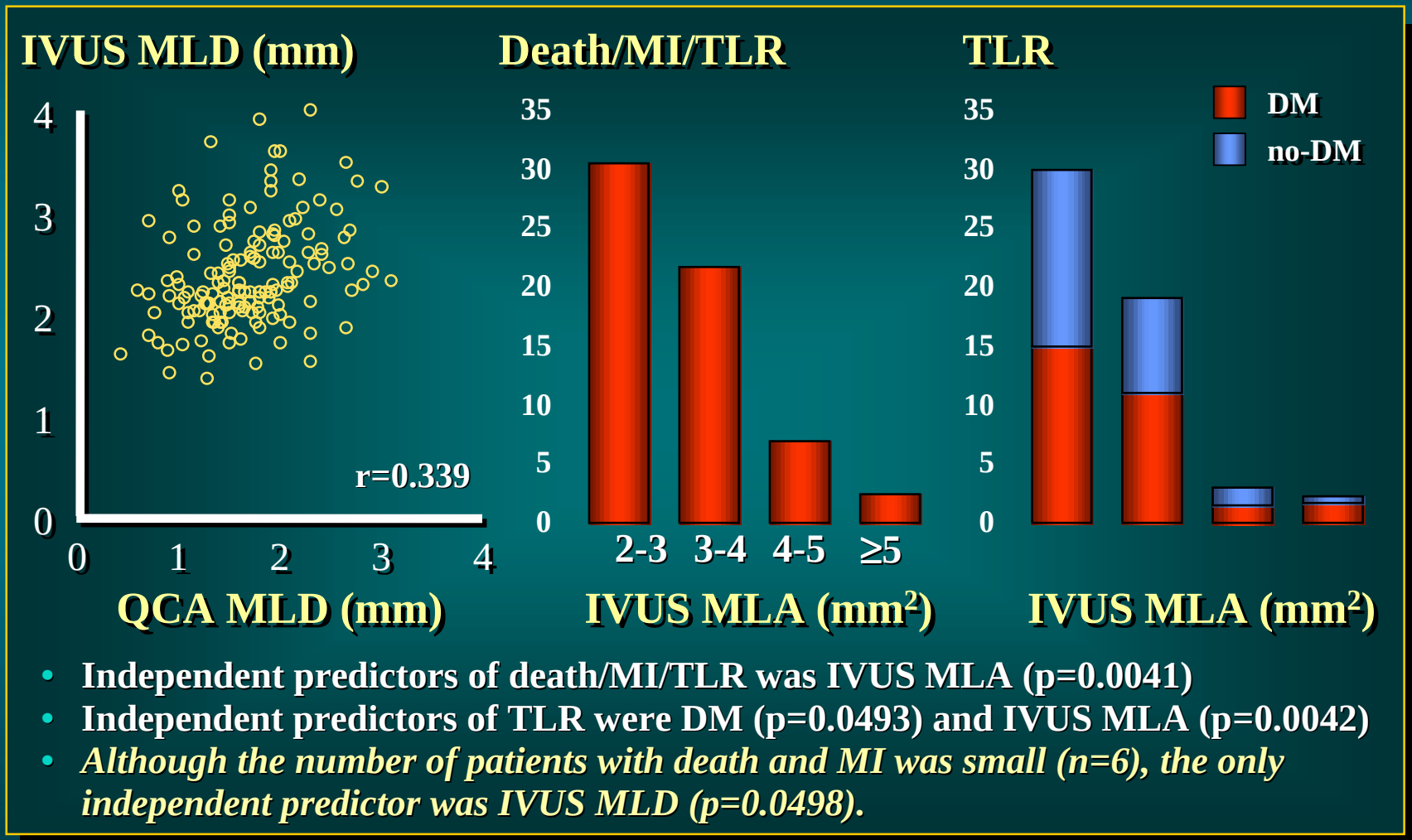
0 → 2mm → 6mm



Important IVUS Observations: *Lumen Compromise*

- What separates lesions with asymptomatic plaque rupture from plaque ruptures that cause acute symptoms?

Clinical Follow up in 357 intermediate lesions in 300 pts deferred intervention after IVUS imaging



- Independent predictors 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 and MI was small (n=6), the only independent predictor was IVUS MLD (p=0.0498).*

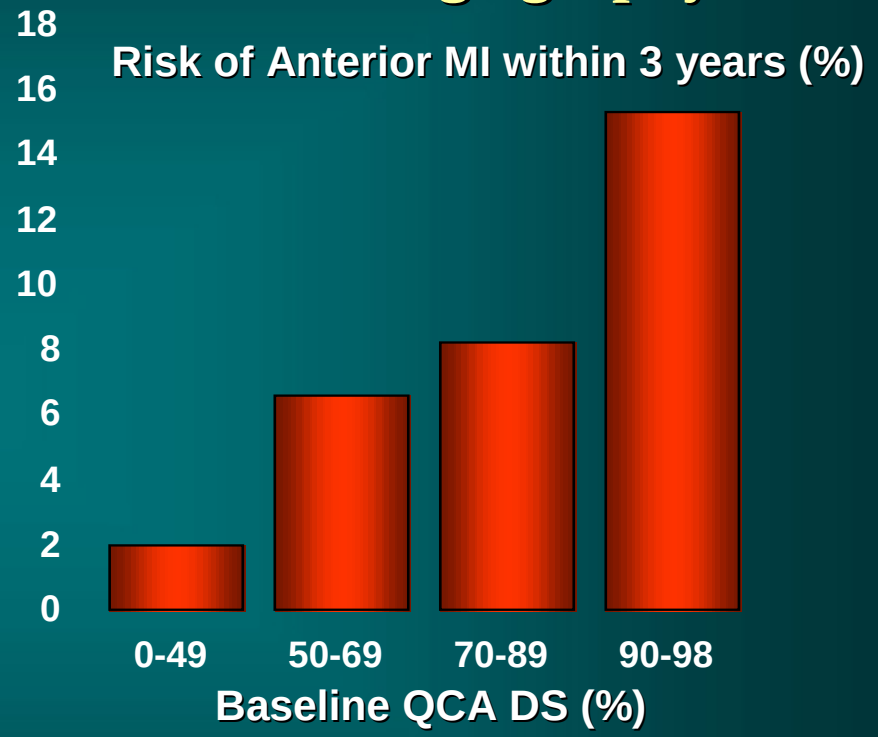
Risk of MI

42 Consecutive Pts with Angiography Both Before and After MI

- 29 patients had a newly occluded artery
  - In 19 pts, the artery previously had a <50% DS
  - In only 10 pts the occlusion was at the site of the most severe stenosis

Little et al. Circulation 1988;78:1157-66

118 Pts in CASS after Baseline Angiography

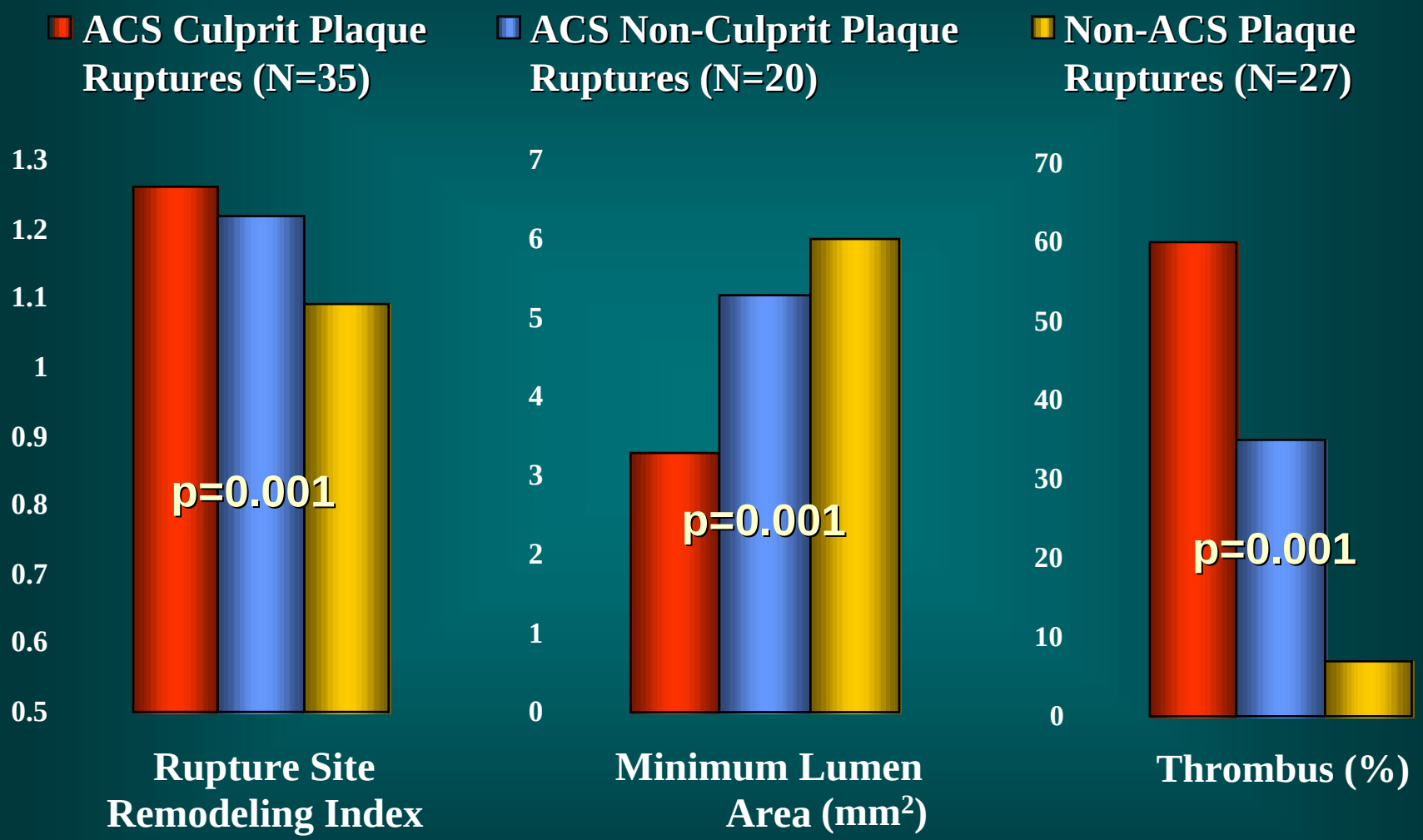


Ellis et al. J Am Coll Cardiol 1988;11:908-16

"Because the aggregate risk of rupture associated with many non-significant lesions (each with an admitedly lower individual risk potential) exceeds that of the fewer significant lesions, an MI will more likely originate from a nonsignificant lesion."

Kern and Meier. Circulation 2001;103:3142-9

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



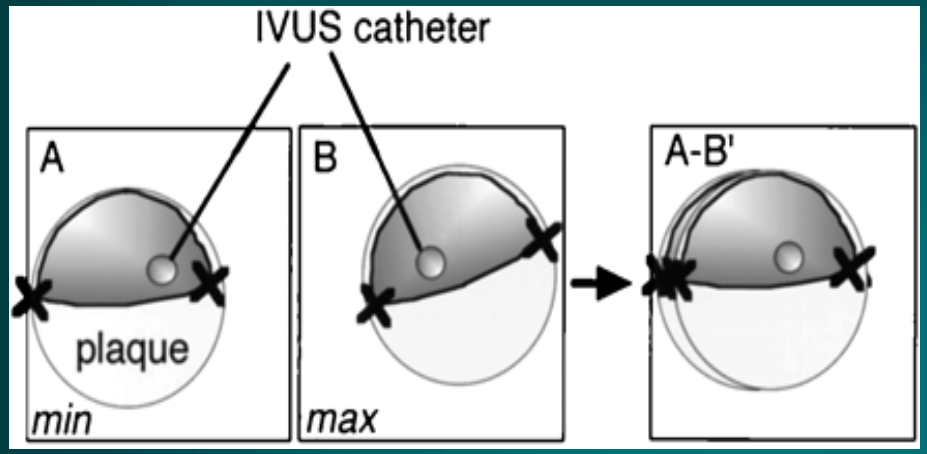
Independent predictors of ACS were MLA and thrombus (both p=0.01)

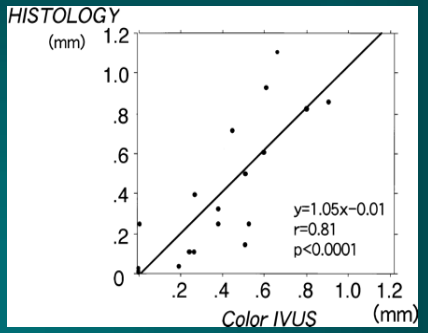
Fuji et al. Unpublished Observations

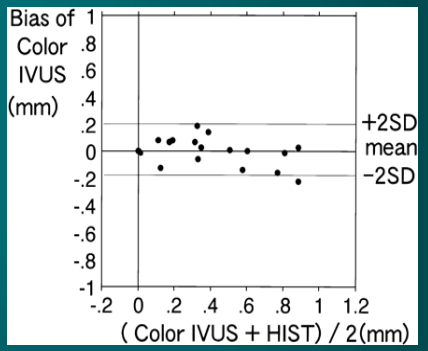
Limitations of IVUS

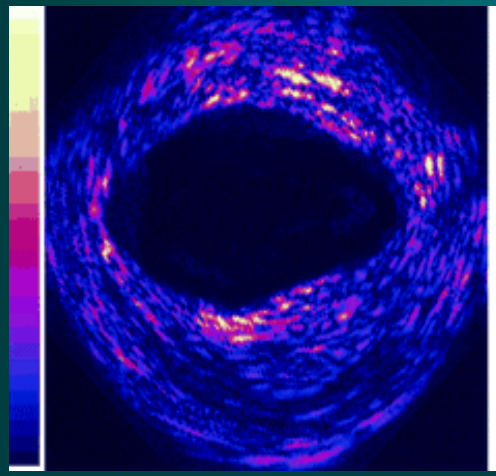
- **Measurement of fibrous cap**
  - ***Histologic studies suggest that the fibrous cap in vulnerable plaques measures <65 microns***
  - ***IVUS resolution is >100 microns***
- **Assessment of plaque composition**

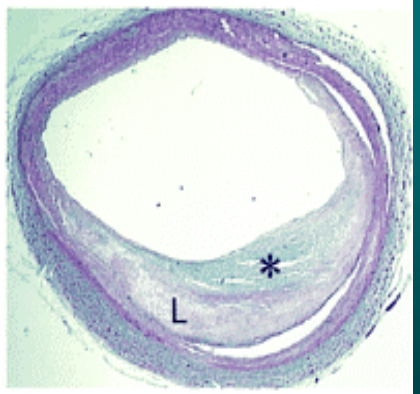
IVUS Can Measure Fibrous Cap Thickness In Vitro, but NOT *In Vivo*





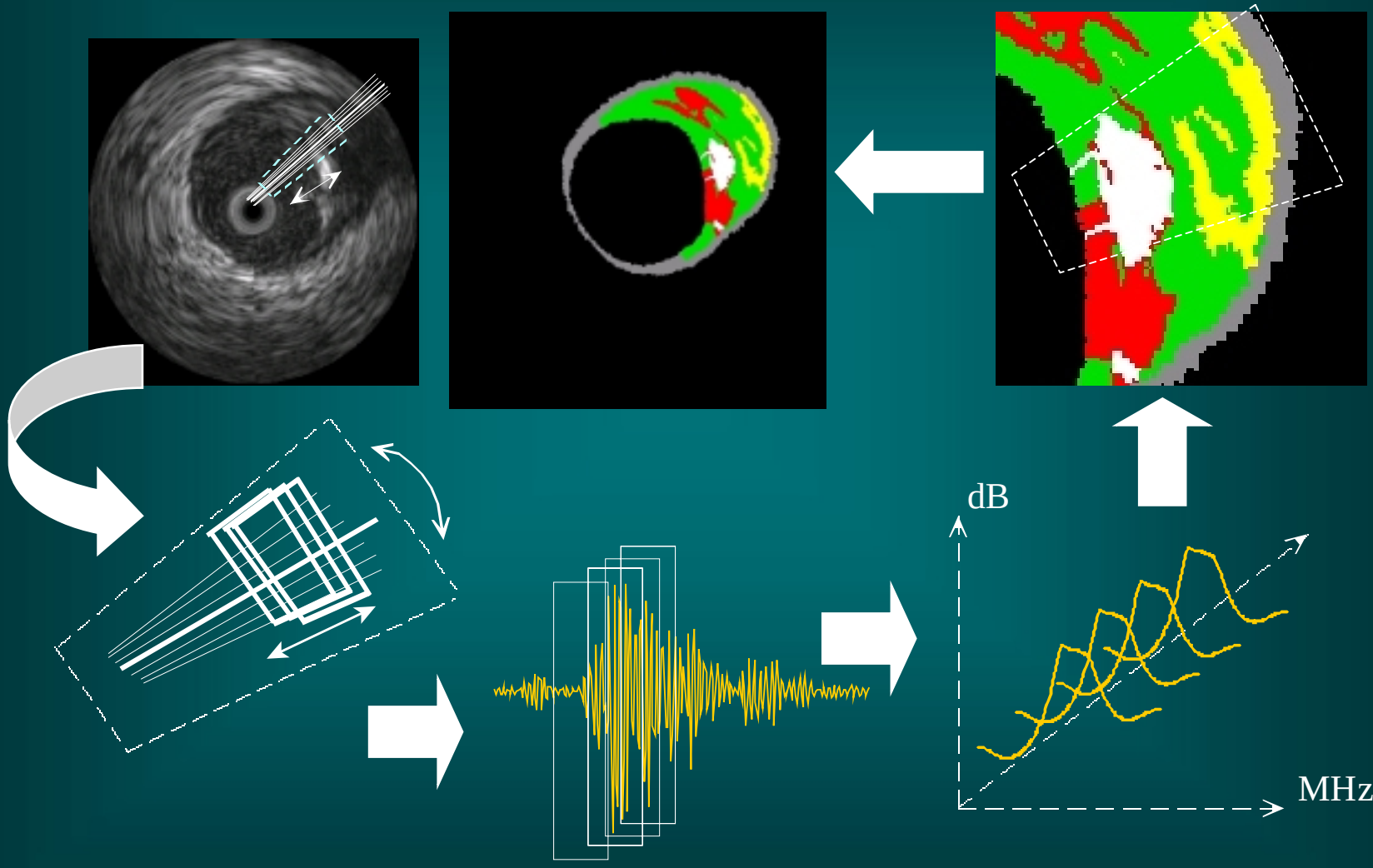






Hiro et al. Circulation 2001;103:1206-11

Virtual Histology™

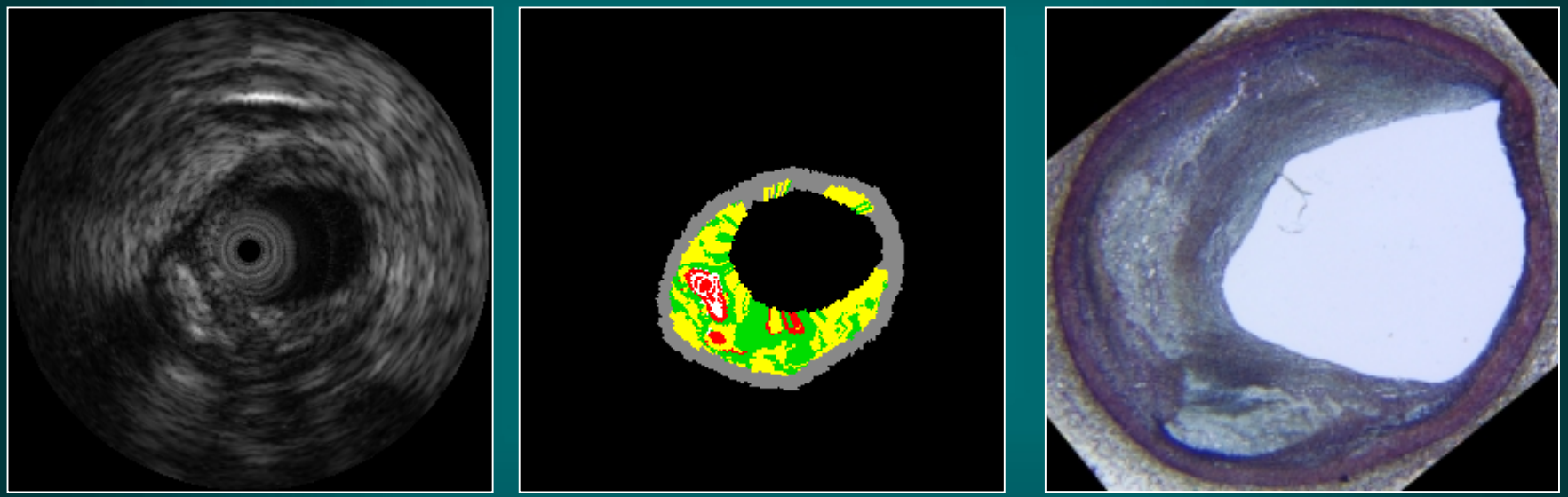


Fibrous, Fibrofatty, Lipidic-necrotic, Calcium

Predictive Accuracies of Training and Test Datasets

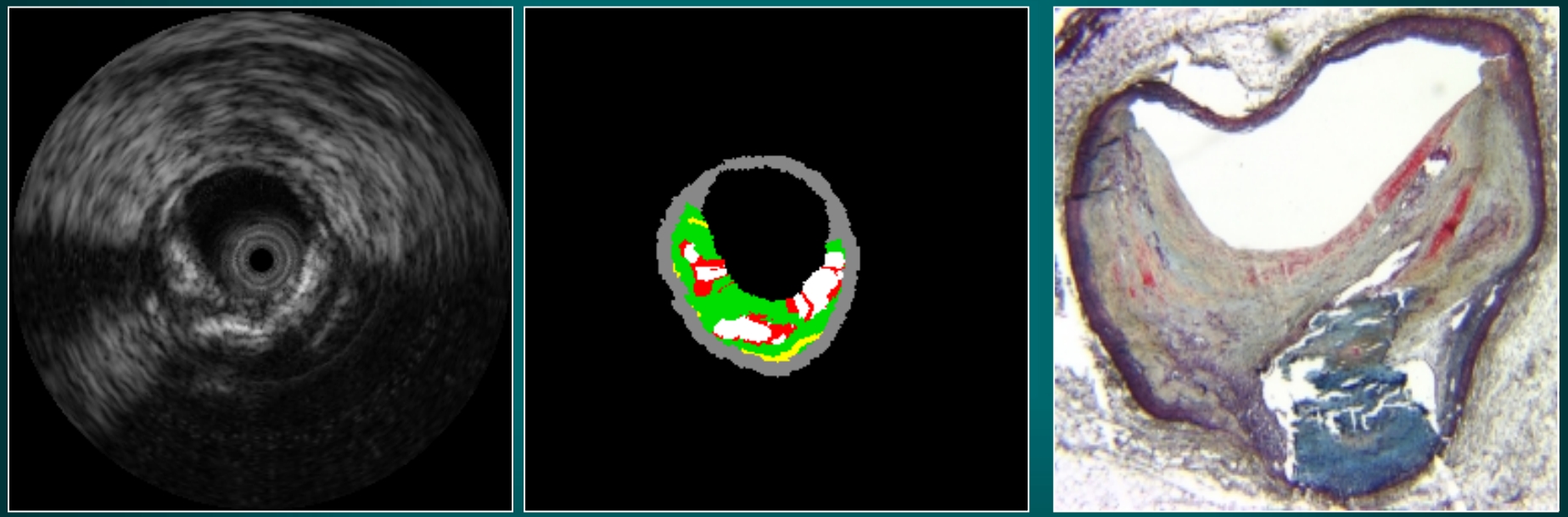
	Fibrous (n=101)		Fibro-Lipidic (n=56)		Calcified (n=50)		Lipidic-Necrotic (n=70)	
	Training	Test	Training	Test	Training	Test	Training	Test
FFT^2	90.4	69.6	92.3	81.2	92.8	82.6	90.9	71.0
Welch	88.9	66.7	92.3	76.8	91.8	86.5	82.6	72.5
AR	90.4	79.7	92.8	81.2	90.9	89.5	92.8	85.5

Ex-Vivo Validation Virtual Histology™



Fibrous, Fibro-lipidic, Lipidic-necrotic, Calcium

Ex-Vivo Validation Virtual Histology™



Fibrous, Fibro-lipidic, Lipidic-necrotic, Calcium

What about IVUS compared with other invasive diagnostic modalities?

	Structure	Plaque Composition	Fibrous Cap	Function	•Safe •Validated in vivo •Practical •Available
IVUS	+				+
IVUS+Virtual Histology	+	+			
OCT	+	+	+	+	
Thermography				+	
Palpography	+			+	

Conclusions

- Almost everything that we know about IVUS and vulnerable plaque has come from extrapolating studies of IVUS in ACS - *NOT from prospective correlative studies*
- Culprit lesions in ACS are, *in general,* characterized by
  - Positive remodeling
  - Hypoechoic, eccentric, ruptured plaques with evidence of thrombus
  - With a complex interaction between remodeling and plaque composition and instability in ACS.
- Positive remodeling
  - Prevents lumen compromise
  - "Paradoxically" may contribute to ACS and to MACE after PCI
  - May be less common in diabetics with ACS
- Negative remodeling
  - Contributes to lumen compromise
  - Probably can occur both early and late
- Calcium is a marker of plaque mass, not a determinant of instability

But. . .

- The relationship between ACS/MI, positive remodeling, "vulnerable" plaques, and ruptured plaques may not be so simple.
  - Frequency of an MI is related to the severity of the underlying stenosis
  - Not all pts with ACS/MI have positive remodeling
  - Not all pts with ACS/MI have plaque rupture
  - Not all ruptured plaques cause ACS/MI. In some pts plaque rupture is asymptomatic and may be followed by healing, negative remodeling, calcification, and disease progression. In other patients the development of a thrombus (superimposed on plaque rupture) decreased lumen dimensions and results in ACS/MI
- While the concept of using multiple complementary imaging techniques may seem attractive, any clinical approach must be practical and safe.