

# **In Search of the Vulnerable Plaque: Summary of Current Issues**

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CARDIOVASCULAR RESEARCH  
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COLUMBIA UNIVERSITY  
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# The Limits of Opening Arteries

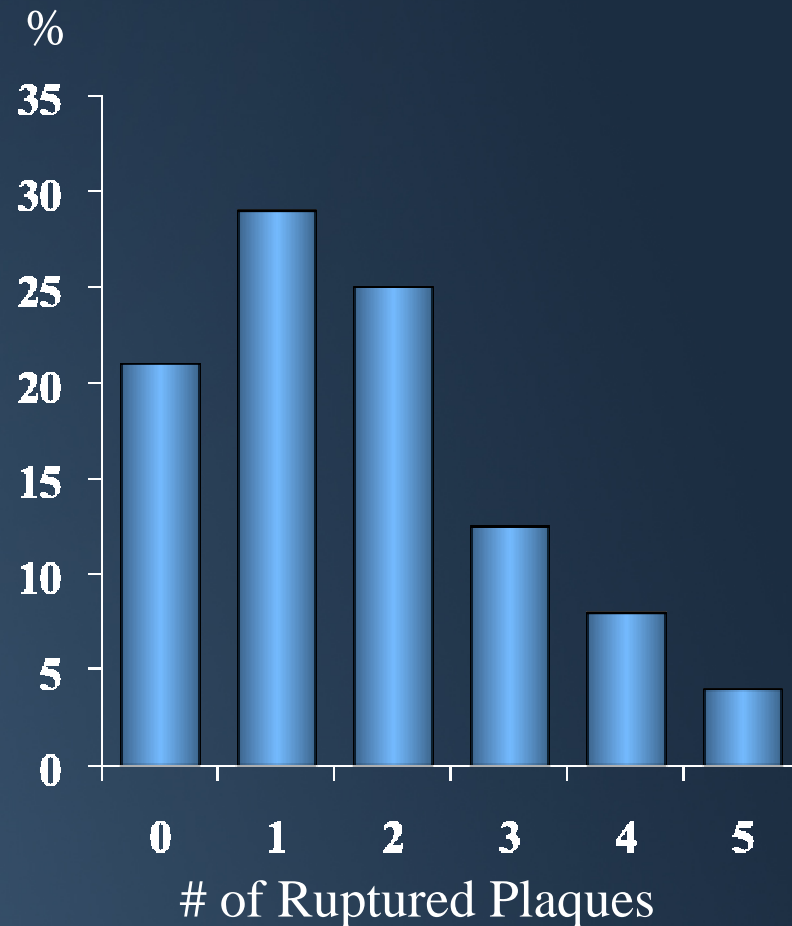
NYTimes March 28, 2004

- A changing notion of how heart attacks occur ought to lower expectations for the traditional methods used to prevent arteries from clogging shut. It has long been customary for cardiologists to treat narrowing arteries by either enlarging and holding open the restricted channel or performing bypass surgery to carry blood around the narrowed section. The problem is, the vast majority of heart attacks are now known to originate in sections of artery that have not yet narrowed.
- As described in an article by Gina Kolata in last Sunday's Times, the old view of the progression of cardiovascular disease held that fatty deposits, or plaques, accumulate in the arteries slowly over decades, much as sludge builds up in a pipe, until one day the opening becomes so narrow that no blood can get through, and the patient suffers a heart attack. The newer view, which has taken hold in recent years but is little known to the public, is that heart attacks occur when an area of plaque ruptures and causes a blood clot to form, abruptly blocking the flow. In perhaps 75 to 80 percent of these cases, the plaque was not obstructing an artery, would not have been treated or bypassed and produced no symptoms.
- Experts agree that artery-opening methods -- like bypass surgery, or insertion of a balloon to mash down plaque and a wire-cage stent to keep the channel open -- can alleviate crushing chest pain and save some lives. But patients should not assume that their cardiovascular problems are "fixed" by such procedures, and patients without symptoms whose arteries are narrowing should be wary about undergoing these procedures to ward off a potential heart attack. **They may have hundreds of vulnerable plaques elsewhere that are more apt to burst and trigger a heart attack than are the more stable plaques in the narrow section. Most such patients might better be treated with drugs to lower their cholesterol levels, control their blood pressure and prevent blood clots, or should adopt a healthier life style by giving up smoking, eating heart-healthy foods and exercising.**
- This profound change in thinking about cardiovascular problems makes us yearn for the day when there can be much wider testing of one therapy against another to identify those that work best from those that may be oversold.



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

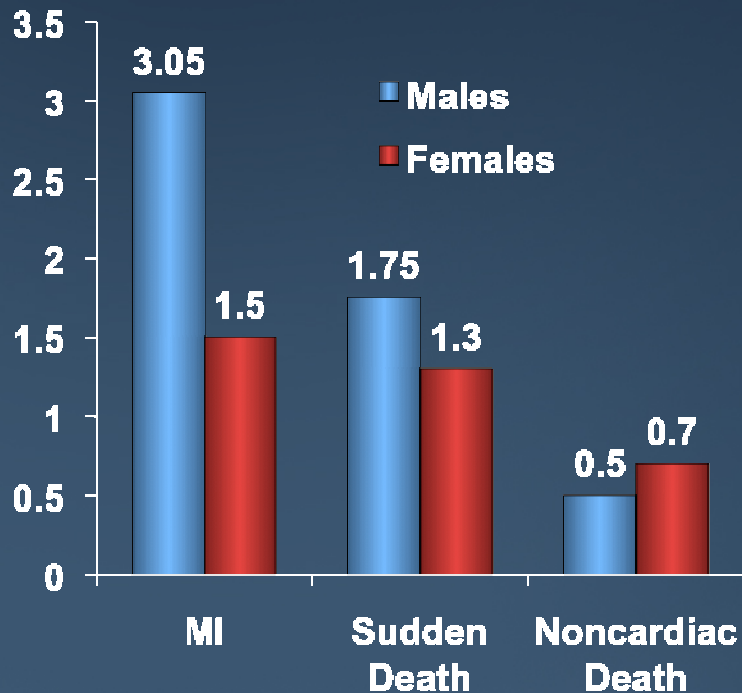
- 50 ruptured plaques
  - 9 culprit lesion
  - 41 nonculprit lesion
- 19 pts had at least 1 nonculprit plaque rupture (79%)
  - 17 pts had 1 plaque rupture in a second artery
  - 3 pts had plaque ruptures in all 3 arteries





# Number of thin-cap fibroatheromas in patients dying with MI, sudden death, or noncardiac causes and studied at necropsy

## Cross-sectional analysis

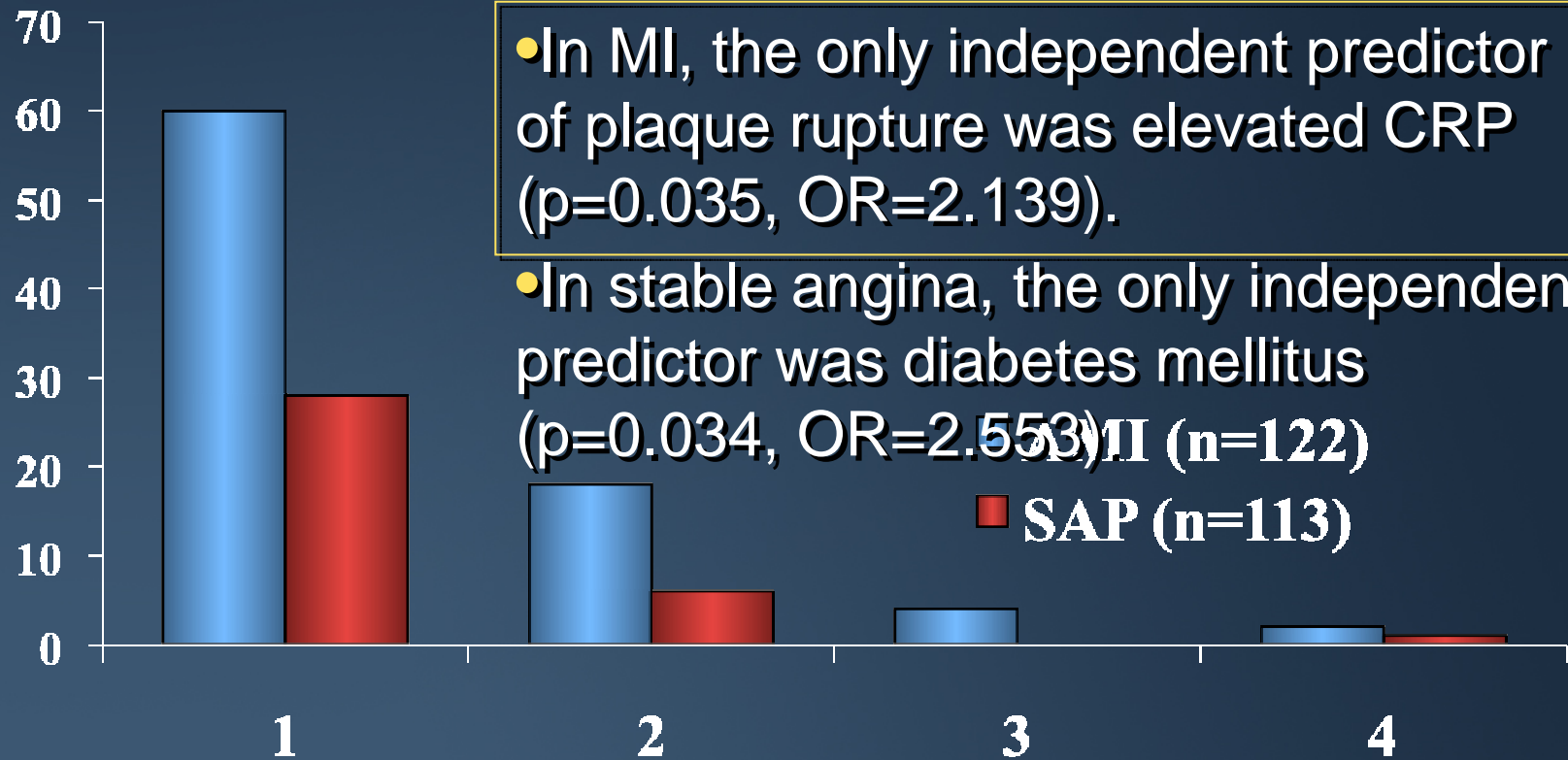


## Longitudinal analysis

	All pts	Pts with $\geq 1$ ruptured plaque	Pts with $\geq 1$ TCFA or ruptured plaque	Pts with CV death
# of patients	50	14	20	33
# of ruptured plaques (0.38/pt)	19 (0.38/pt)		19 (0.95/pt)	15 (0.45/pt)
# fibroatheromas	193			
# TCFAs (0.46/pt)	23 (0.46/pt)	15 (1.21/pt)	23 (1.15/pt)	18 (0.55/pt)

# Ruptured plaques in patients with MI and stable angina

% of patients



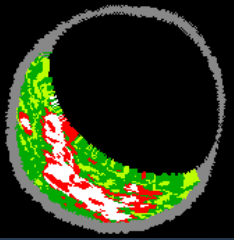
- In MI, the only independent predictor of plaque rupture was elevated CRP ( $p=0.035$ ,  $OR=2.139$ ).

- In stable angina, the only independent predictor was diabetes mellitus ( $p=0.034$ ,  $OR=2.553$ ).

■ MI (n=122)  
■ SAP (n=113)

Number of ruptured plaques per patient





# PROSPECT: Imaging Summary

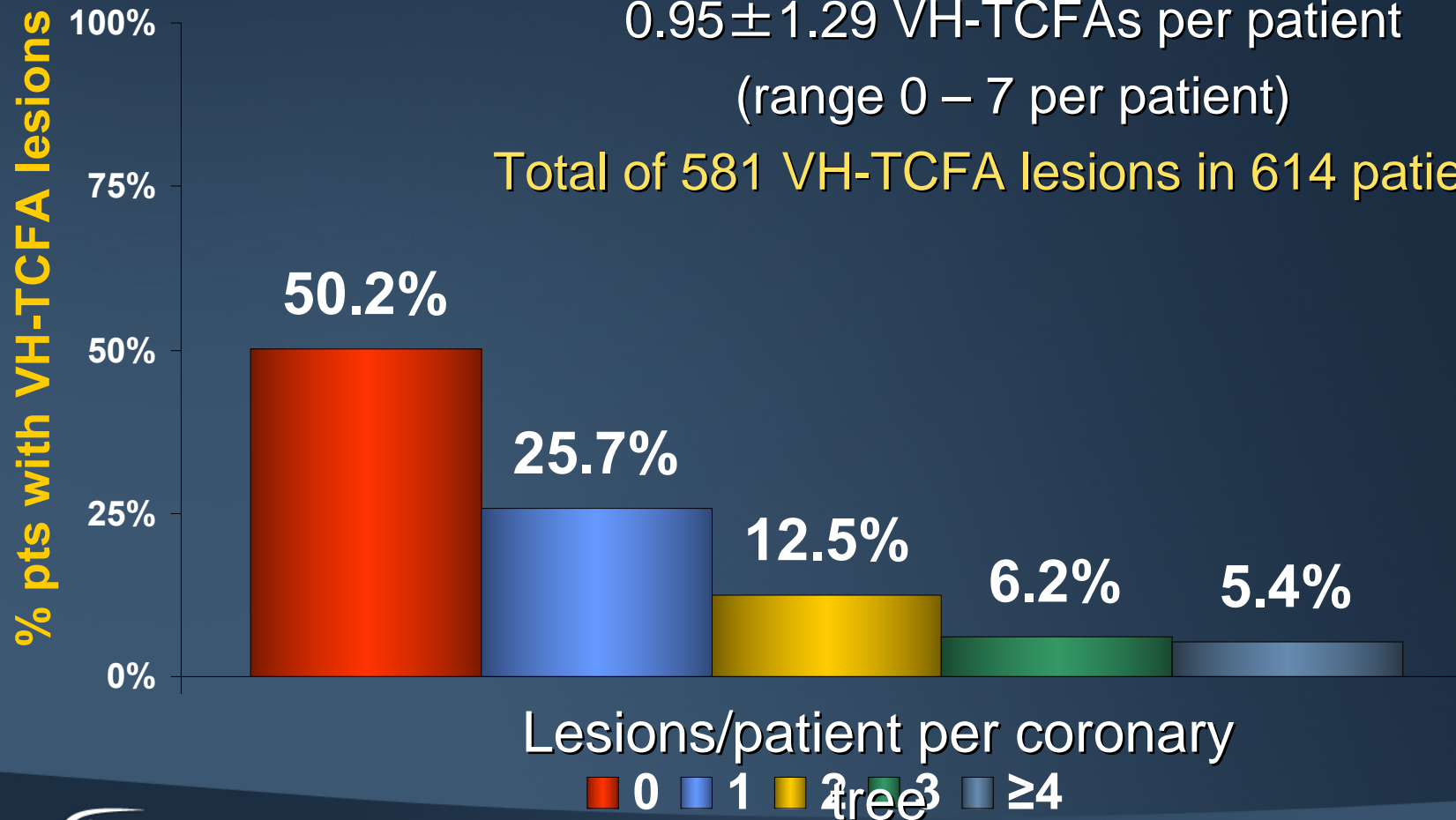
Per patient incidence of VH-TCFAs

49.8% of patients have  $\geq 1$  VH-TCFA

$0.95 \pm 1.29$  VH-TCFAs per patient

(range 0 – 7 per patient)

Total of 581 VH-TCFA lesions in 614 patients



# Location of 82 TCFAs in 34 patients with AMI and 17 patients with stable angina and three vessel OCT

In 34 AMI patients, there were 50 TCFAs (1.5/patient), 16 in the infarct related artery and 34 in the non-infarct related artery

Length of artery imaged beginning at the coronary ostium (mm)

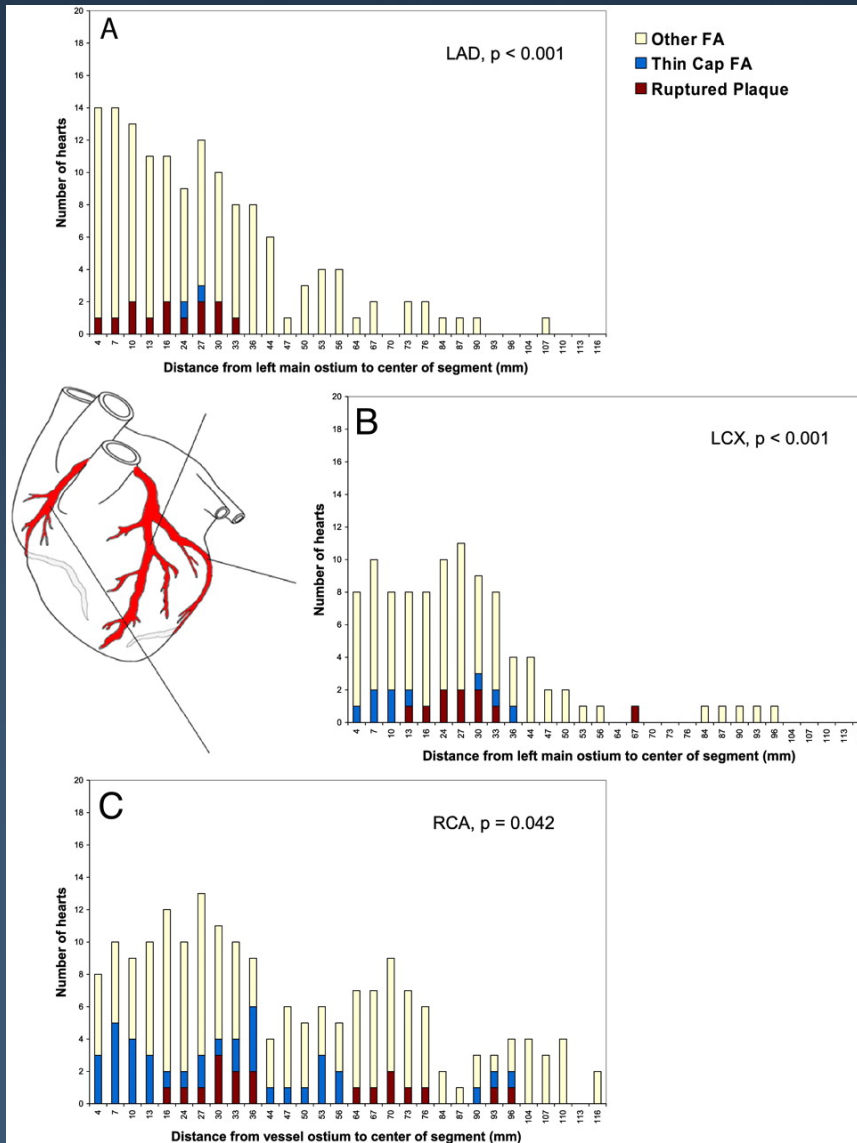
LAD	72±24mm
LCX	56±30mm
RCA	97±31mm

# Vulnerable plaque locations are predictable





# Pathology spatial Distribution of Advanced Coronary Lesions

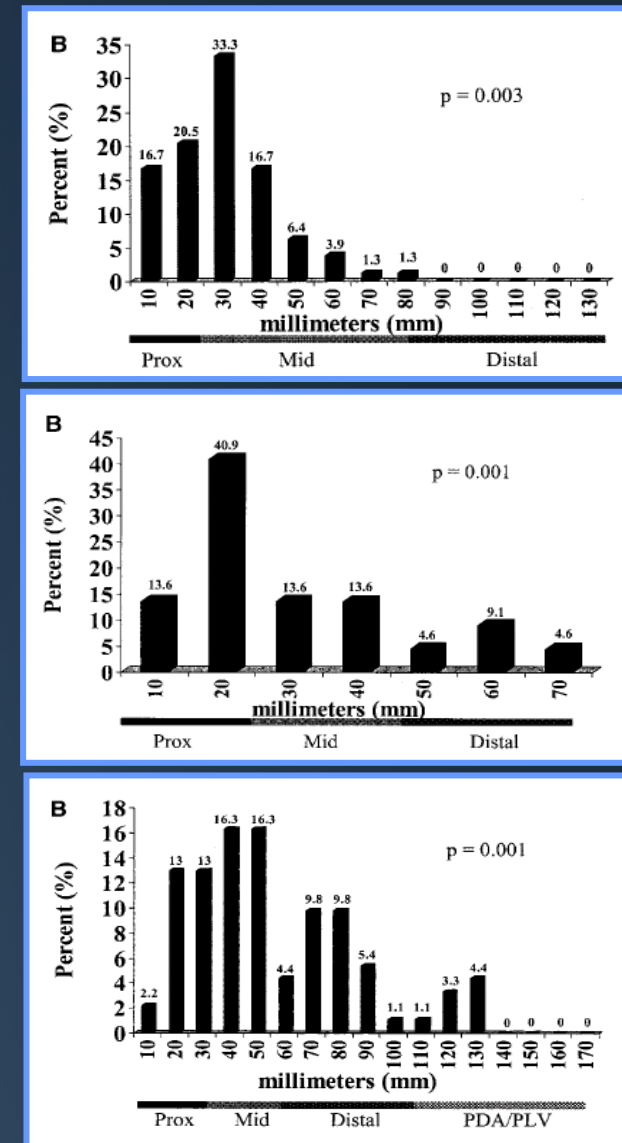


LAD

LCX

RCA

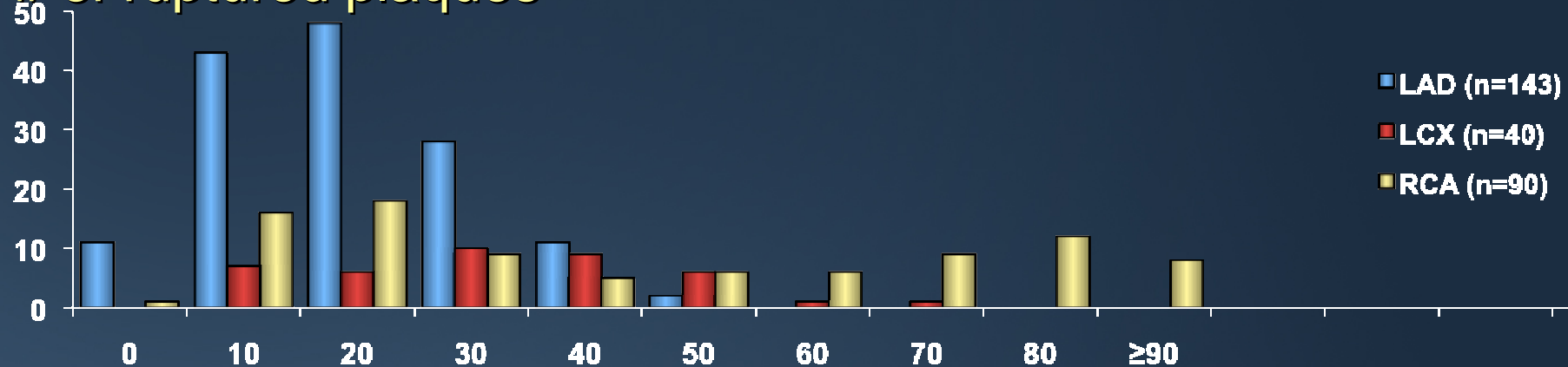
# Angiographic location of acute coronary occlusions



(Cheruvu et al. J Am Coll Cardiol 2007;50:940-9)  
 (Wang et al. Circulation 2004;110:278-84)

# Location of 273 ruptured plaques in 158 pts with ACS and 48 pts with stable angina and 3-vessel IVUS

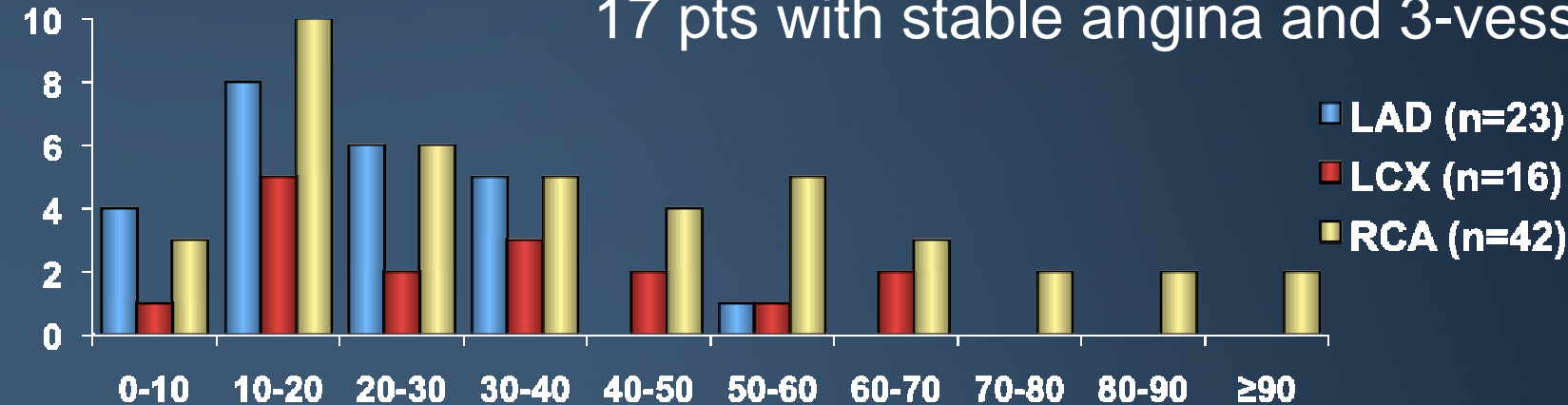
# of ruptured plaques



Distance from coronary ostium (mm)

Location of 82 TCFAs in 34 pts with AMI and 17 pts with stable angina and 3-vessel OCT

# of TCFAs

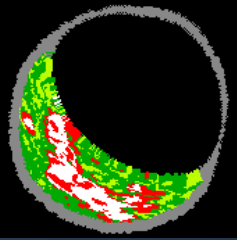


Distance from coronary ostium (mm)

(Hong et al J Am Coll Card 2005;46:261-5)  
(Fujii et al J Am Coll Cardiol. 2008;52:787-8)

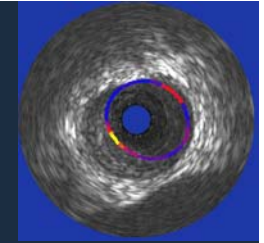
**Are all non-culprit events in the first year post-PCI related to vulnerable plaques? Or are some related to incomplete revascularization at the time of initial PCI?**





# PROSPECT: Imaging Summary

## IVUS of angiographic non-culprit lesions



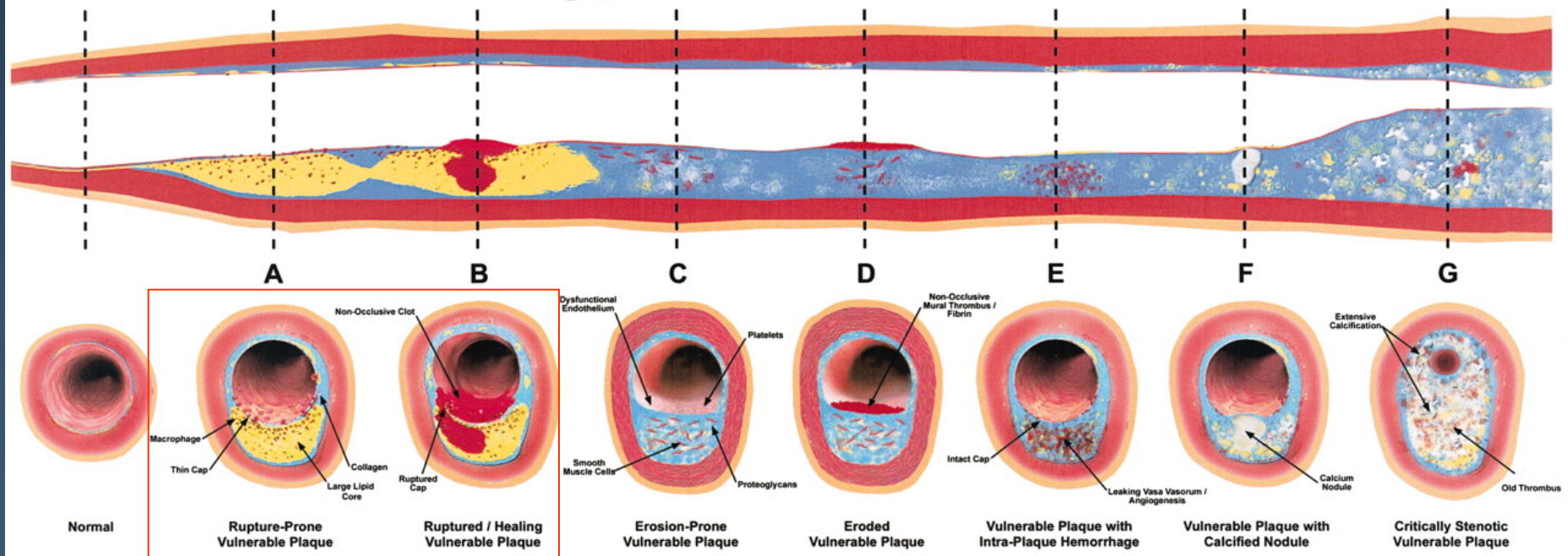
By IVUS (in 786 of the 1798 total angiographic lesions)

<b>EEM area, mm<sup>2</sup></b>	16.72 ± 6.36	<b>MLD, mm</b>	2.82 ± 0.64
<b>Lumen area, mm<sup>2</sup></b>	8.89 ± 4.12	<b>Mean LD, mm</b>	3.26 ± 0.72
<b>Plaque area, mm<sup>2</sup></b>	7.83 ± 4.12	<b>Mean VD, mm</b>	4.04 ± 0.88
210 (26.7%) angiographically mild lesions had an MLA <4.0 mm <sup>2</sup>			
<b>Plaque burden %</b>	47 ± 11	<b>Mean VD, mm</b>	4.45 ± 0.87
<b>MLA, mm<sup>2</sup></b>	6.36 ± 3.75	<b>Max VD, mm</b>	4.90 ± 1.02
<b>Remodeling index</b>	0.94 ± 0.16	<b>Lumen ecc.</b>	0.93 ± 0.70



# Are all vulnerable plaques thin-cap fibroatheromas?

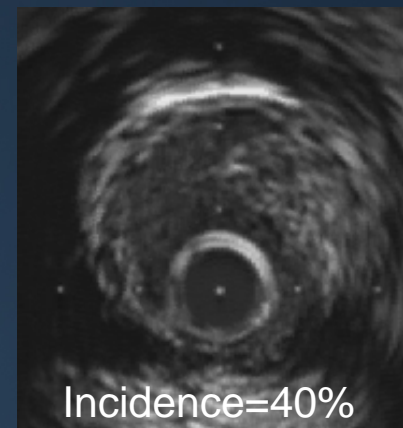
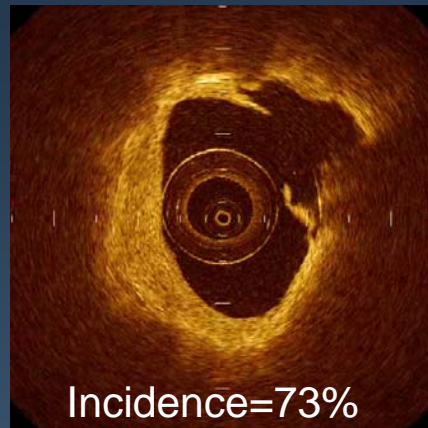
## Different Types of Vulnerable Plaque



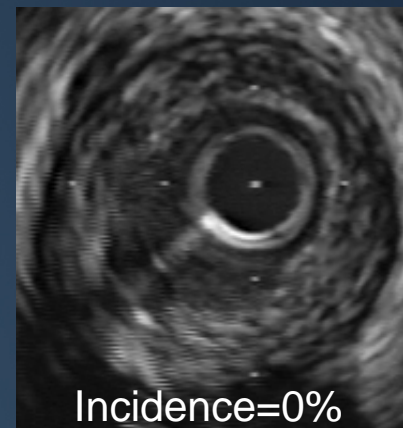
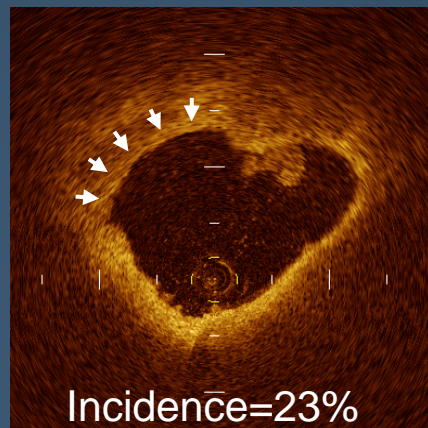
←→  
70% of ACS  
culprit lesions

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

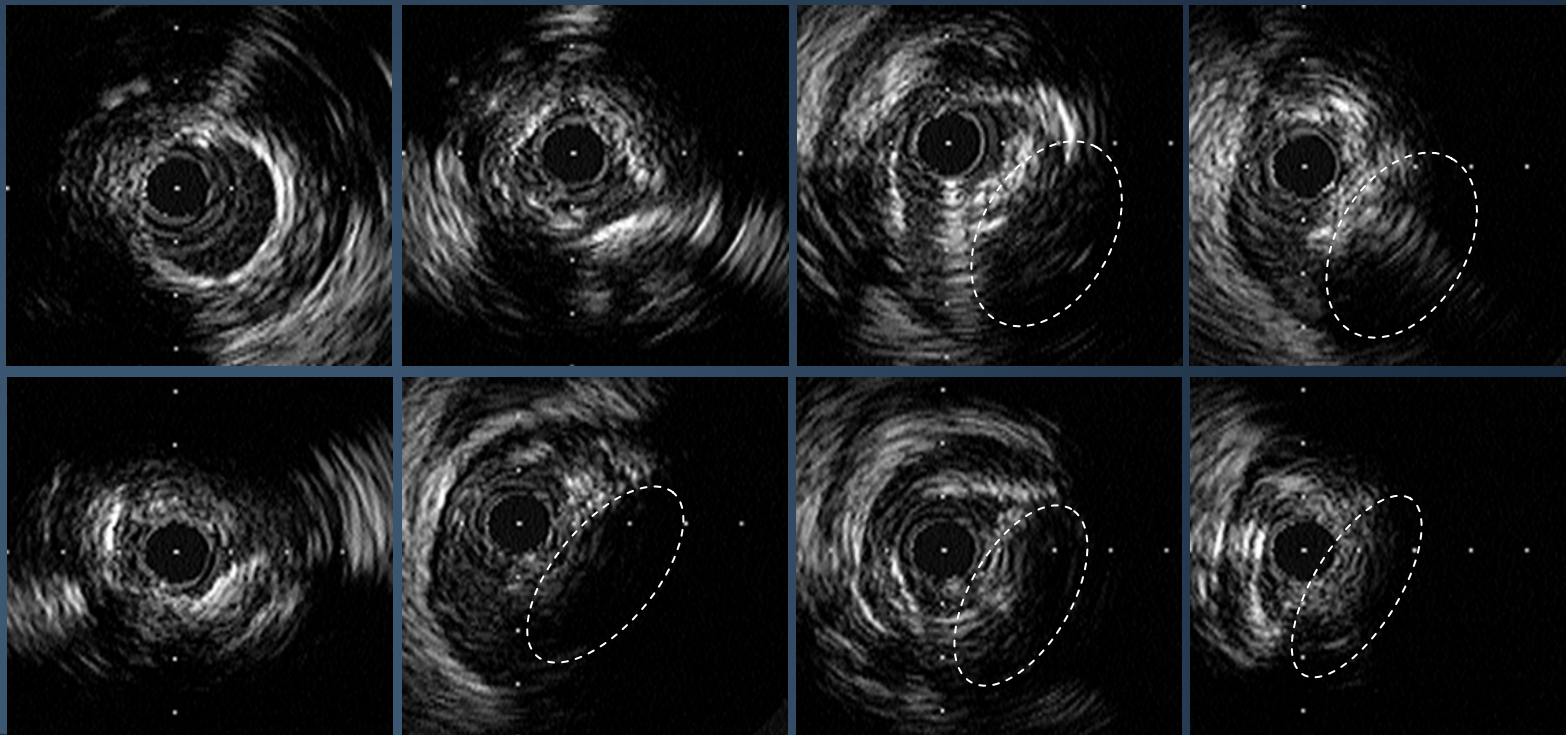
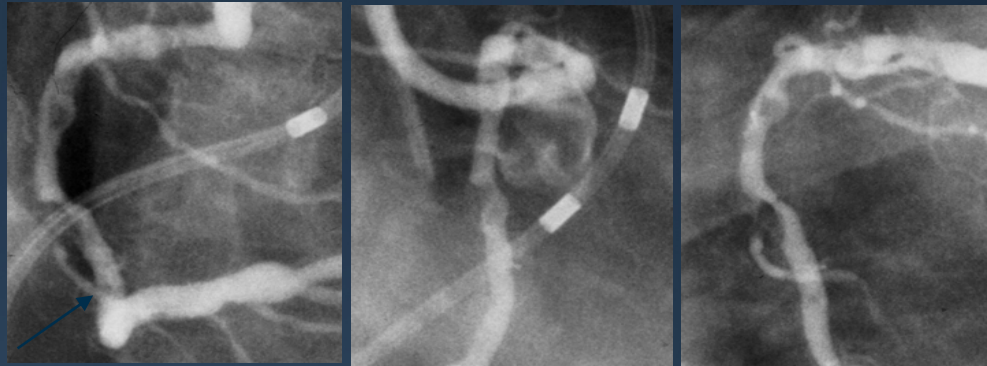
## Plaque rupture



## Plaque erosion





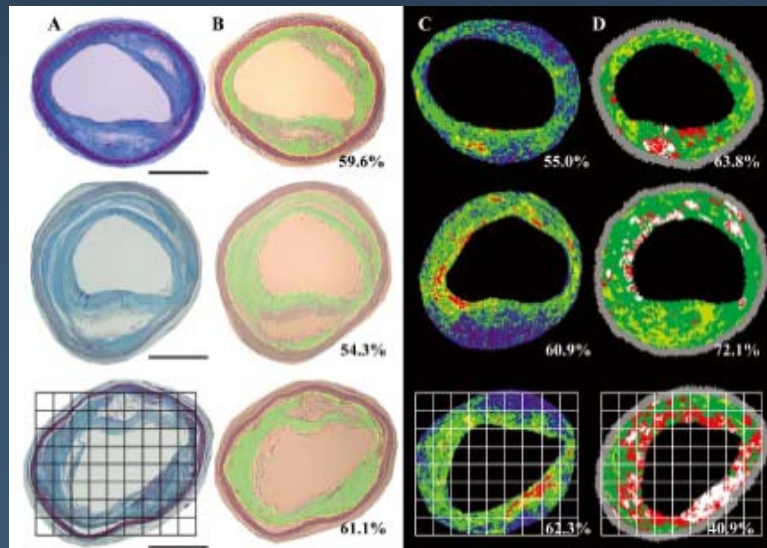


**Do all of the new intravascular imaging modalities agree when diagnosing a TCFA?**





# In vitro comparison of IB-IVUS With VH-IVUS in 392 histologic sections from 46 coronary arteries



- In the direct qualitative comparison, the overall agreement between the histological and IB-IVUS diagnoses was higher (Cohen's  $\kappa = 0.81$ , 95% CI: 0.72–0.89) than between the histological and IVUS-VH diagnoses (Cohen's  $\kappa = 0.30$ , 95% CI: 0.14–0.41) (Table 2).
- Although the location of each tissue component depicted by IVUS-VH did not always accurately reflect the histological location, the overall agreement of IVUS-VH in the “quantitative” comparison (0.73) was better than that in the “qualitative” comparison (0.66), whereas the IB-IVUS values were similar (0.83 and 0.81).

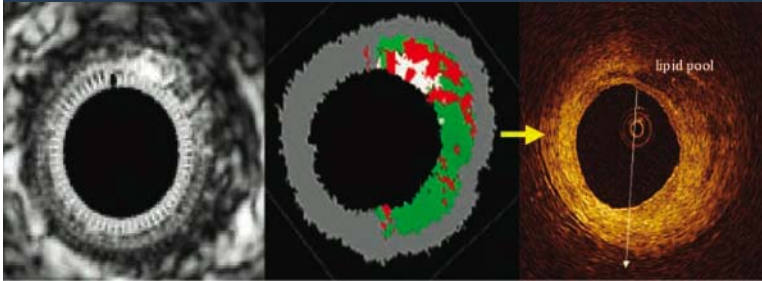
# VH-IVUS vs Palpography (N=27 patients, 60 high strain spots, and 63 low strain spots)

- Weak inverse correlation between %dense calcium and strain level ( $r=-0.20$ ,  $p=0.03$ )
- No significant correlation between %necrotic core ( $r=0.11$ ,  $p=0.25$ ) or fibrotic or fibrofatty plaque vs strain level
- Strain was higher when necrotic core was in contact with the lumen ( $1.03 \pm 0.5\%$  vs  $0.86 \pm 0.4\%$ ,  $p=0.06$ )
- Necrotic core in contact with the lumen was the only independent predictor of high strain (OR=5.0,  $p=0.003$ )
- Sensitivity of VH-IVUS 75% and specificity 44% to detect regions of high strain.

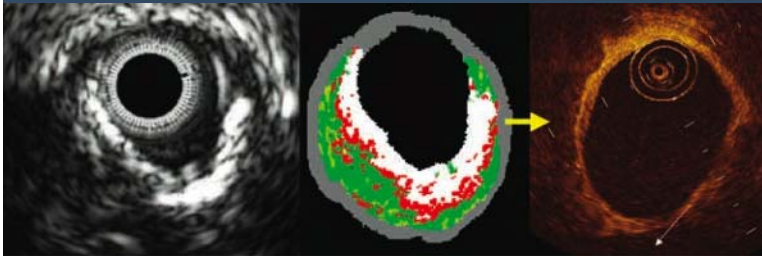
Perhaps vulnerable plaques are identified by concordance between structure and function

# OCT vs VH-IVUS TCFA diagnosis in 126 lesions in 56 pts

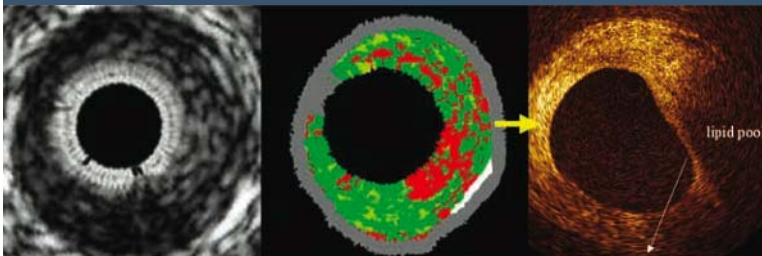
VH-IVUS (+) and OCT (-)



VH-IVUS (-) and OCT (+)



VH-IVUS (+) and OCT (+)



OCT

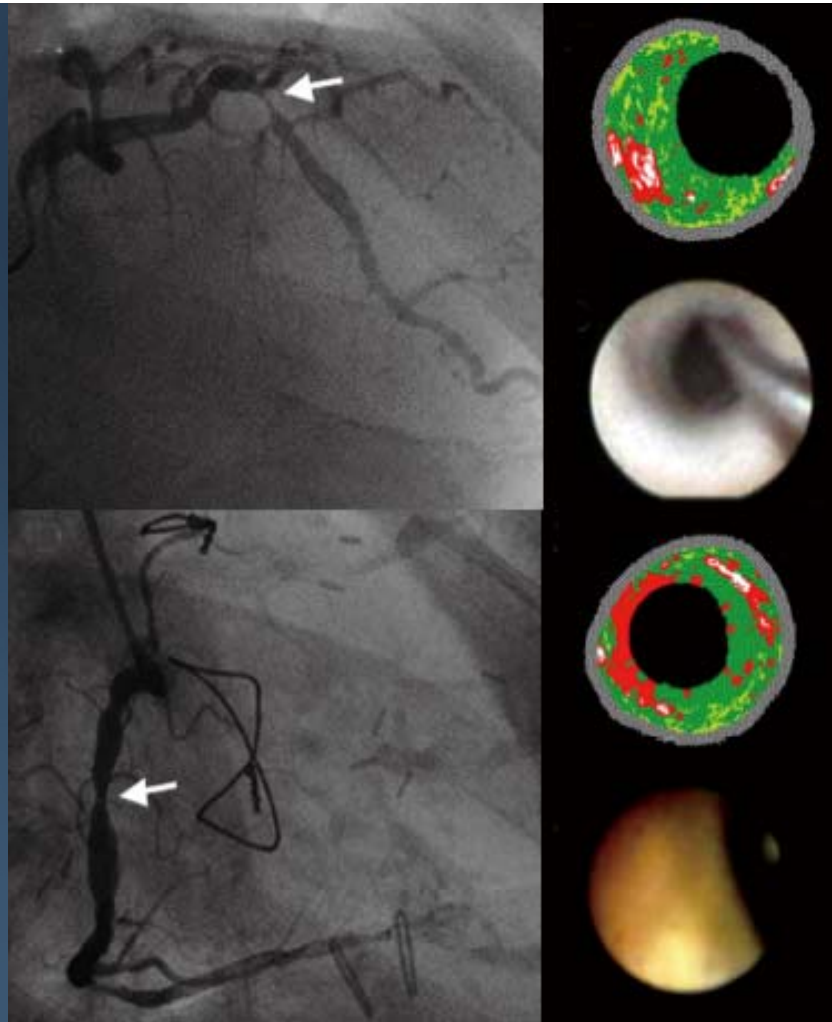
VH-IVUS

	+	-
+	28 (22%)	33 (26%)
-	8 (6%)	57 (46%)





# Angioscopy vs VH-IVUS TCFA diagnosis in 57 culprit lesions in 57 pts



## Angioscopy

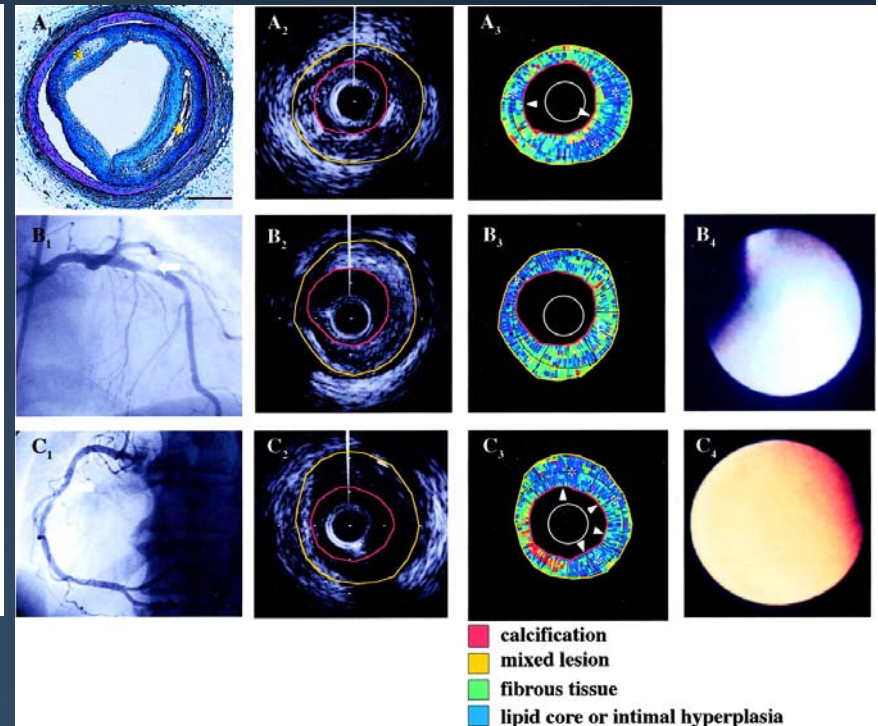
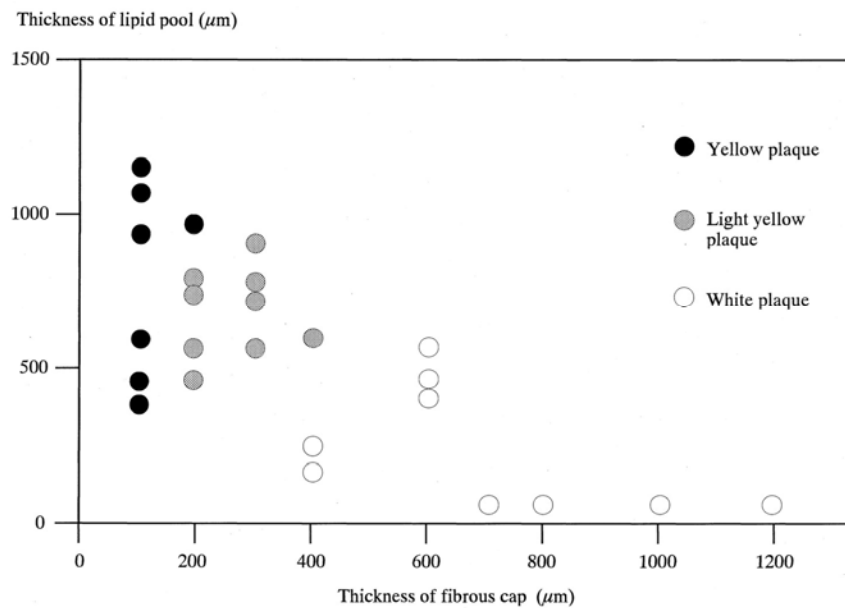
VH-IVUS

	+	-
+	17	8
-	6	26

When TCFA detected with angioscopy was used as the gold standard, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for was 68%, 81%, 74%, 76%, and 75%, respectively.



# Relation between IB-IVUS thickness of fibrous cap, thickness of lipid core, and angioscopic appearance: Angioscopic plaque color reflects thickness of fibrous cap rather than size of lipid core



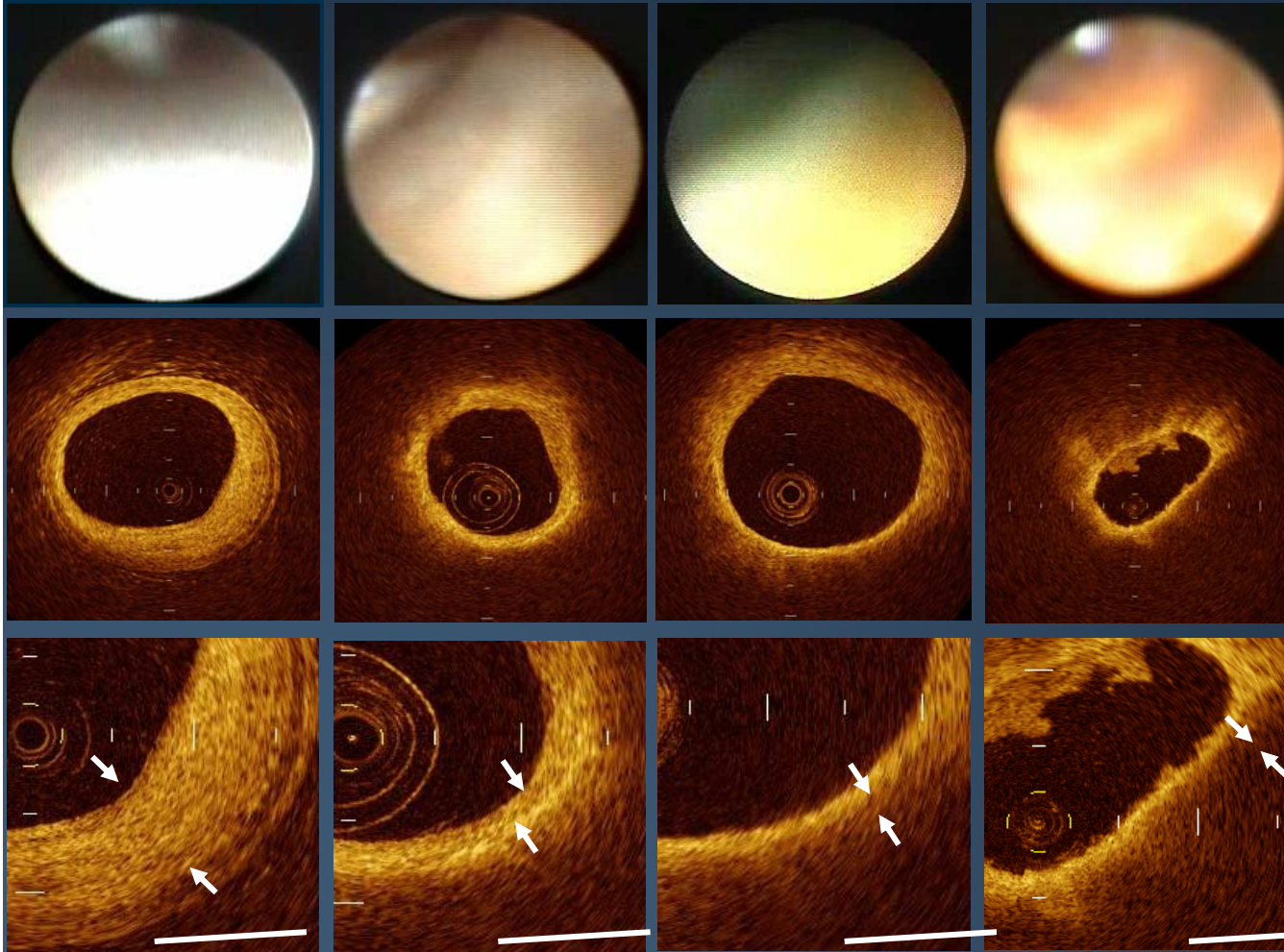
# OCT vs Angioscopy Assessment of Plaque Vulnerability (n=30)

White

Light Yellow

Yellow

Intense Yellow



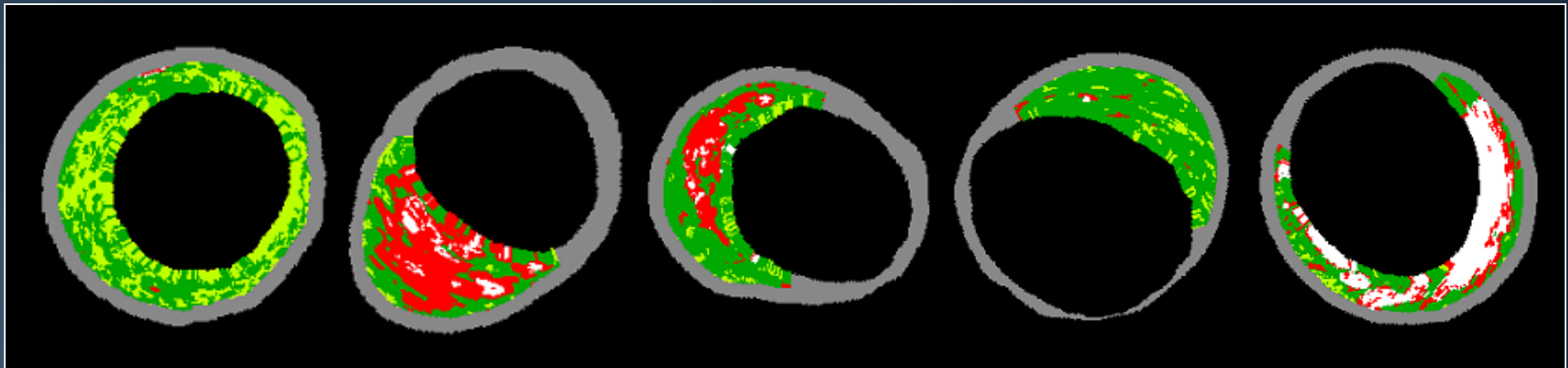
Angioscopic lesion color depends on fibrous cap thickness, not on the amount of lipid

- **Who should be studied?**
  - **All patients?**
  - **High risk patients?**
  - **Primary vs secondary prevention?**
  - **All arteries or just the PCI artery?**
- **What is the risk of multivessel invasive imaging?**
- **What is the cost?**
- **What is the impact of modern medical therapy: ASA, clopidogrel, statin?**
- **What is the temporal stability of TCFAs**
  - **How quickly do they form?**
  - **How often do they heal spontaneously?**
  - **How often do they rupture without causing events?**





# Change in non-culprit lesion phenotype in 106 patients (201 lesions) with plaque burden >40% from the Global VH Registry with baseline and 8-month follow-up VH analysis



Pathological  
intimal  
thickening  
(PIT)

Thin-cap  
fibroatherom  
a (TCFA)

Thick-cap  
fibroatherom  
a (ThFA)

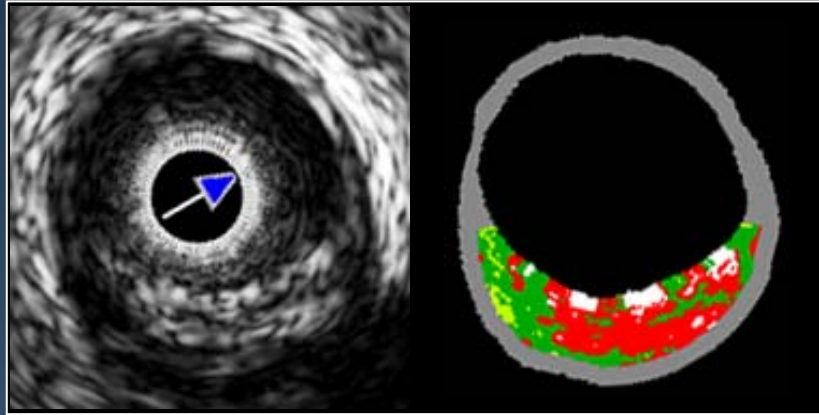
Fibrotic

Fibrocalcifi

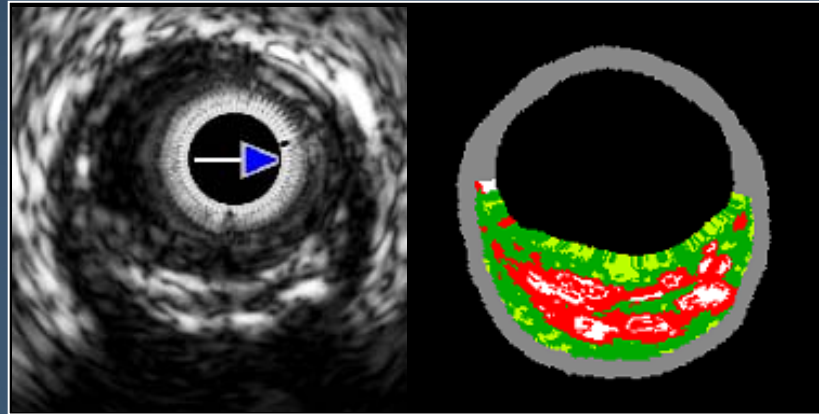
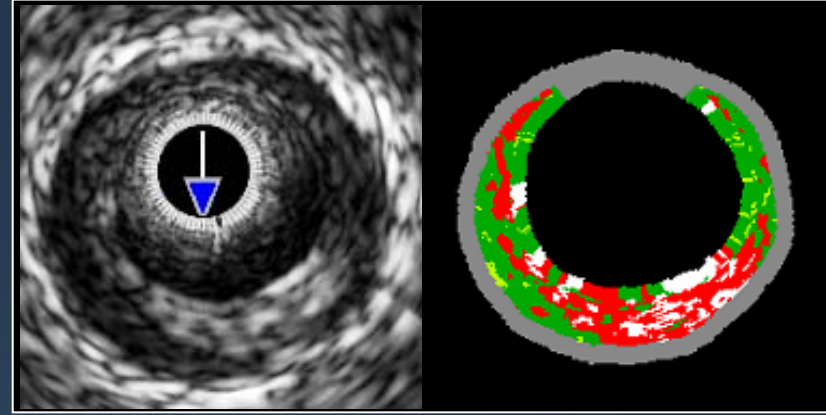


- **During follow-up. . .**
  - **75% of TCFAs healed and 25% remained unchanged although the location of the necrotic core in contact with the lumen shifted axially.**
- **Compared to TCFAs that healed, TCFAs that did not change were more proximal in location and had larger lumen area, vessel area, plaque area, calcium area, and necrotic core area.**
- **12 new TCFAs were noted**
  - **6 late-developing TCFAs were PIT and 6 were ThFA at baseline.**
- **No fibrotic or fibrocalcific plaques evolved into a TCFA.**

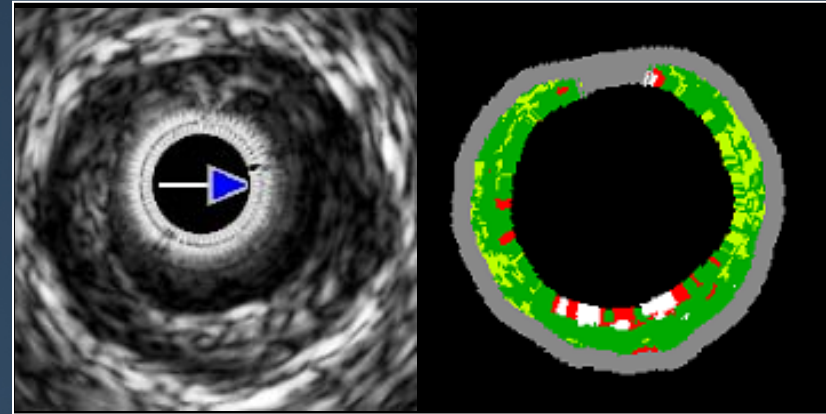


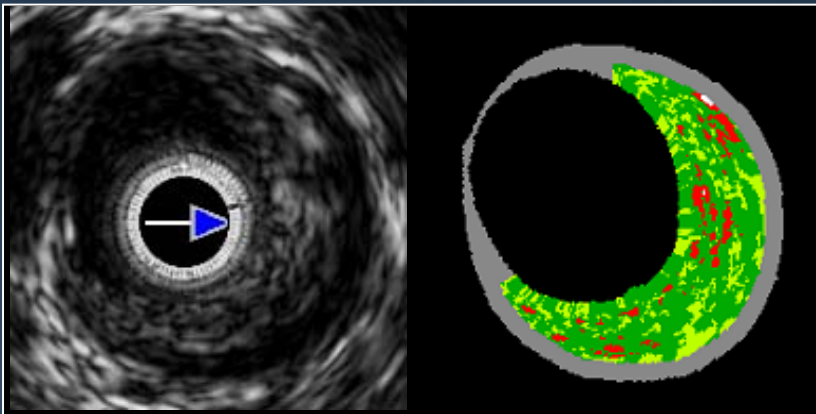


Baseline

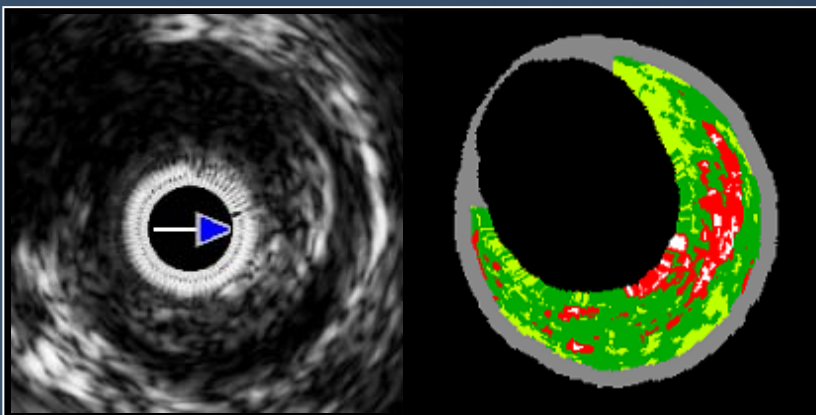
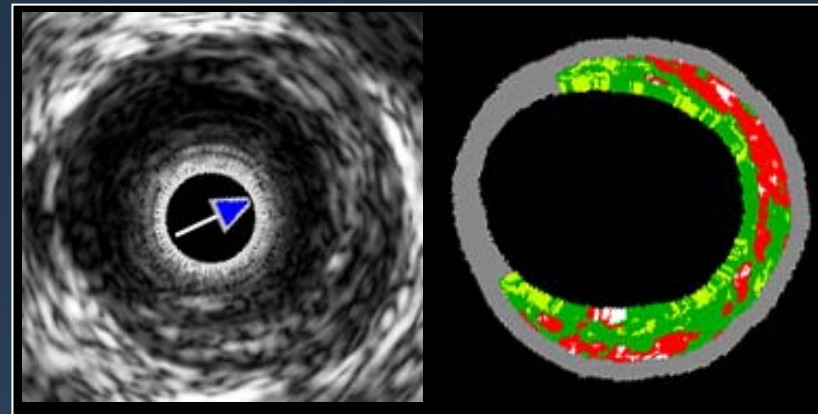


Follow-up

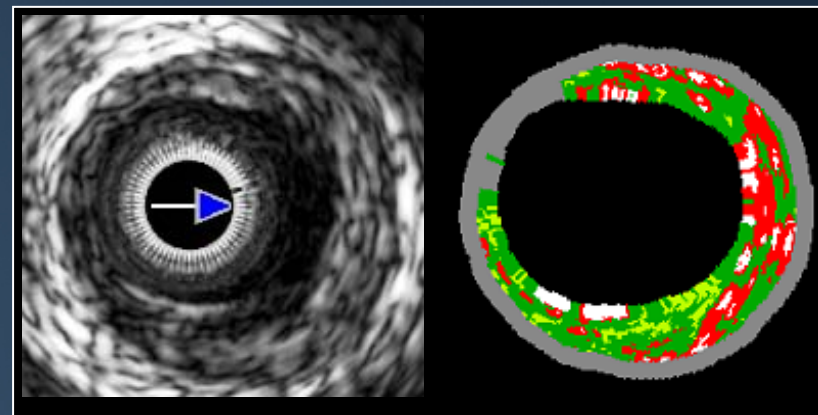




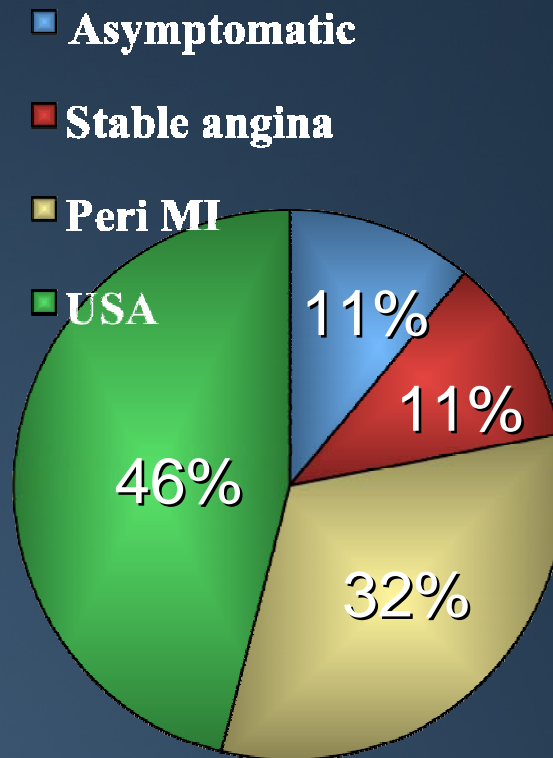
Baseline



Follow-up



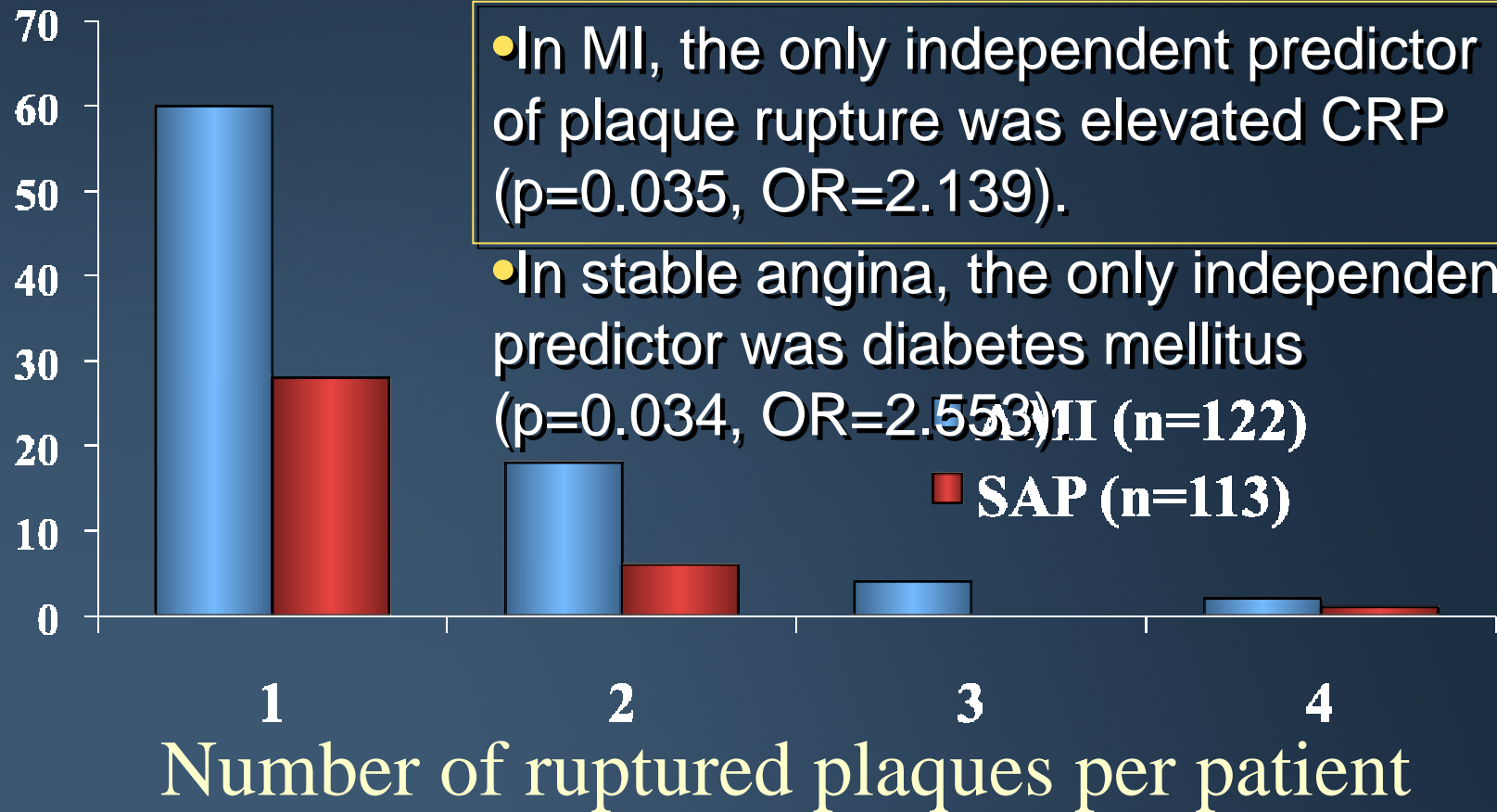
# Symptoms in 254 patients with 300 plaque ruptures in 257 arteries





# Ruptured plaques in patients with MI and stable angina

% of patients



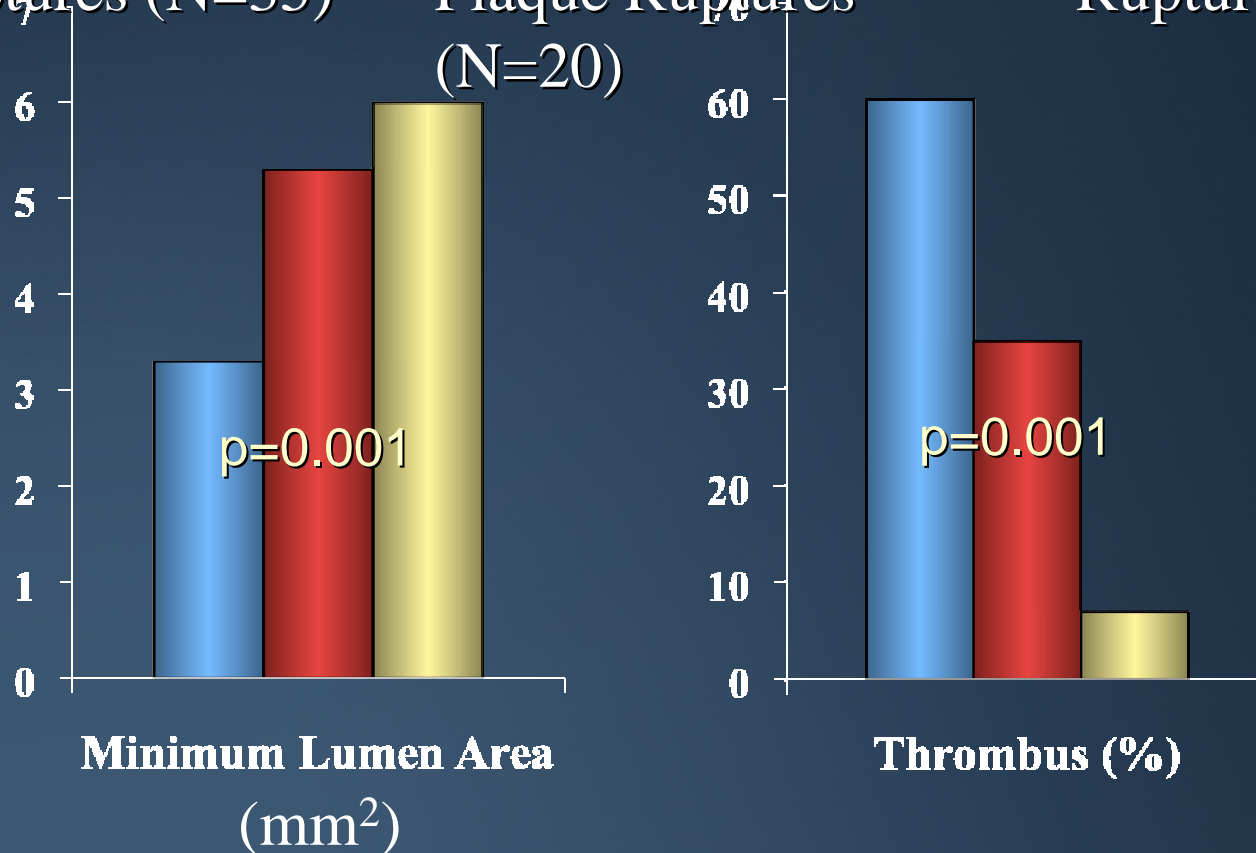
- In MI, the only independent predictor of plaque rupture was elevated CRP ( $p=0.035$ ,  $OR=2.139$ ).

- In stable angina, the only independent predictor was diabetes mellitus ( $p=0.034$ ,  $OR=2.553$ ).

■ MI (n=122)  
■ SAP (n=113)

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

- ACS Culprit Plaque Ruptures (N=35)
- ACS Non-Culprit Plaque Ruptures (N=20)
- Non-ACS Plaque Ruptures (N=27)



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

# Conclusion

- I make the assumption that we will be able to detect TCFAs. After all, we are smart people, and a lot of money and time is being spent on this problem.
- The successful technique is the one that will predict events, not just correlate with pathology. None of the techniques that I have discussed is “there” yet.





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