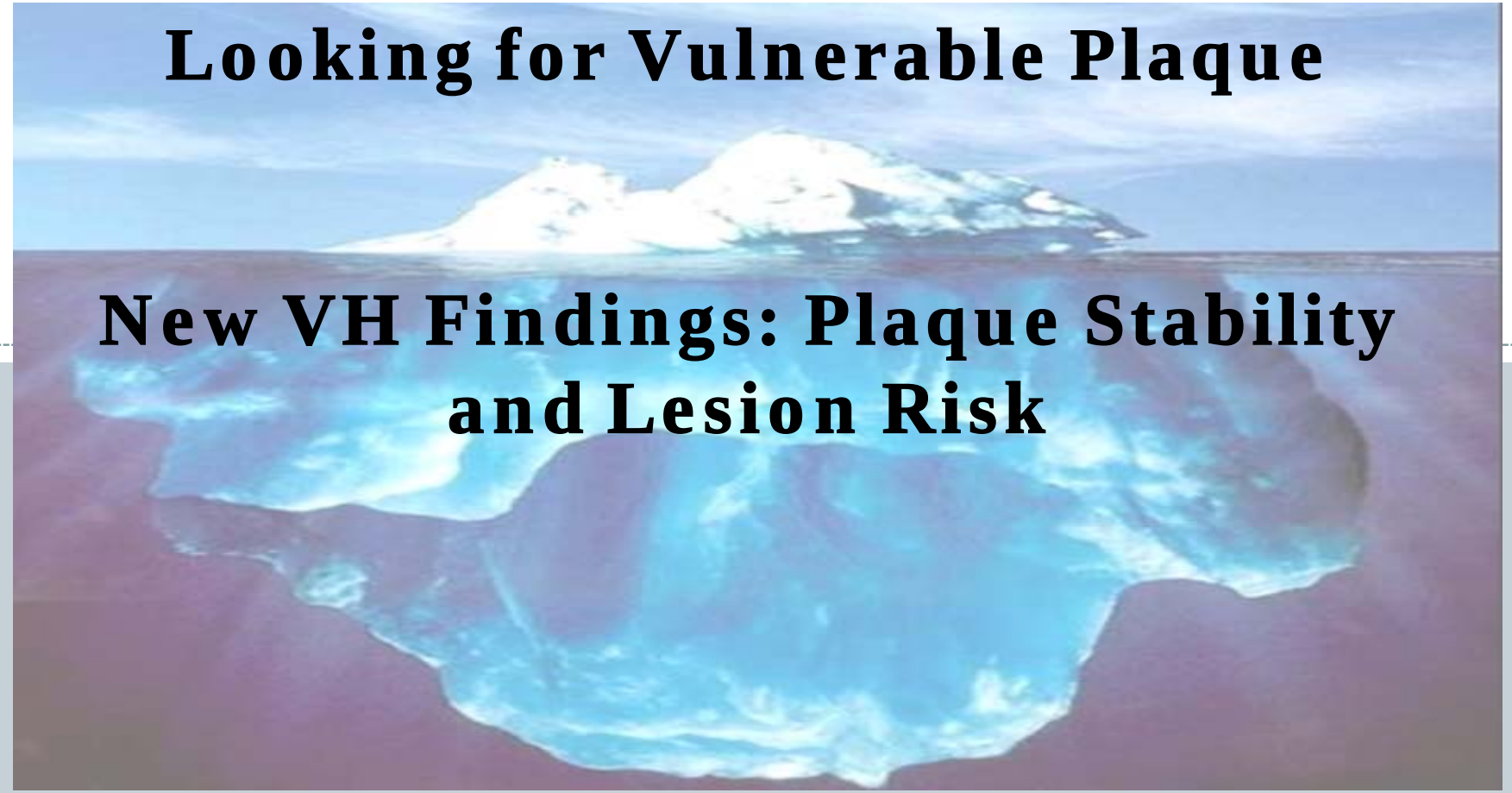
Looking for Vulnerable Plaque



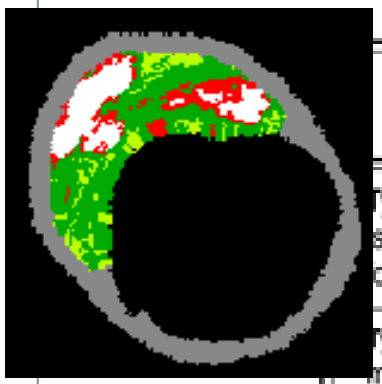
New VH Findings: Plaque Stability and Lesion Risk

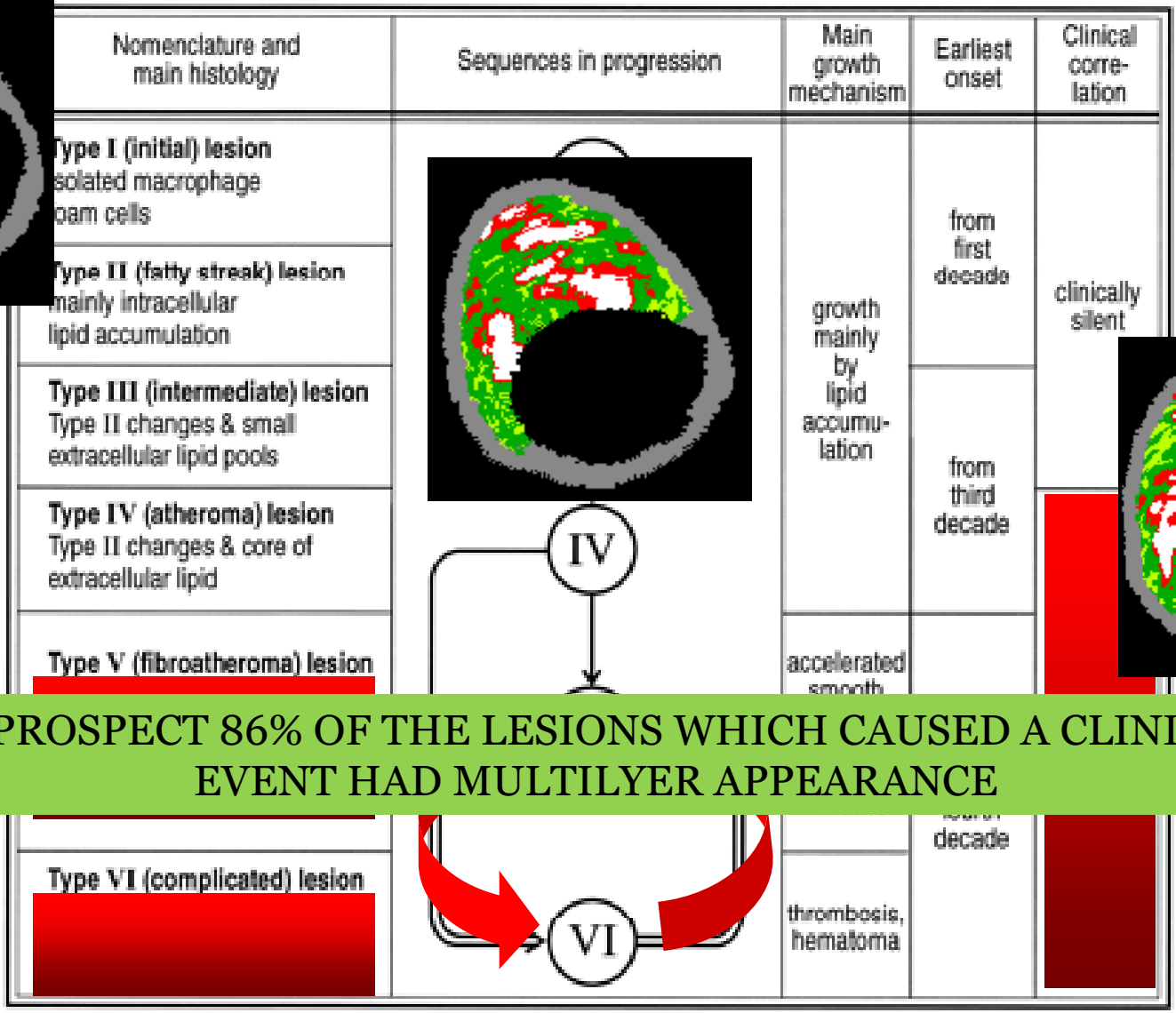
MP MARGOLIS, MD, PHD

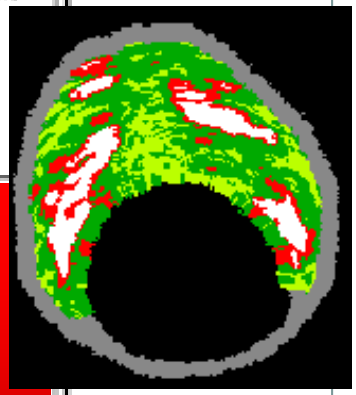
The Focus of the Presentation

- To remind us, that history keeps repeating itself
- If you understand the past, you may be able to predict the future
- Coronary mortality has been #1 killer around the world far too long
- To prove concepts based on post mortem data *in vivo* is time consuming but also an opportunity to understand how fast plaques progress (we can study not just one but several time points) and at what stage of progression lesions become clinically high risk – cause a clinical event

Pathways in evolution and progression of human atherosclerotic lesions; Significant Plaque Growth is Very much Hemorrhagic in nature





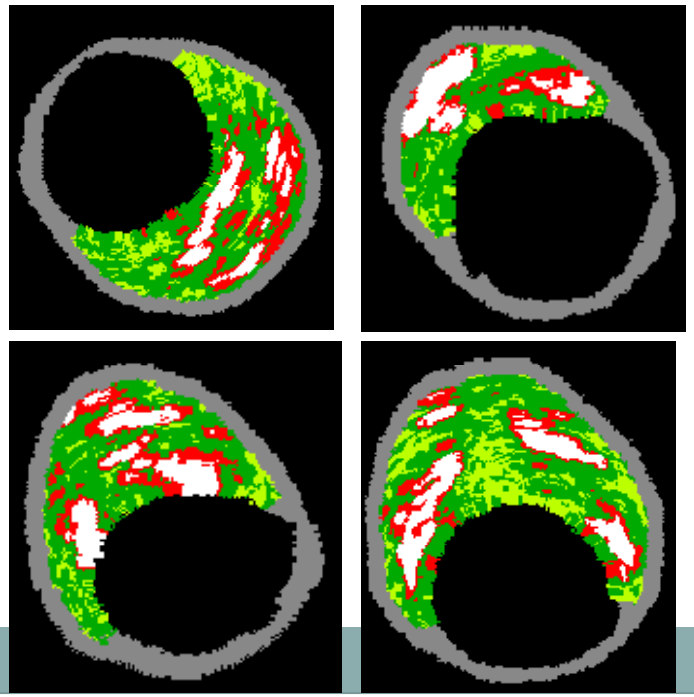


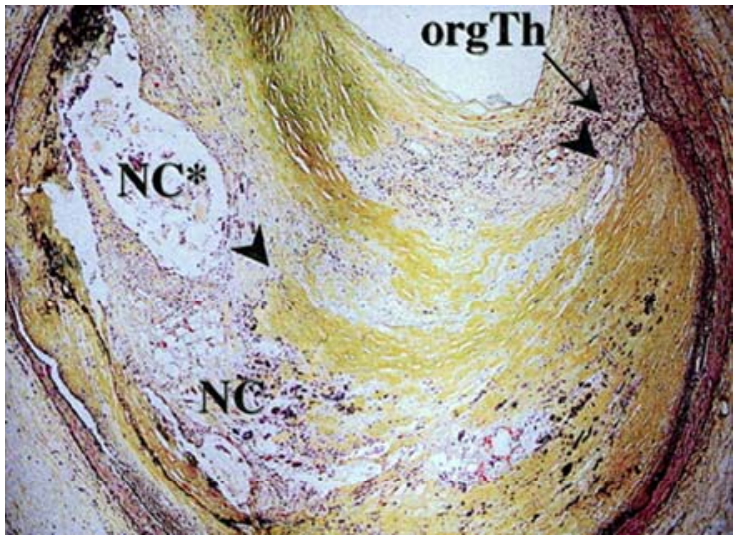
IN PROSPECT 86% OF THE LESIONS WHICH CAUSED A CLINICAL EVENT HAD MULTILYER APPEARANCE

A Definition of Advanced Types of Atherosclerotic Lesions and a Histological Classification of Atherosclerosis Stary et al

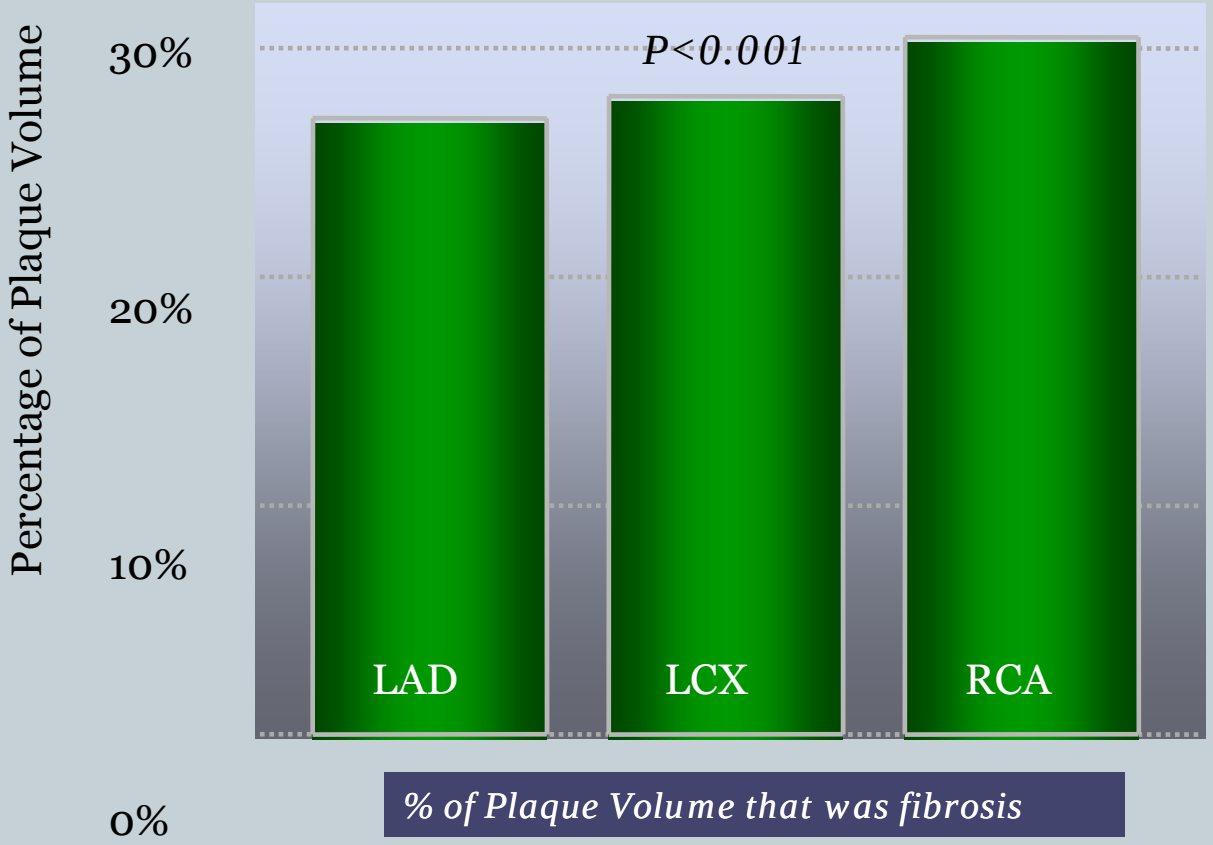
THIS LESION HAS BEEN A PROBLEM SEVERAL TIMES ALREADY

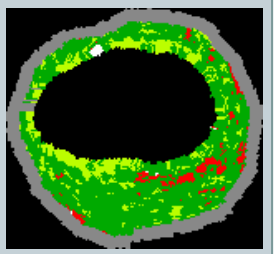
50% of patients with SCD had no idea they had CAD due to clinically silent plaque ruptures.
Majority of the patients with SCD have 2 vessel disease post mortem
75% of the lesion which cause a SCD have evidence of 2-5 healed ruptures at the lesion site



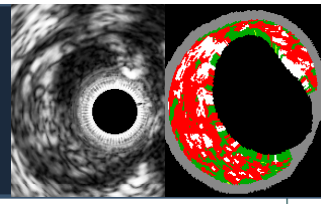


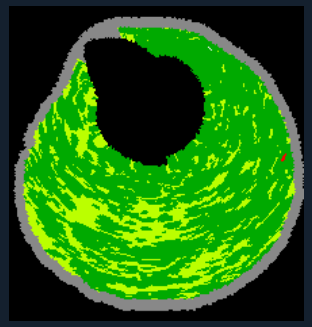
Bulk of Plaque Volume is Fibrosis



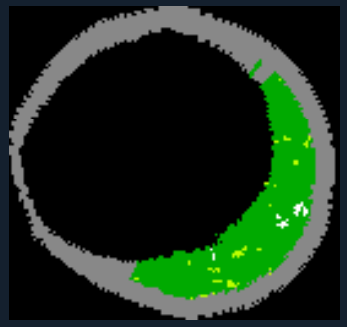


PROSPECT: Fibrosis Does not cause a Clinical Event

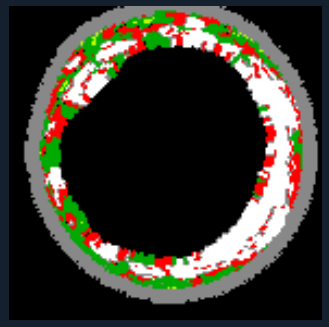




Pathological Intimal thickening



Fibrotic



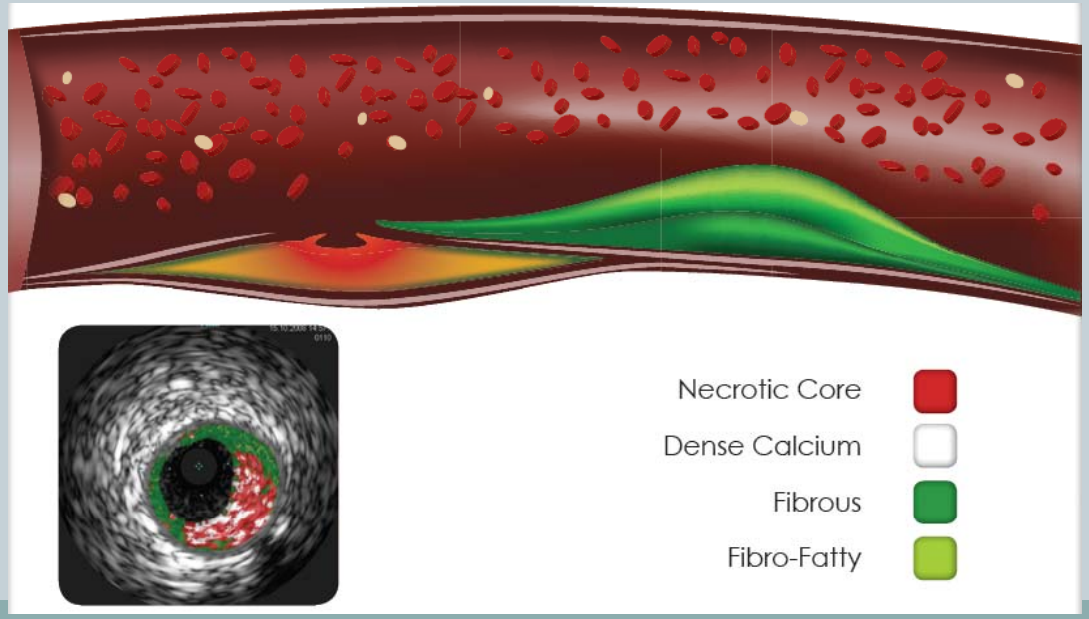
Fibrocalcific

Lesion HR	0.22 (0.10, 0.49)	1.22 (0.44, 3.39)	1.25 (0.17, 9.01)	2.60 (0.36, 18.84)
P value	0.0002	0.70	0.83	0.34
Prevalence*	67.9%	19.7%	5.6%	2.7%

*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

Why Majority of Vessel Obstruction is Fibrotic and not related to Lesion risk?

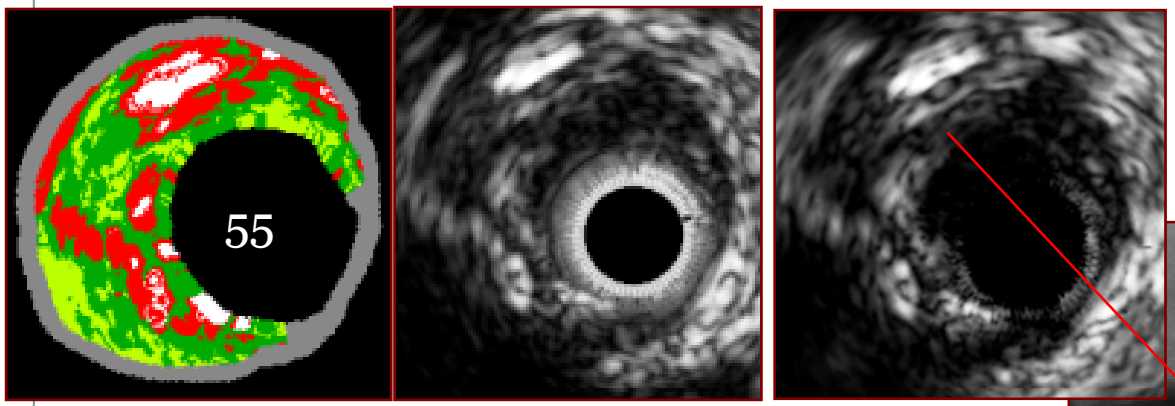
- The rupture of a TCFA – silent or clinical
  - Angiographic narrowing? – usually just thrombus
  - Site of the plaque rupture? – 60% of the time proximal to the thrombotic min lumen narrowing by angiogram and angiographically non-significant

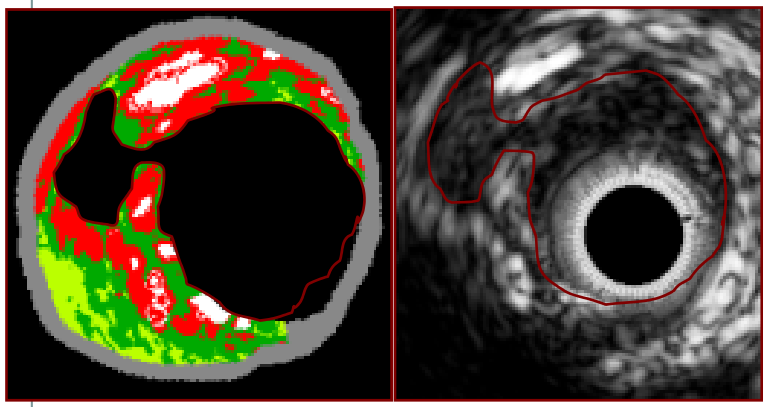


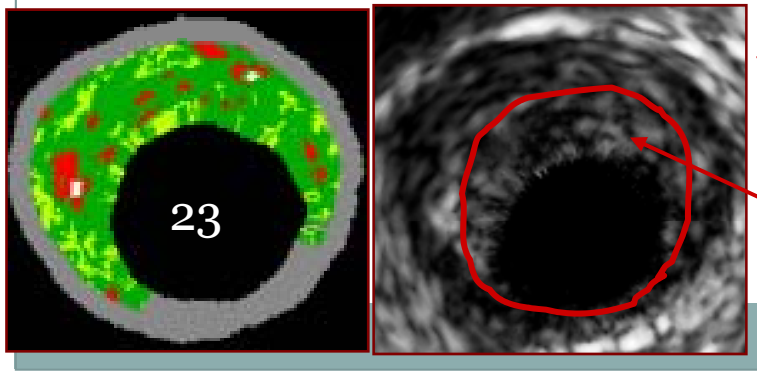
Koenig, Margolis, Virmani, Klauss. Nature Clinical Practice 2008

Example Case 29

VH RF Grayscale IVUS





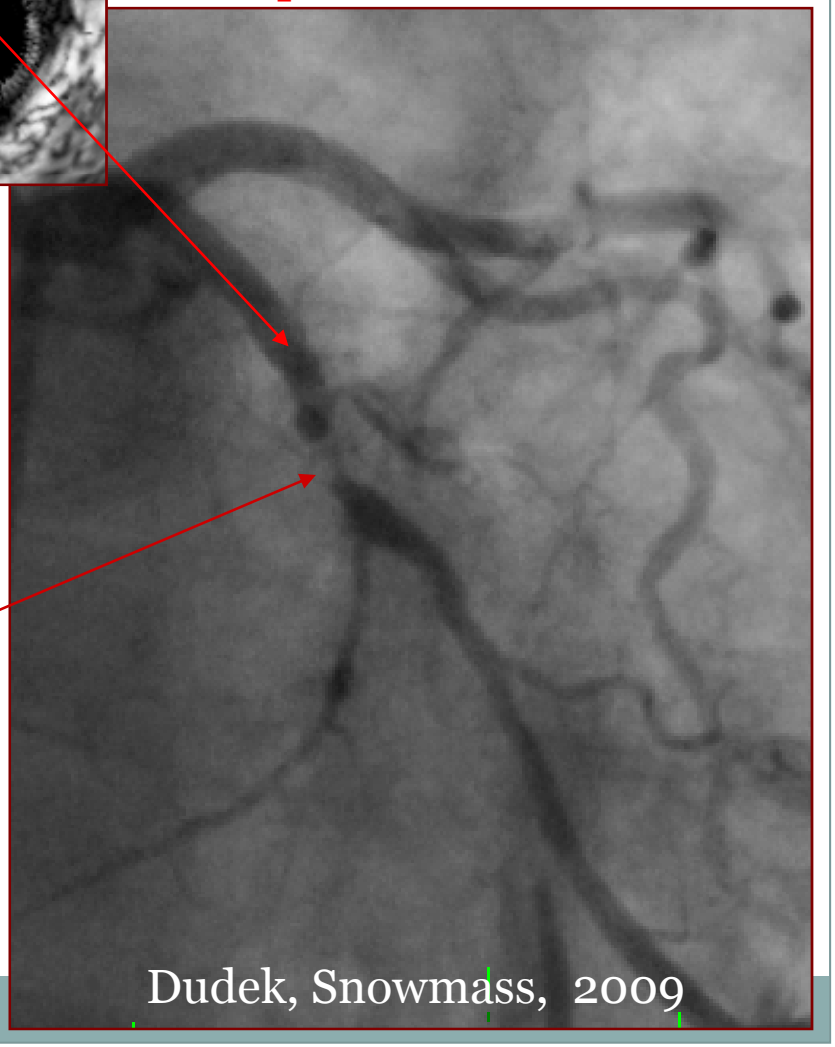


The average length of a TCFA is 6-8 mm

MLA

Thrombus

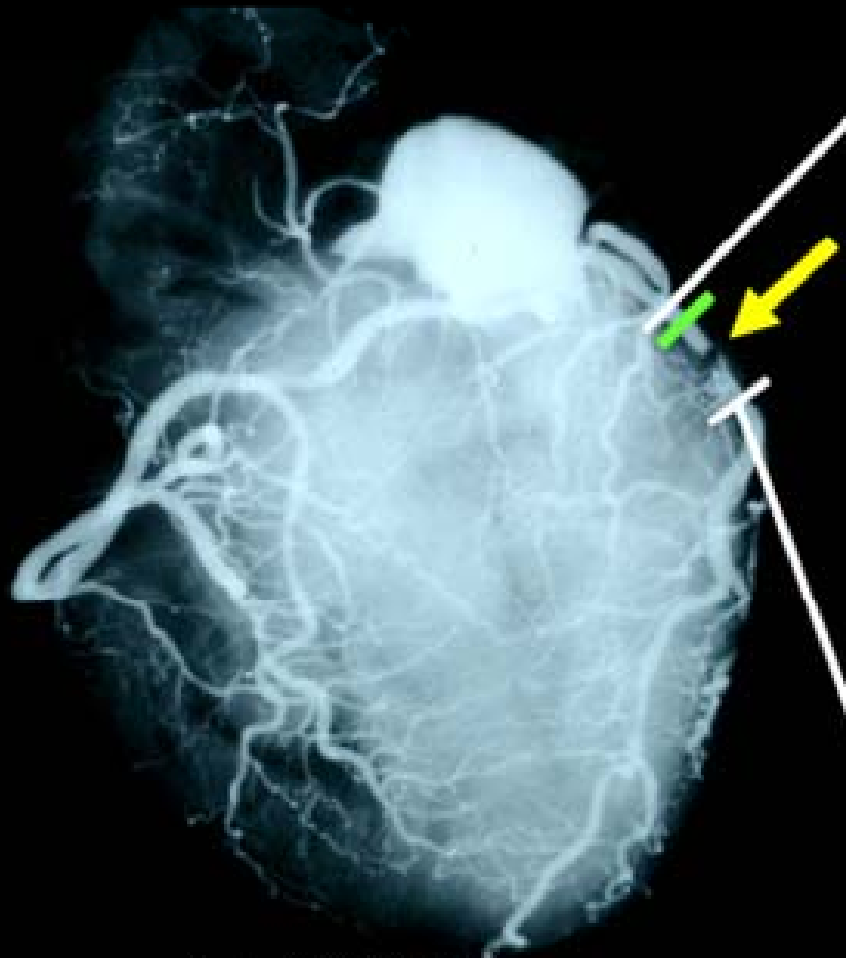
Rupture of the Culprit of the Culprit (TCFA) proximal to MLA



Dudek, Snowmass, 2009

Severity of stenosis: *angiography vs pathology*

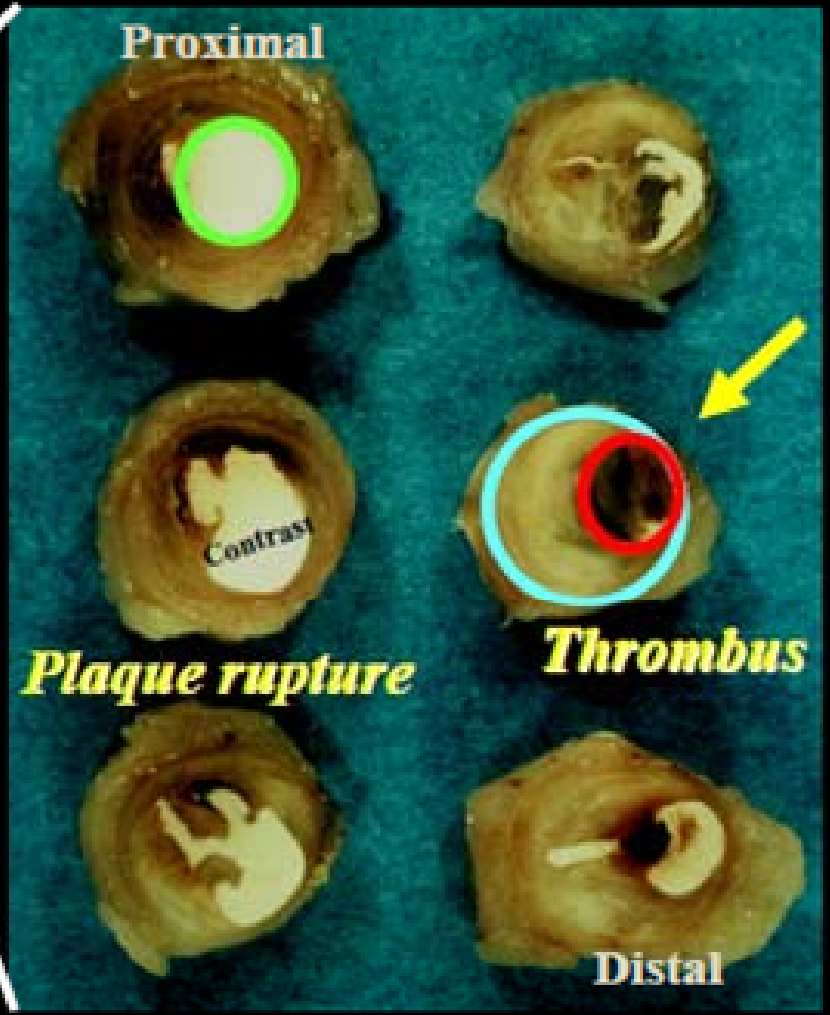
Angio: longitudinal luminal view



Falk, TCT 2009

'Diffuse' disease → stenosis↓

Pathology: cross-sections

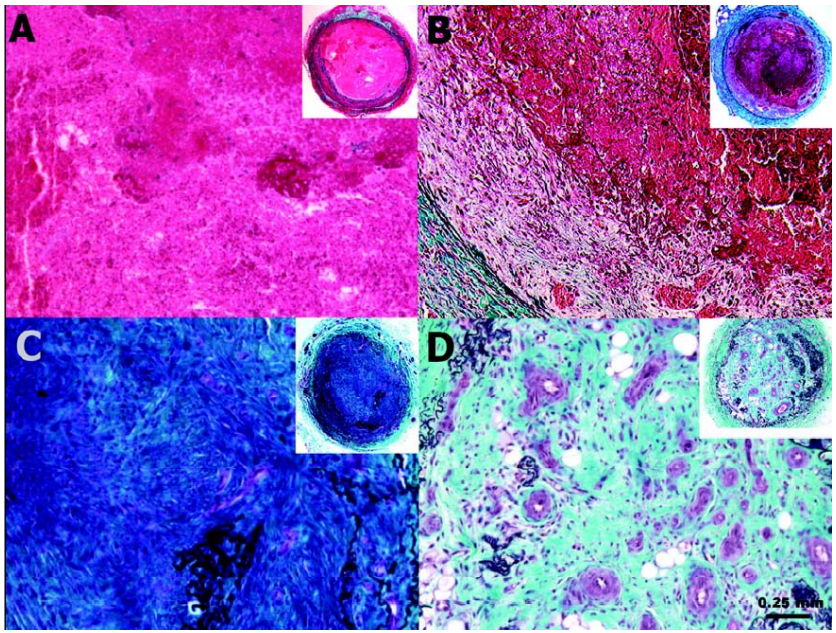


Local remodeling → stenosis↑

The Organization of Intraluminal Thrombus

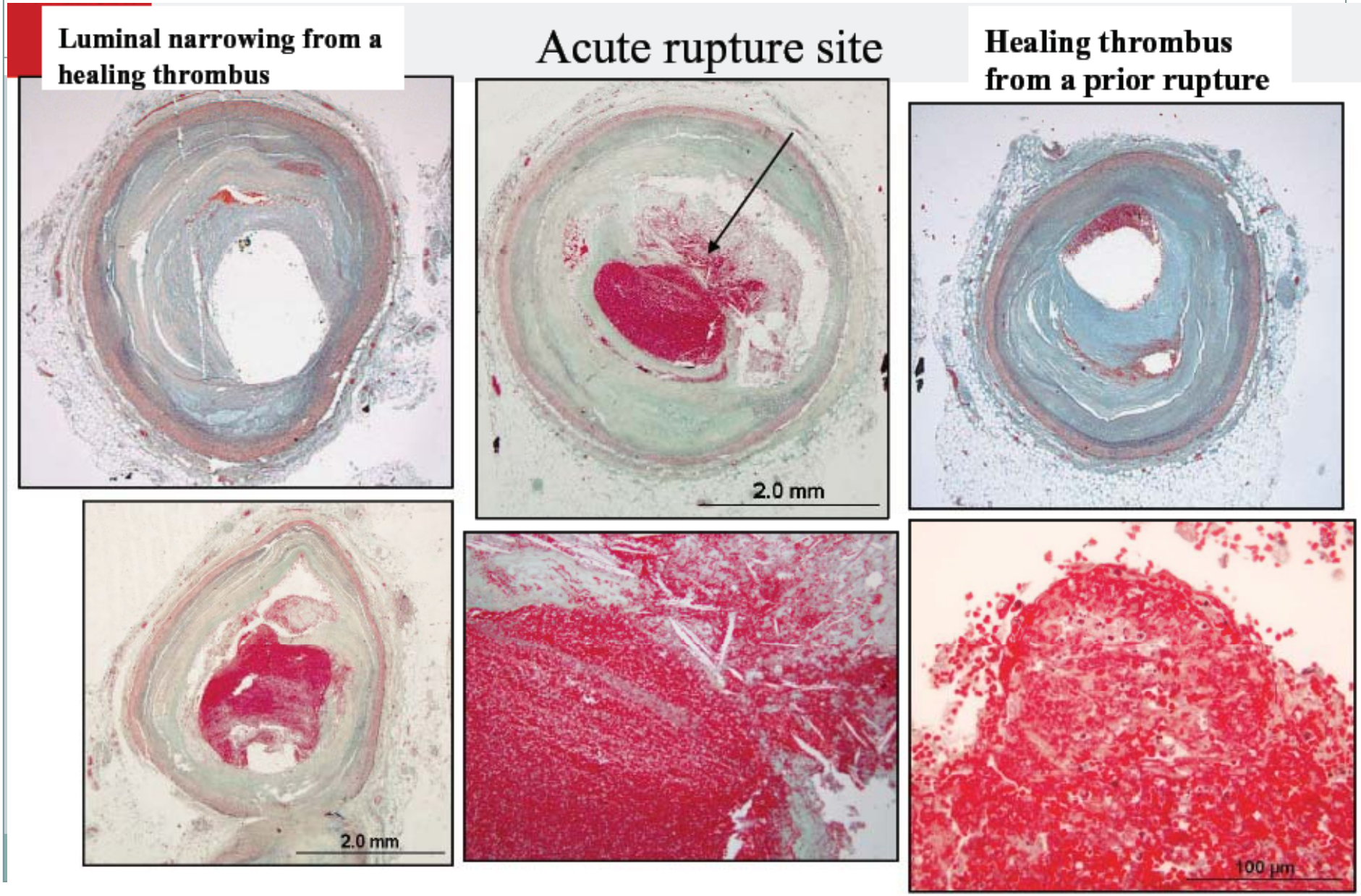
(A) Acute thrombus (≤ 6 h); Red blood cell rich thrombus with platelets, inflammatory cells and fibrin meshes

(C) six-week-old thrombus; Dense fibrocellular matrix

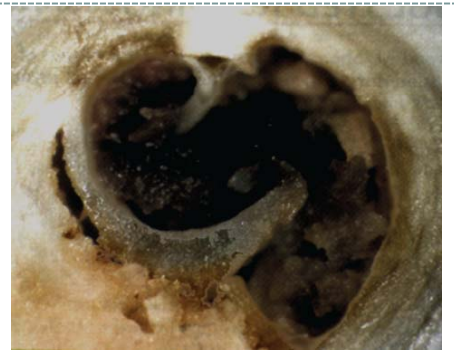


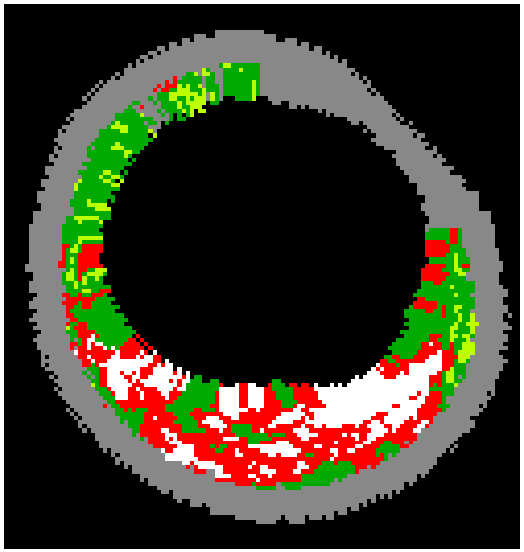
Sirol M, Fuster V et al, CIRCULATIONAHA/2004/522110

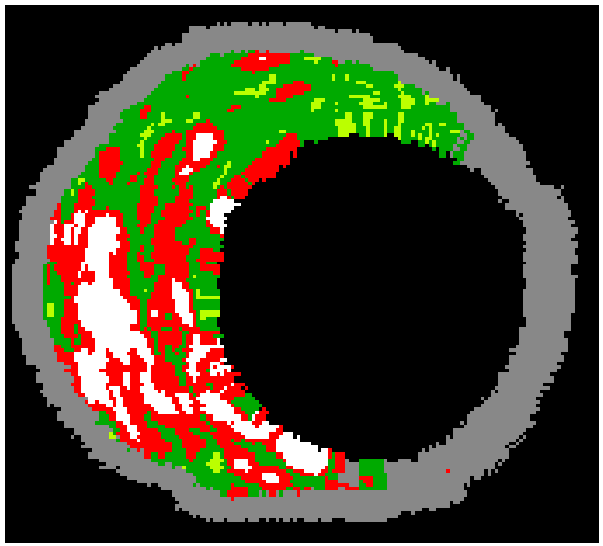
Acute Rupture Site and Plaque Progression

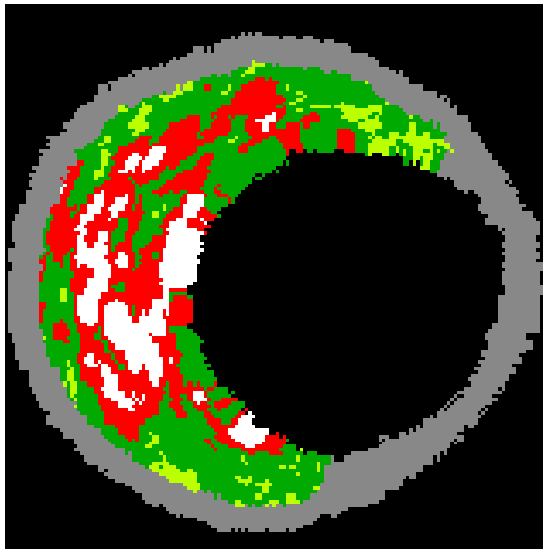


Vulnerable Plaque is a Necrotic Lesion







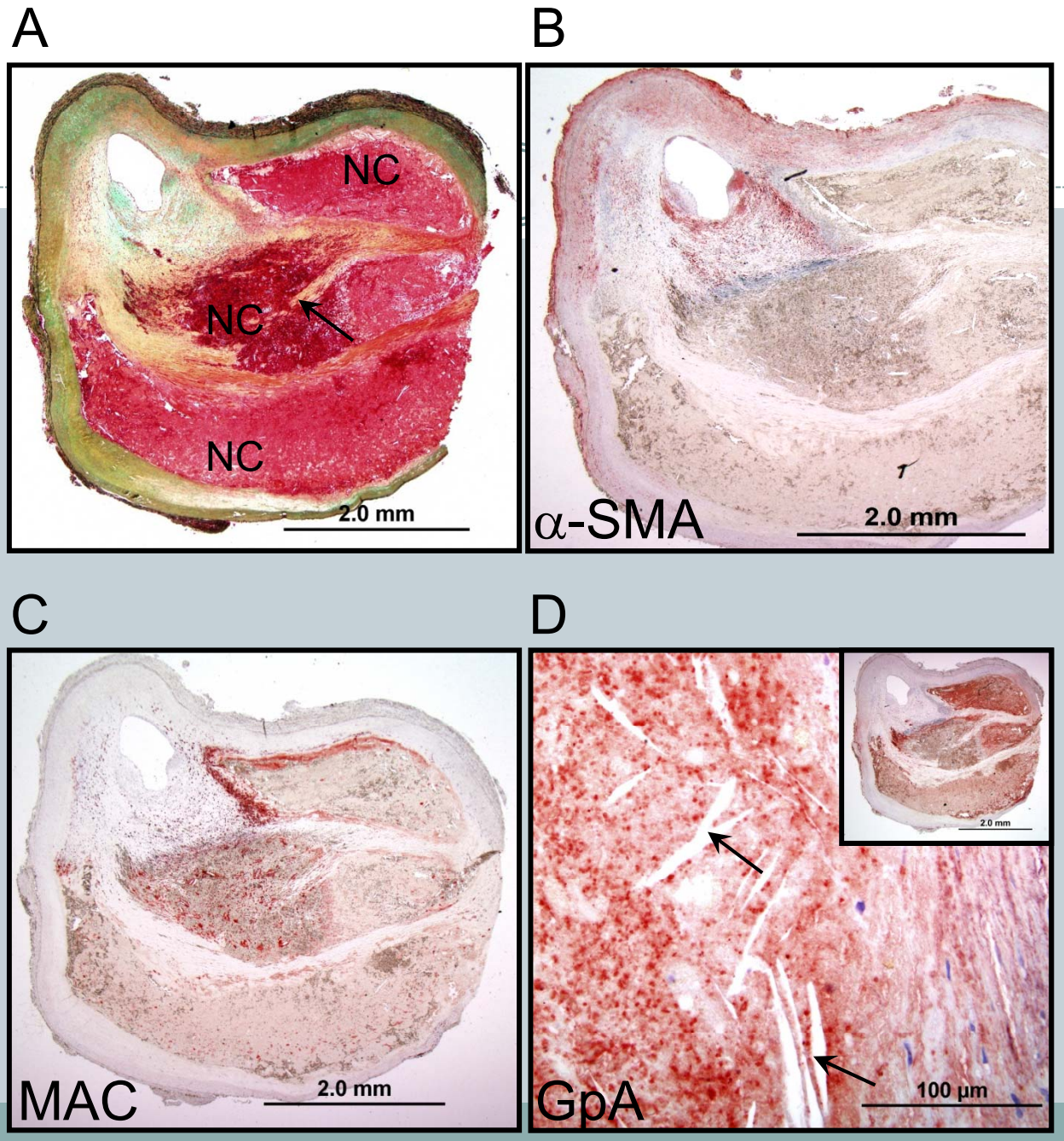


VH TCFAs

TCFA

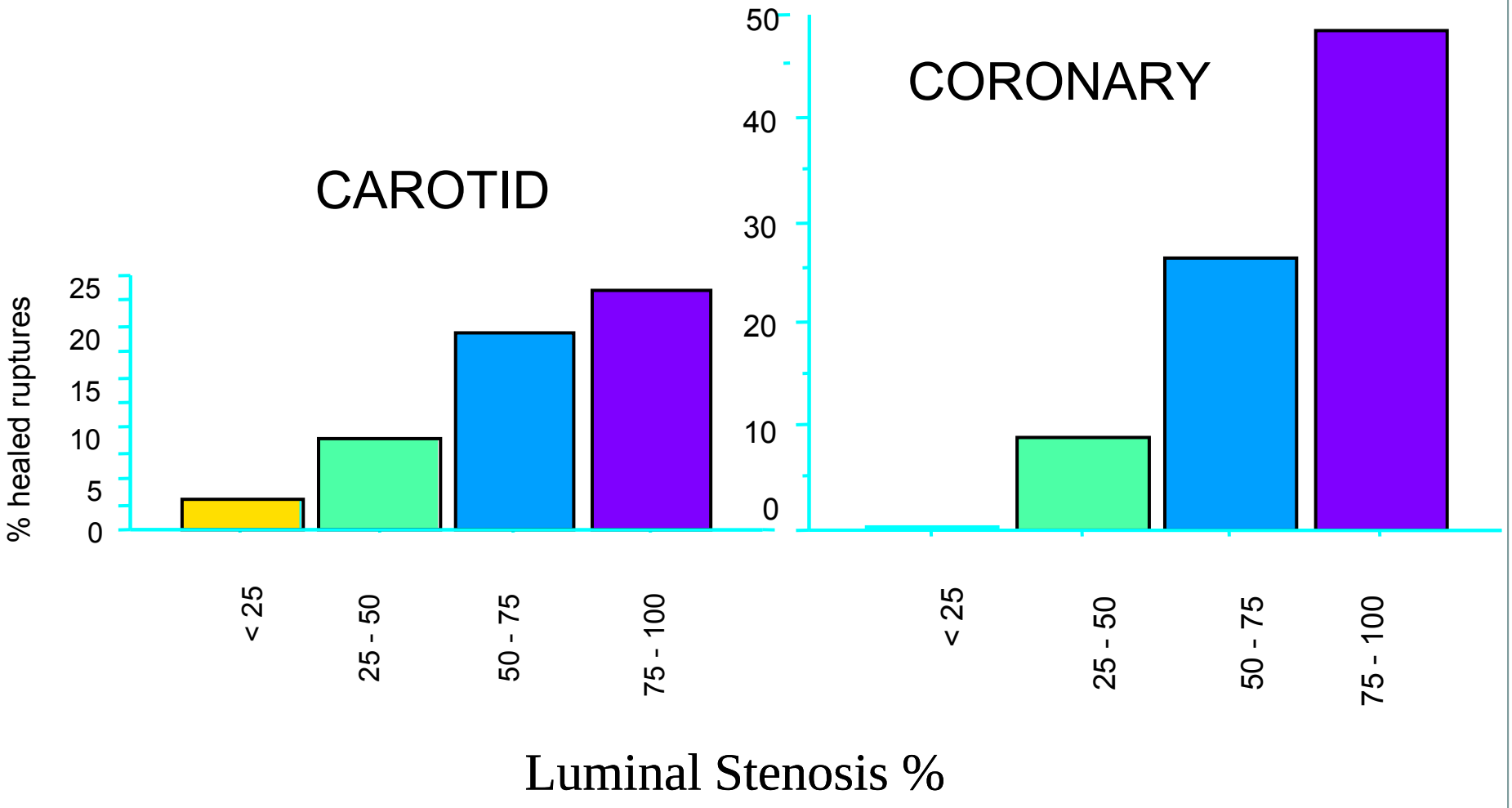
PIZZA

Courtesy of Dr Massimo Sangiorgi

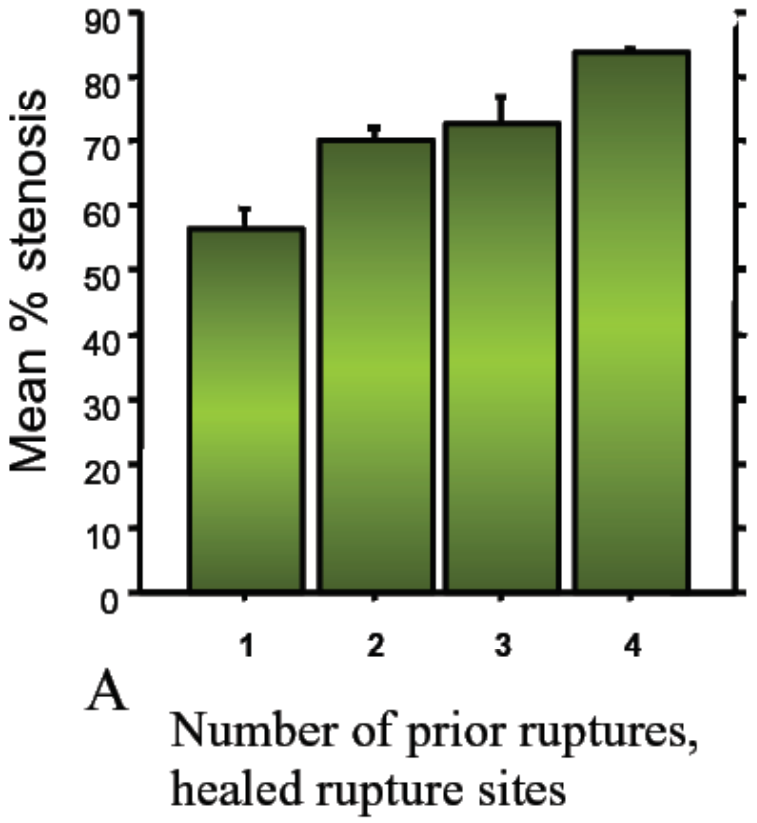


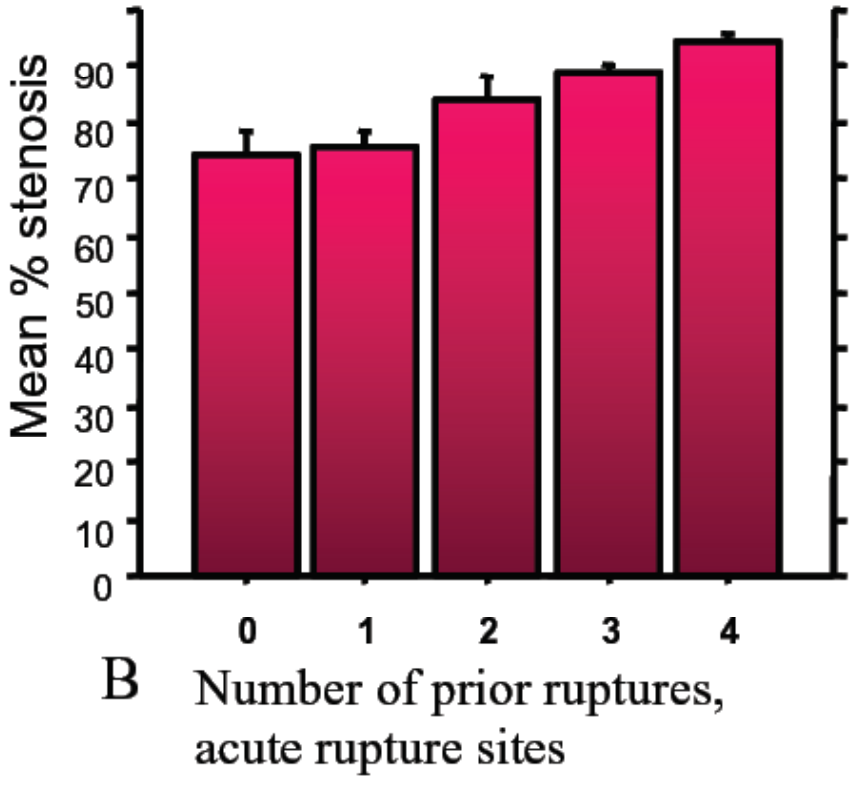
Courtesy to Dr M Sangiorgi

Prior Ruptures Increase Lumen narrowing



Prior Ruprures Increase Plaque Burden

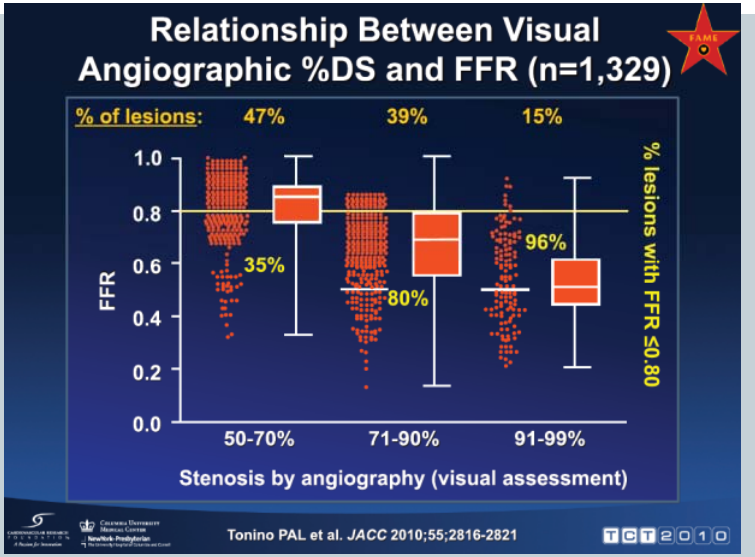




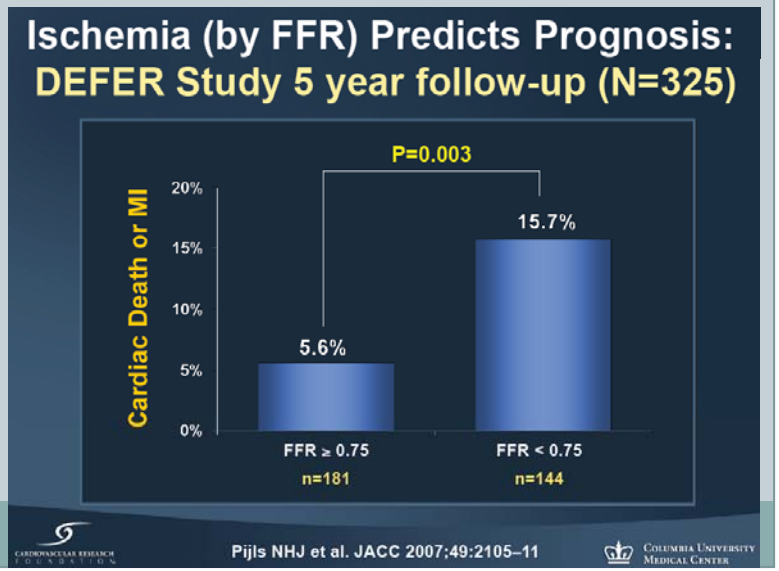
Kolodgie, Virmani et al 2002

Lesion Ischemia and Risk of Clinical Event

- Angiographically significant lesion (>70% stenosis)? 24% are non-ischemic

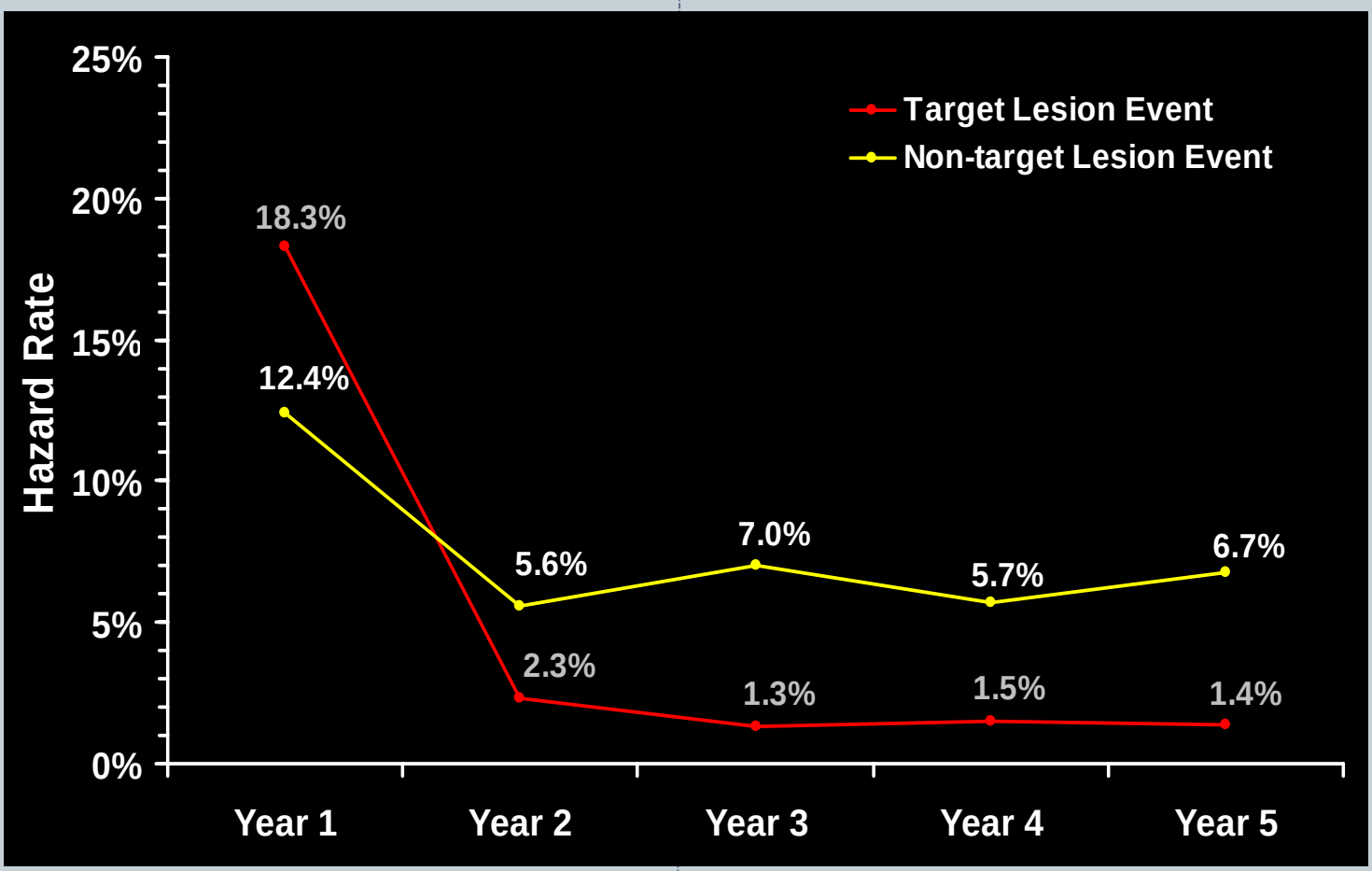


- Ischemia producing lesion?
  - Significantly higher risk of death or MI if ischemic by FFR



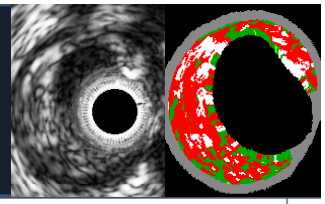
Optimal PCI, on average 6-7% annual rate of events from non-target lesions

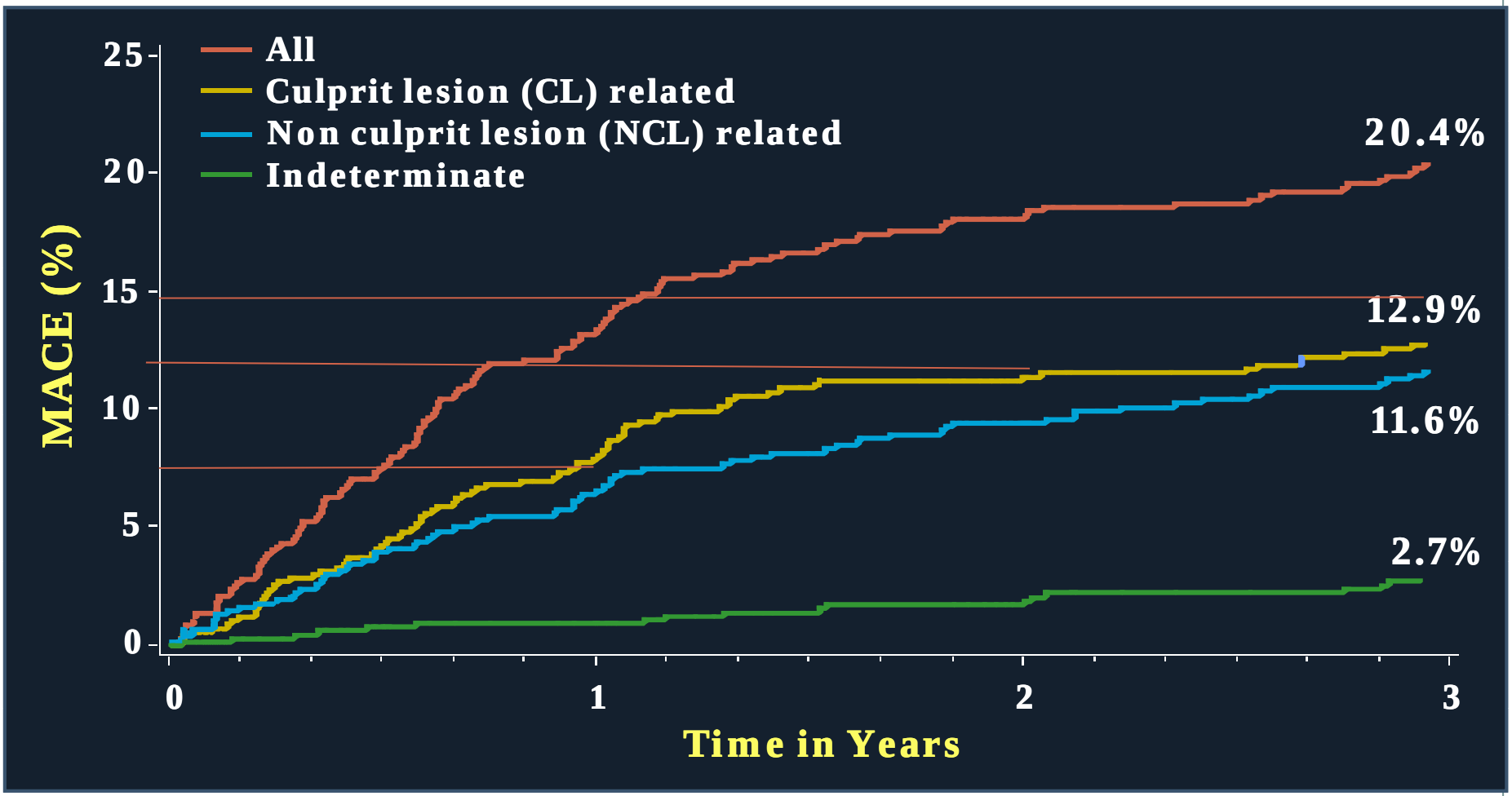
5-year outcomes after stenting: HCRI database



Cutlip et al. *Circulation* 2004; 110: 1226–1230.

PROSPECT: MACE



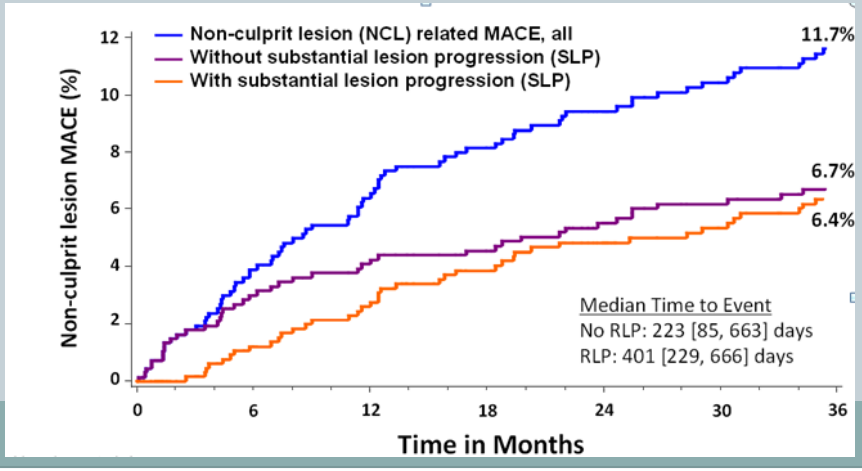


Number at risk

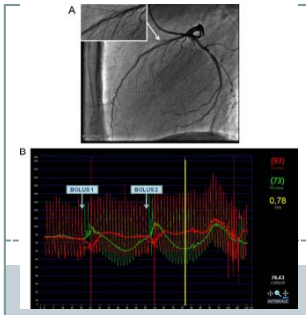
ALL	697	557	506	480
CL related	697	590	543	518
NCL related	697	595	553	521
Indeterminate	697	634	604	583

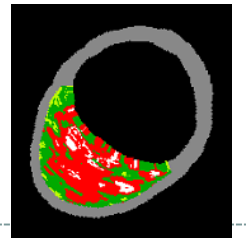
All Angiographically non-significant lesions do not have the same Risk (Prospect sub-analysis, Sanidas et al ACC 2011)

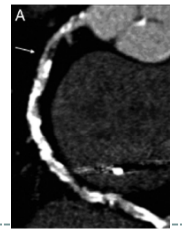
- **Lesions with Substantial Lesion Progression (>20% increase in angiographic stenosis, SLP) are less severe at baseline compared to those without SLP (DS 26.4% vs. 53.8%, p<0.0001), but more severe at the time of the event (DS 73.8% vs. 56%, p<0.0001)**
- **SLP was associated with comparable baseline PB (median 68.7% vs. 70.1%, p=0.17), MLA (median 3.7mm² vs. 4.0mm², p=0.60), and VH-IVUS phenotype (83.3% vs. 90.9%, p=0.68 classified as fibroatheromas at baseline)**
- **All MIs were associated with SLP (14.1% vs 0%, p=0.05)**



	SLP (n=44)	Non-SLP (n=28)	P-Value
Non-Culprit lesion MACE			
Composite MACE, n	44 (100%)	28 (100%)	0.15
Cardiac death, cardiac arrest or MI, n	6 (14.1%)	0 (0%)	0.053
Cardiac death, n	0 (0%)	0 (0%)	N/A
Cardiac arrest, n	0 (0%)	0 (0%)	N/A
MI, n	6 (14.1%)	0 (0%)	0.053
Q-Wave MI, n	2 (4.8%)	0 (0%)	0.29
Non Q-Wave MI, n	4 (9.2%)	0 (0%)	0.11
Rehospitalization, n	39 (93.2%)	28 (100%)	0.009
Due to unstable angina, n	15 (45.8%)	6 (23.6%)	0.30
Due to increasing angina, n	28 (63.6%)	24 (100%)	0.004
Other non-culprit lesion events			
Revascularization (PCI or CABG), n	44 (100%)	23 (100%)	0.59
Due to MI, n	6 (14.1%)	0 (0%)	0.053
Due to unstable angina, n	14 (44%)	5 (19.6%)	0.23
Due to increasing angina, n	28 (63.6%)	19 (100%)	0.24
Stent thrombosis, n	0 (0%)	0 (0%)	N/A
Death, n	0 (0%)	0 (0%)	N/A



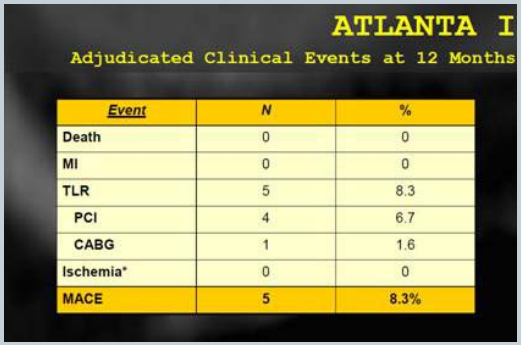




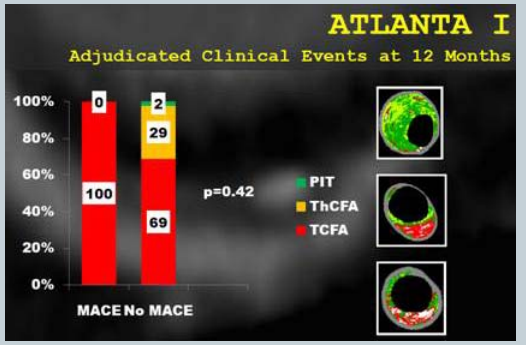
ATLANTA Data

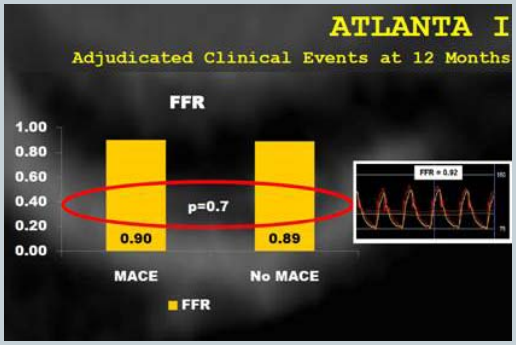
Voros et al (in press, Snowmass 2001)

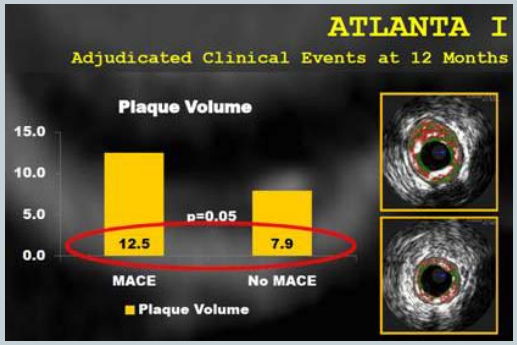
- MSCT, IVUS VH, and FFR in intermediate lesions (not intervened) at index in high risk non-symptomatic patients
- MSCT had ~ 60% predictive accuracy to identify VH TCFAs
- At one year, all MACE (8.3%) took place at TCFA sites, all FFR negative (not intervened)



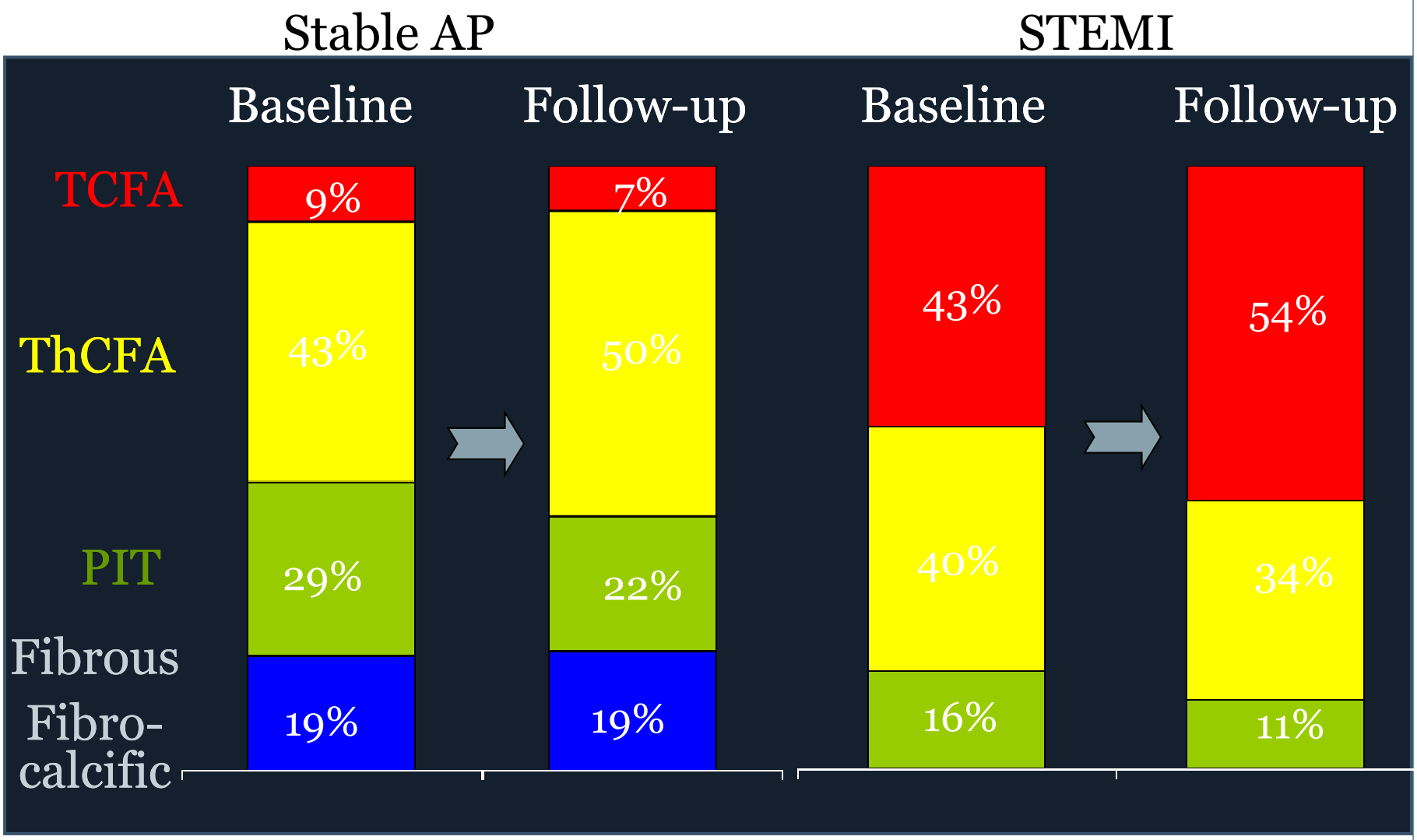
Event	N	%
Death	0	0
MI	0	0
TLR	5	8.3
PCI	4	6.7
CABG	1	1.6
Ischemia*	0	0
MACE	5	8.3%







Clinically Silent Plaque Progression; Temporal Changes in Stable vs STEMI Patients



From Kubo et al, JACC 2010;55:1590-

Zhijing Zhao et al from Horizons data, ACC 2011

- At baseline, nearly 50% of non-culprit lesions were VH-TCFAs in STEMI patients
- During 13 months F/U, unruptured, non-culprit lesions were frequently unstable with a decrease in MLA, increase in NC, and overall transfer from stable to vulnerable plaque morphology.

SUMMARY

- Vulnerable plaques identified by VH IVUS as VH TICFAs are the site of plaque ruptures and disease progression – reduction in MLA, increased amount of necrosis, and fibrotic build up of the arteries as thrombus organizes
- The transfer of ThCFAs to more unstable VH TCFAs is more active in STEMI than stable patients
- Prospect showed that VH TCFAs have almost 20% risk of a clinical event once PB and MLA have reached a significant lesion severity
- Lesions ischemia is important as it relates to lesion severity and oxygen demand, and as seen in FAME and Defer, predicts clinical events
- In the future, non-invasive imaging may provide additional guidance to locate high risk lesions in high risk patient populations