

# Vulnerable Plaque: Anatomic Features Linked to Future Events

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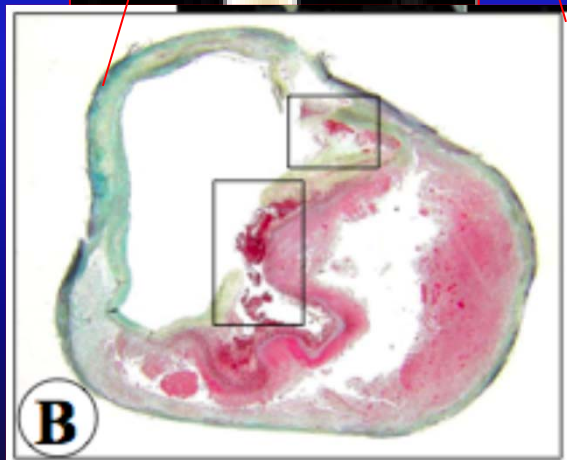
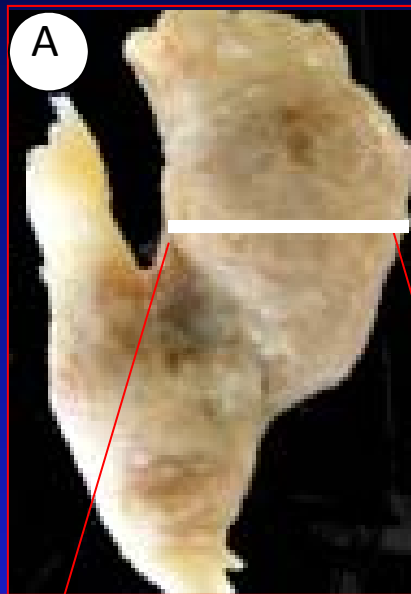


# Natural History of Atherosclerosis

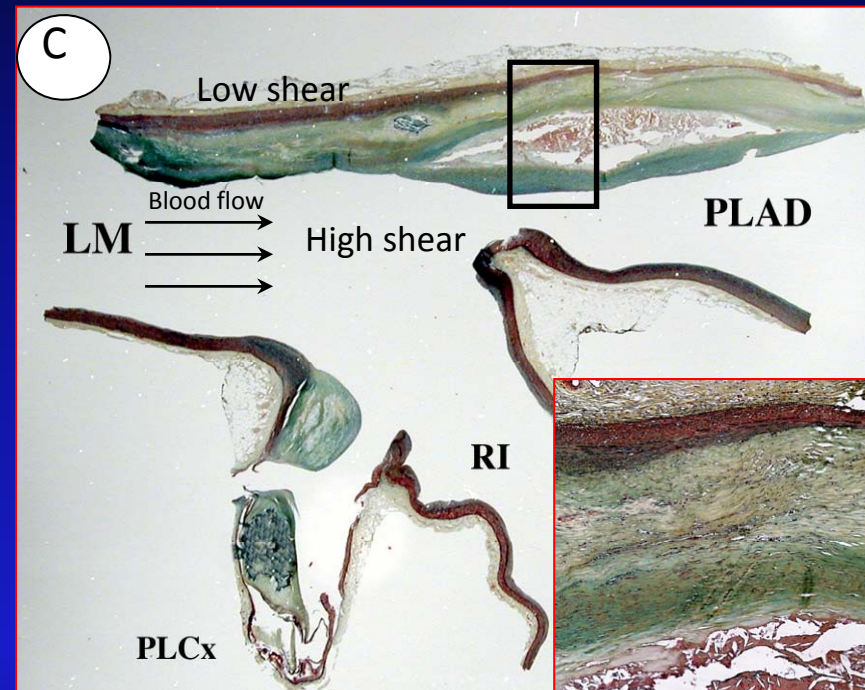
- **Systemic factors** –  
dyslipidemia, diabetes mellitus, smoking, hypertension, age and gender, hsCRP, Lp-PLA<sub>2</sub>, etc.
- **Local factors** –  
branch points, e.g. carotid bifurcation, abdominal aorta just above bifurcation, coronary branch point, and arch vessels at take off, are the sites of atherosclerosis manifestation.
- **Thrombosis** –  
occurs in the coronary arteries at focal points and is most often seen in the proximal segments of the three main coronary arteries (systemic coagulation factors play a role), and occur at sites where there are underlying plaque characteristic that result in thrombosis.

# Branch points are the sites of atherosclerosis and occur in areas of low shear

Carotid Artery



Left Coronary artery



# Non-Progressive and Progressive Coronary Plaques

non-progressive

progressive

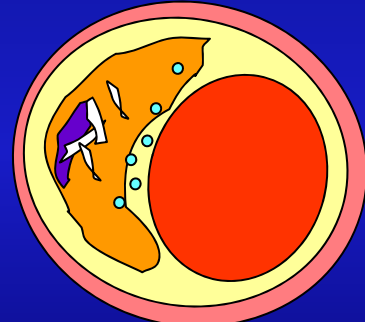
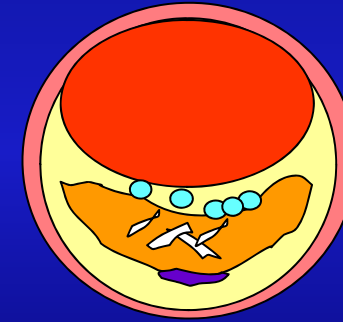
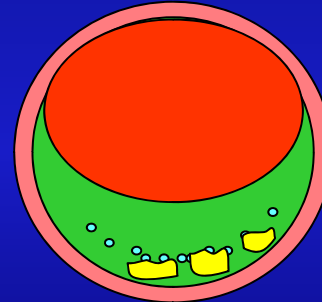
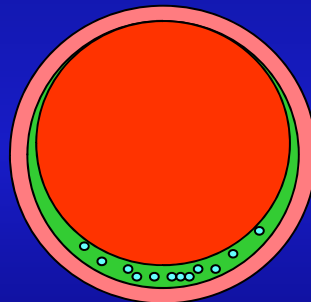
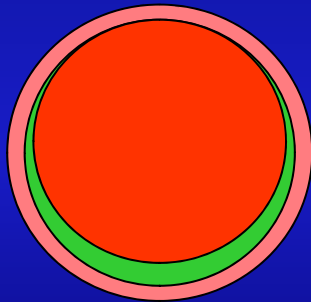
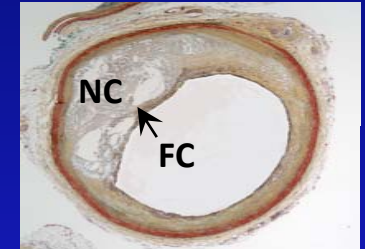
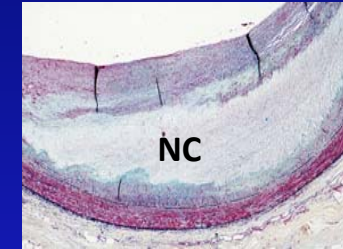
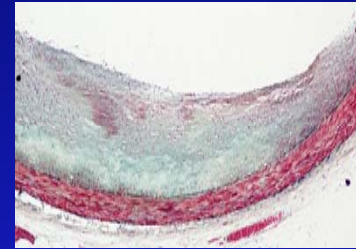
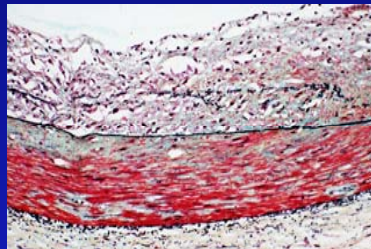
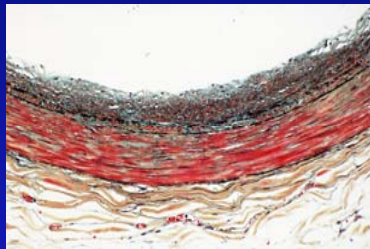
adaptive intimal thickening

Intimal xanthoma

pathologic intimal thickening

fibroatheroma

thin-cap fibroatheroma



lipid pool

necrotic core

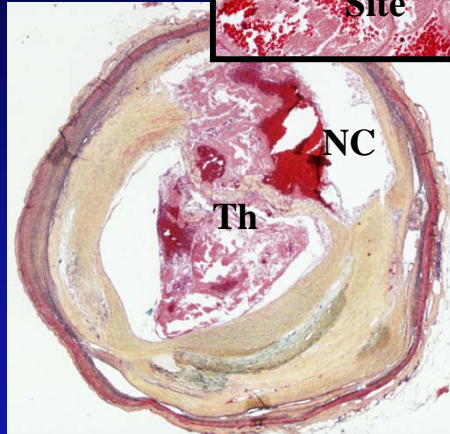
early → late necrosis

# Lesions with Thrombi

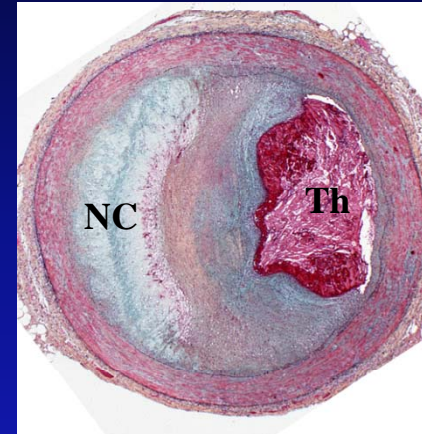
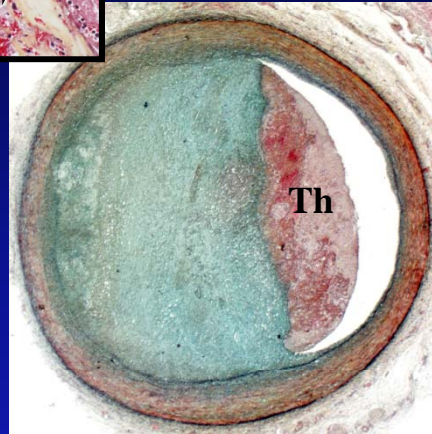
- *Plaque Rupture*
- *Plaque Erosion*
- *Calcified Nodule*

# Causes of Coronary Thrombosis

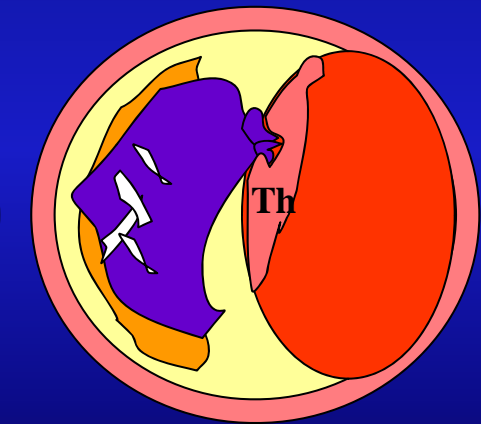
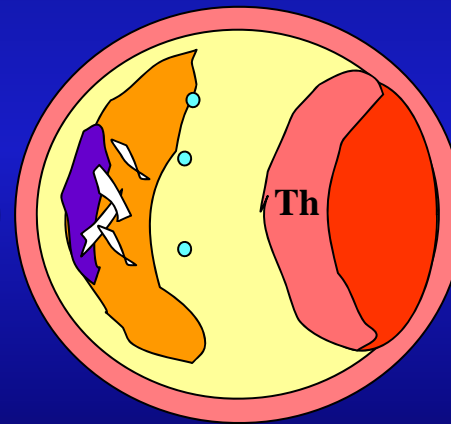
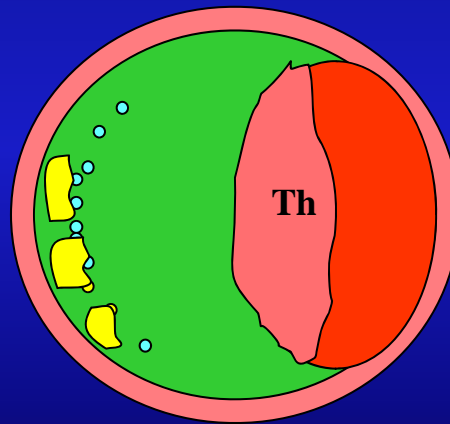
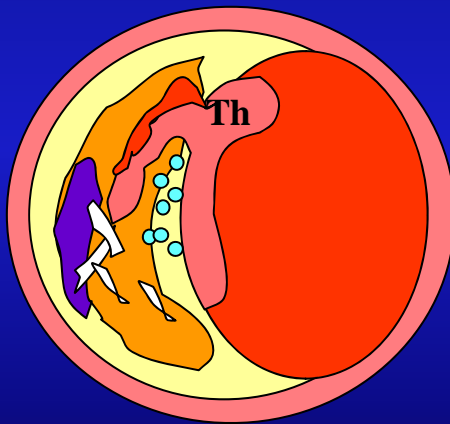
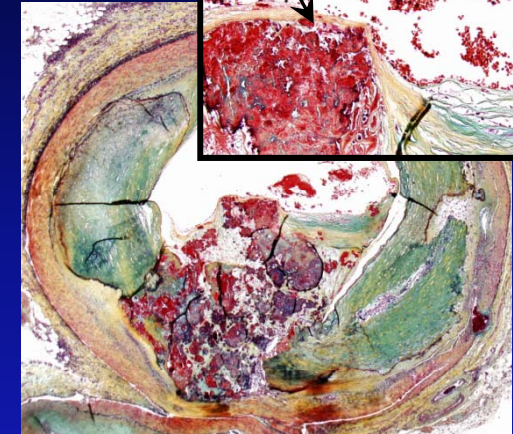
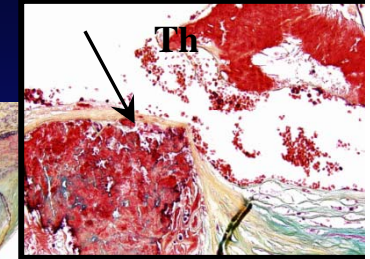
Rupture



Erosion



Calcified nodule



# Gross and Light Microscopic Features of Plaque Rupture

60% of Thrombi in Sudden Coronary Death occur form Plaque Rupture

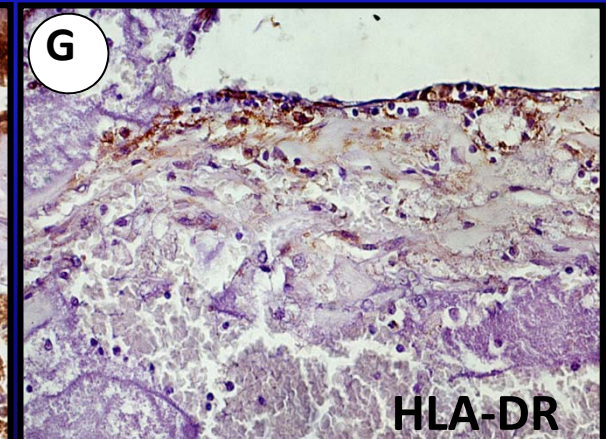
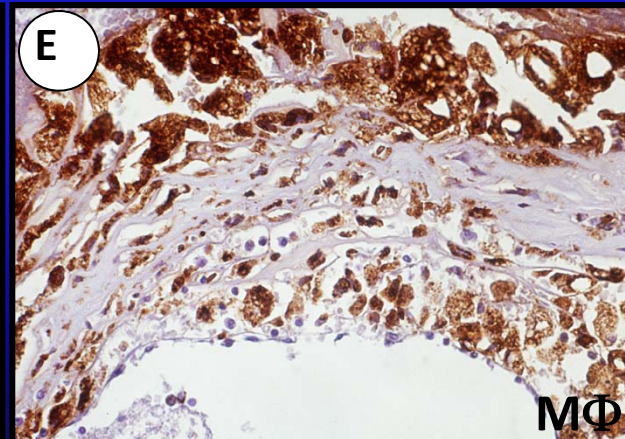
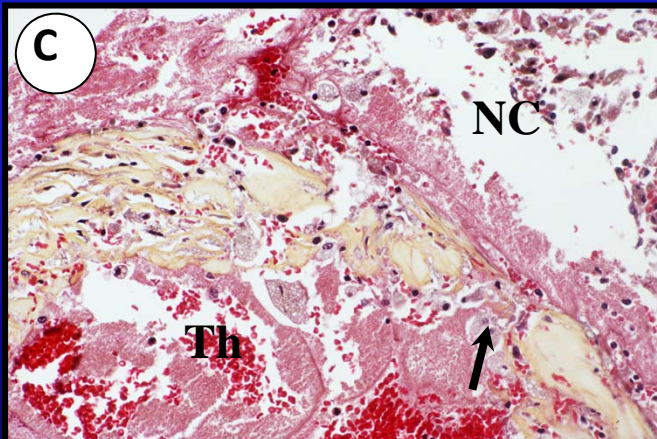
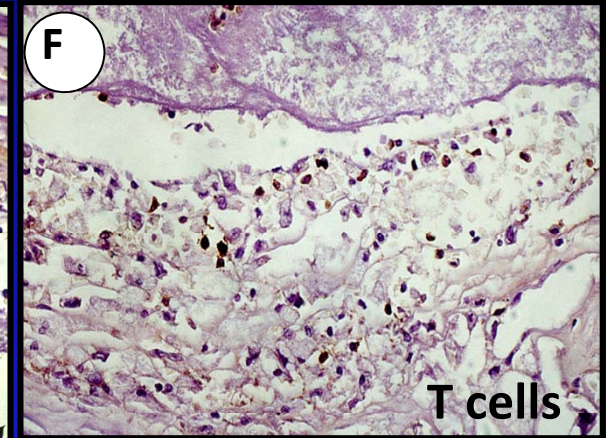
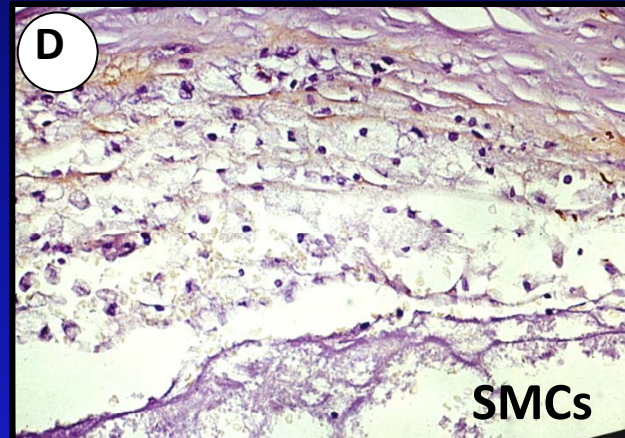
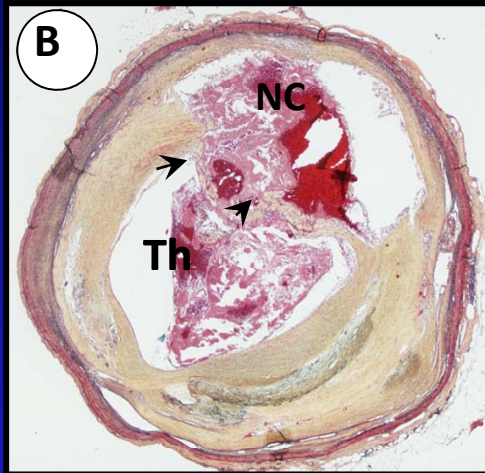
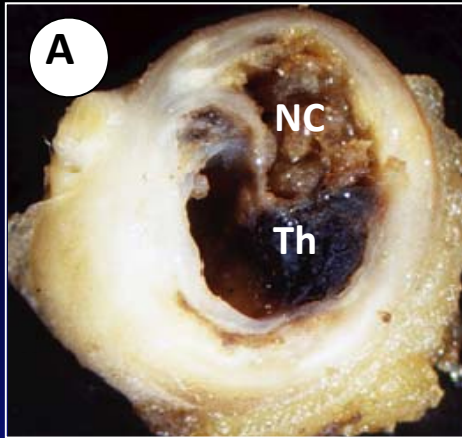
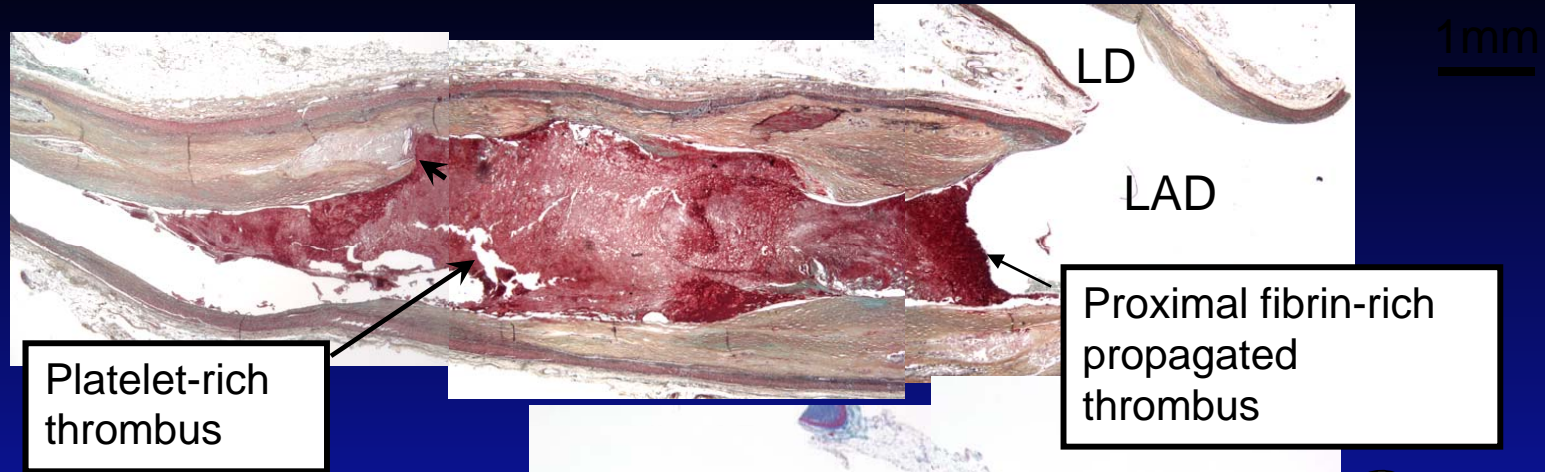


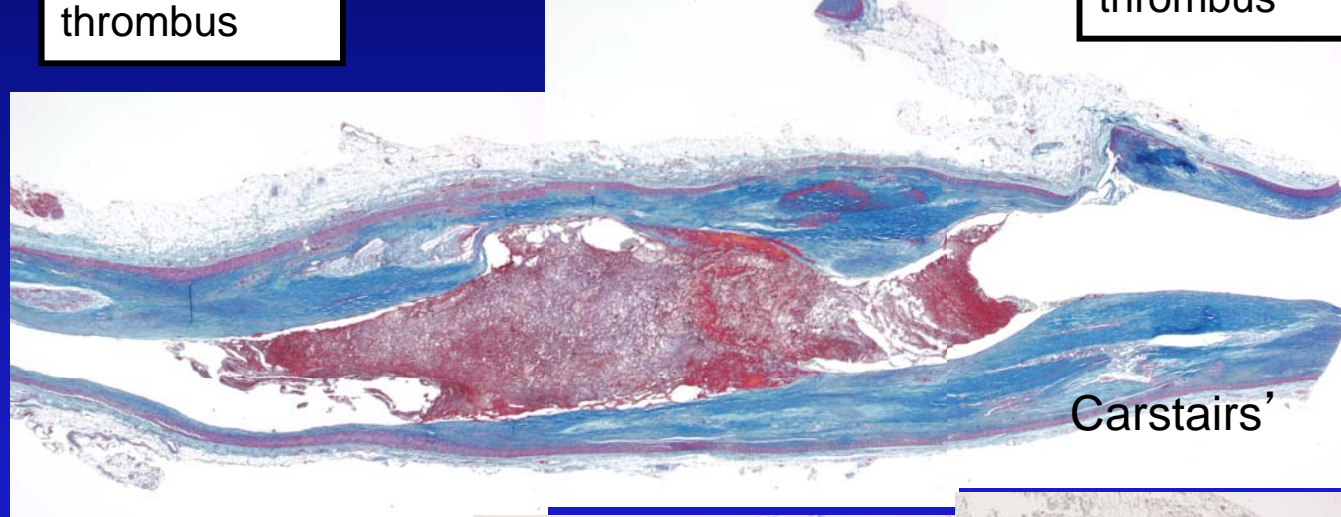
Fig 3-1

# Thrombus Propagation in Plaque Rupture

A



B



C



D

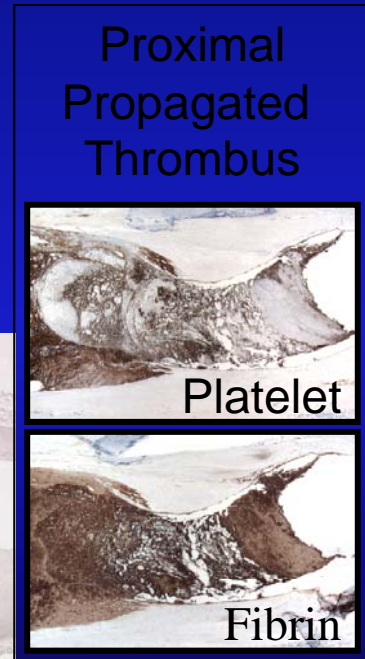
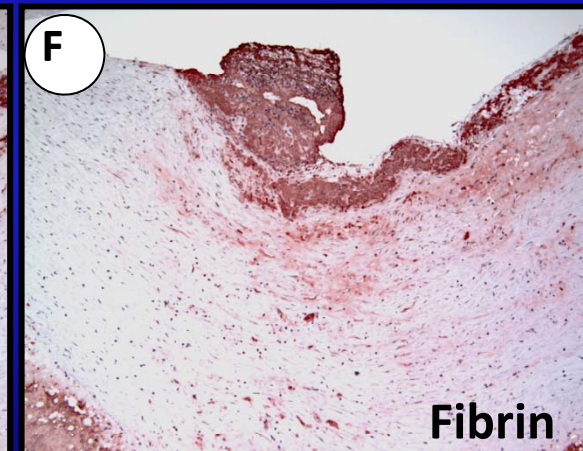
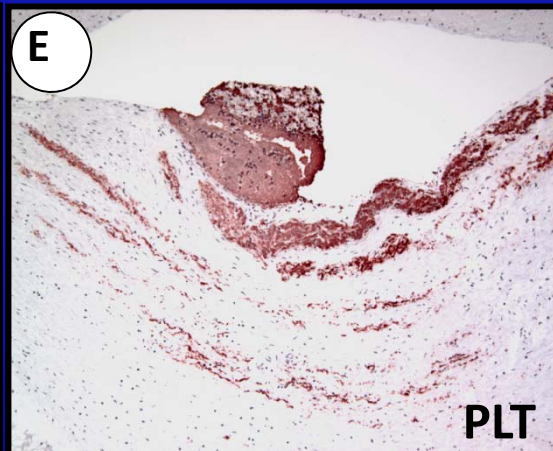
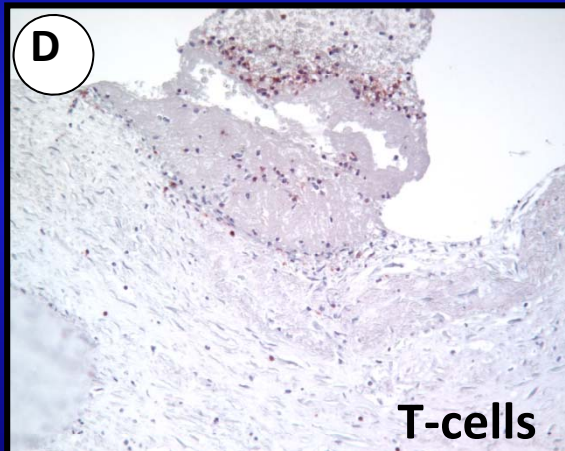
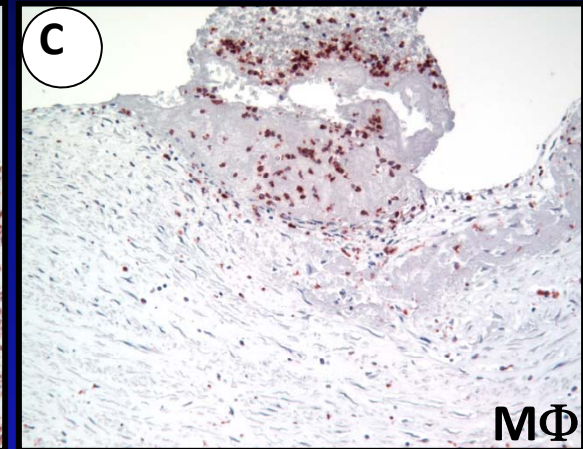
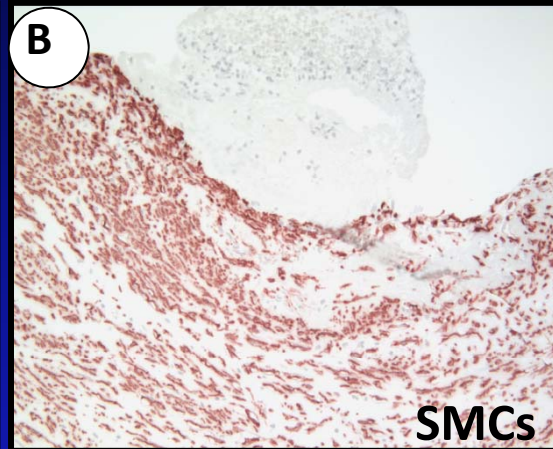
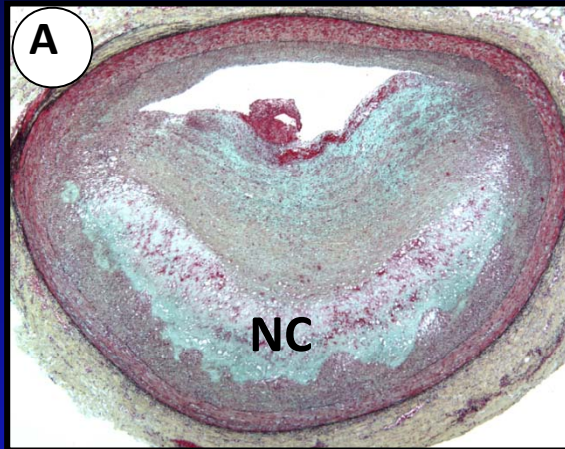


Fig. 3-15



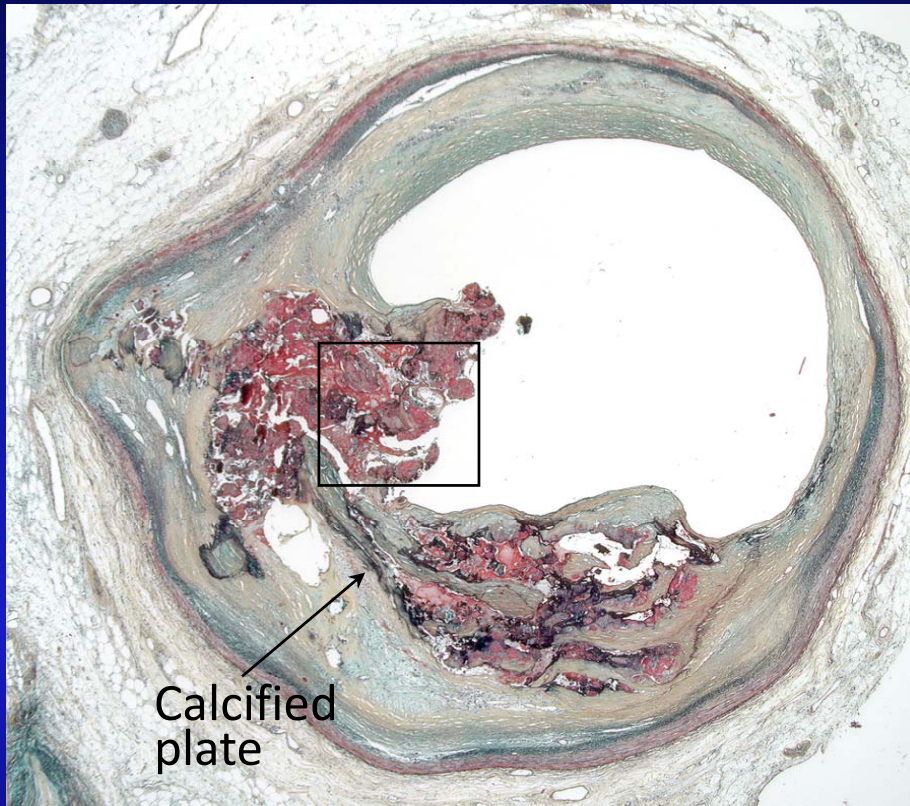
## Plaque Erosion: 30-35% of thrombi in SCD

*Plaque erosion in a 33 year-old female complaining of chest pain for two-weeks and discharged from the emergency room with a diagnoses of anxiety.*

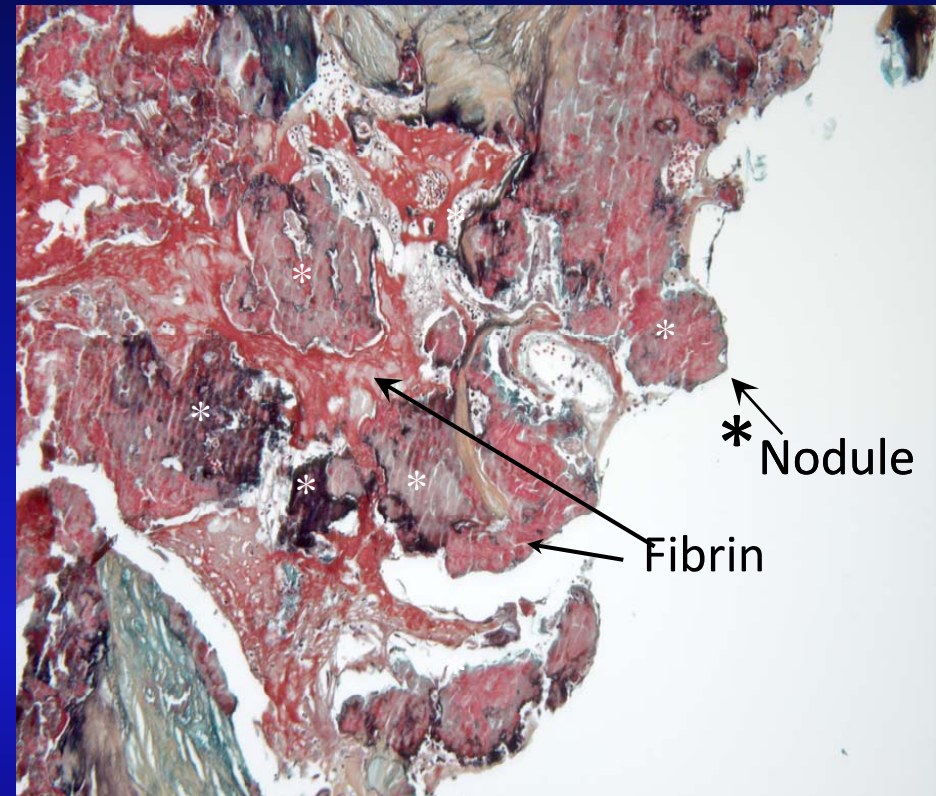


# Calcified Nodule

A



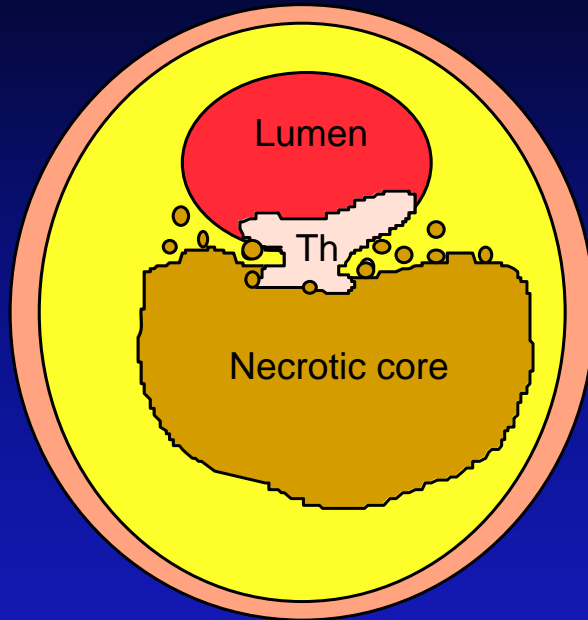
B



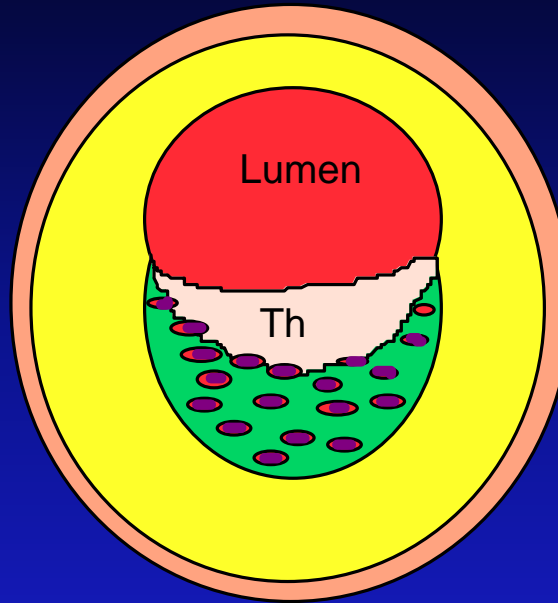
Frequency 2-7% of SCD, Older individuals, usually Men, equally common in tortuous right and left coronary arteries

# Clinical and Morphologic Difference in Plaques Associated with Luminal Thrombi

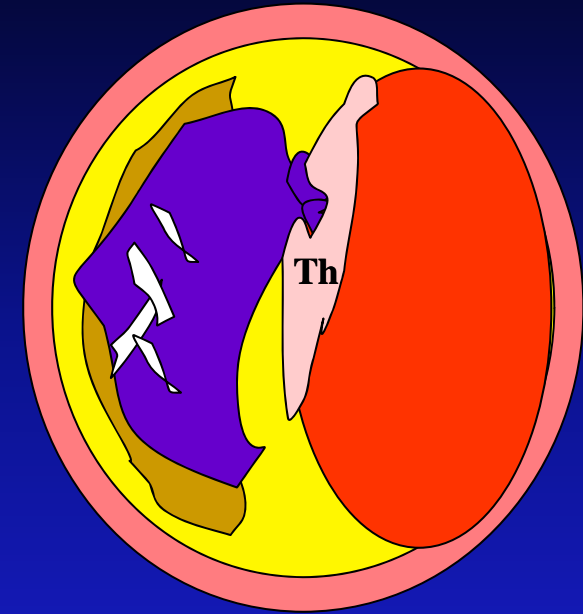
Plaque rupture



Plaque erosion



Calcified nodule

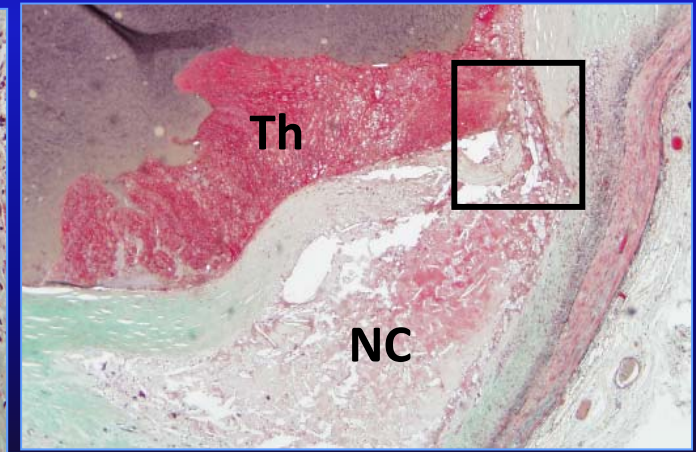
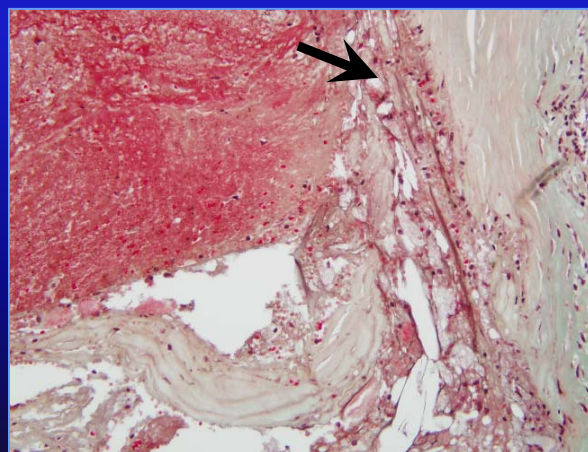
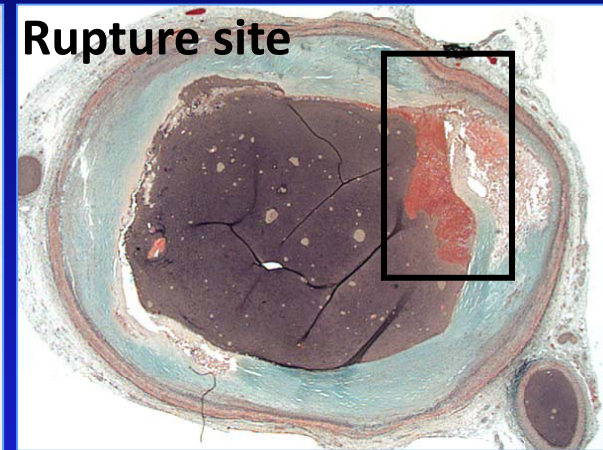
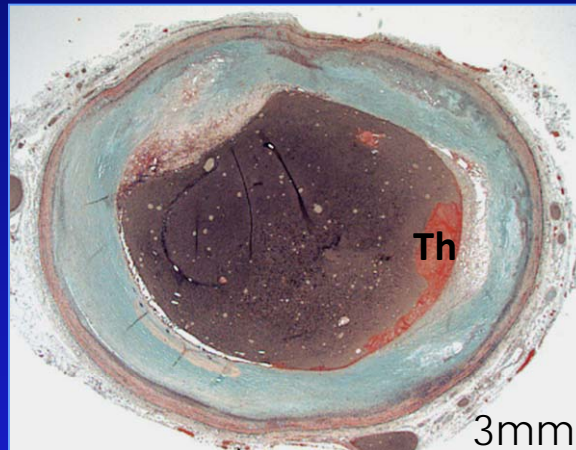
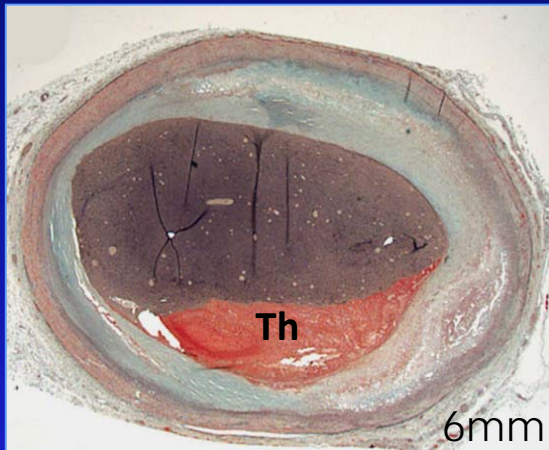
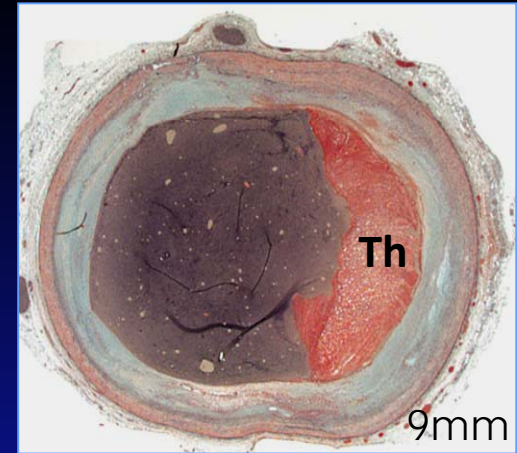


60% thrombi in SCD  
M>F, Older, Ca<sup>++</sup>  
Eccentric = concentric  
Greater % stenosis  
Macs, T cells,  
HLA-DR

30-35% thrombi in SCD  
M=F, younger  
Usually eccentric  
Lesser % stenosis  
SMC rich, proteoglycans

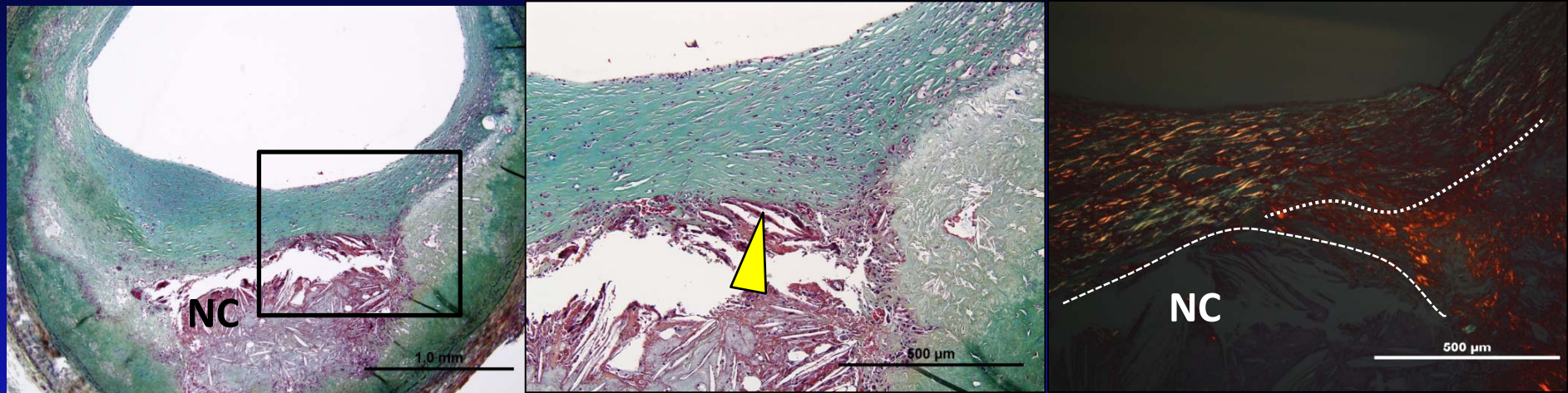
2-7% thrombi in SCD,  
calcified plates,  
M>F, older,  
mid RCA & LAD  
Usually eccentric  
Stenosis variable  
Nodules of calcium

Plaque rupture with mild stenosis and non-occlusive thrombus: a mechanism by which plaques progress from an asymptomatic to symptomatic phase

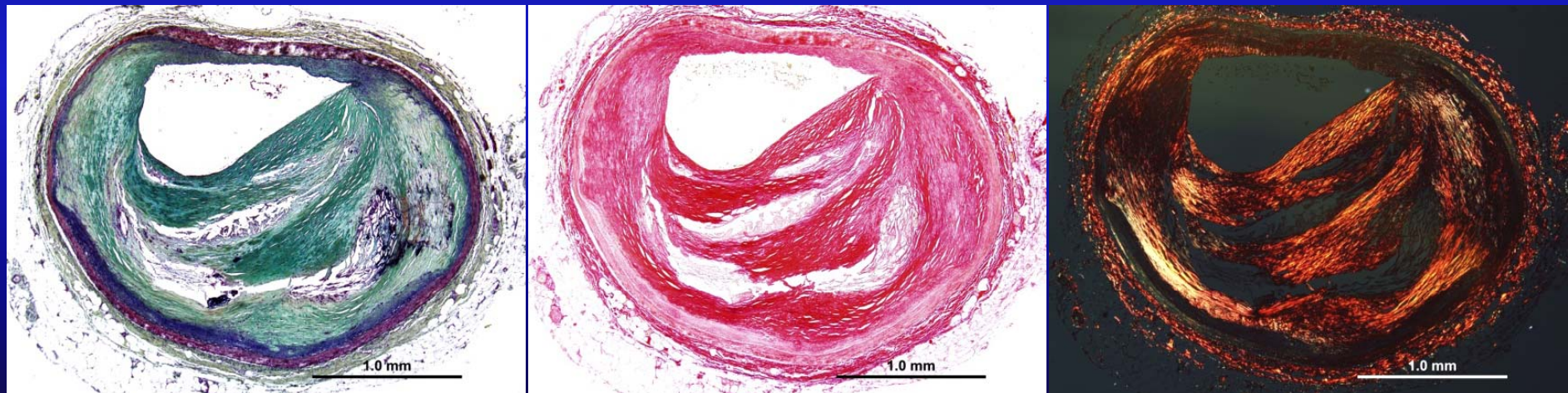


# Healed lesions lead to plaque progression

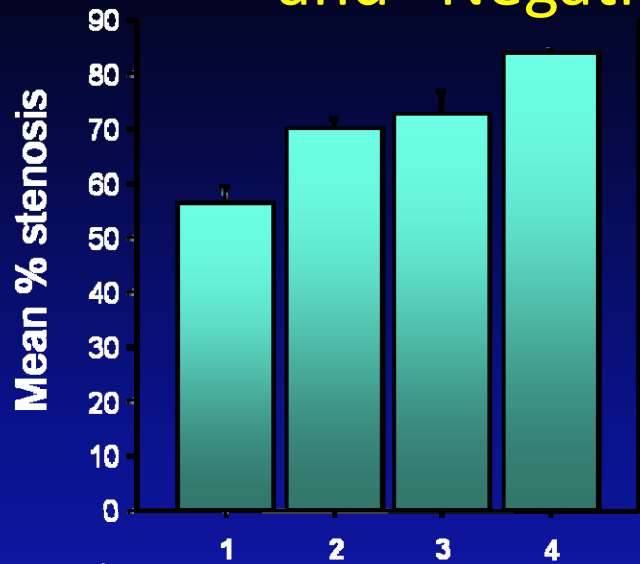
## Healed plaque rupture



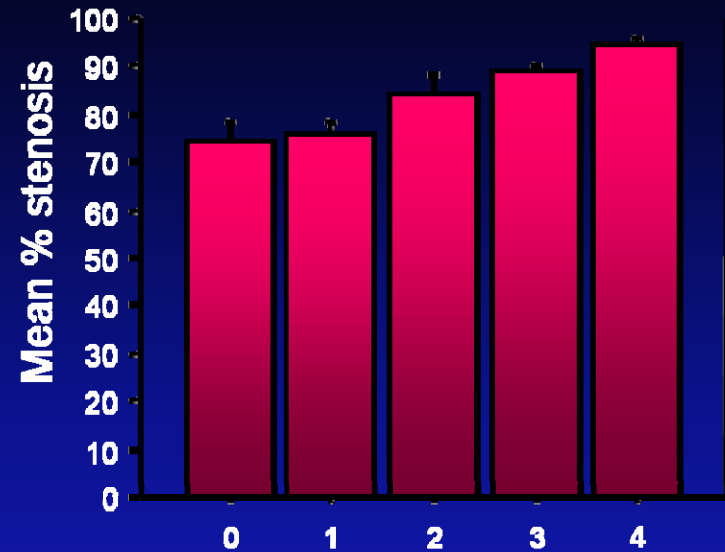
## Multiple healed rupture



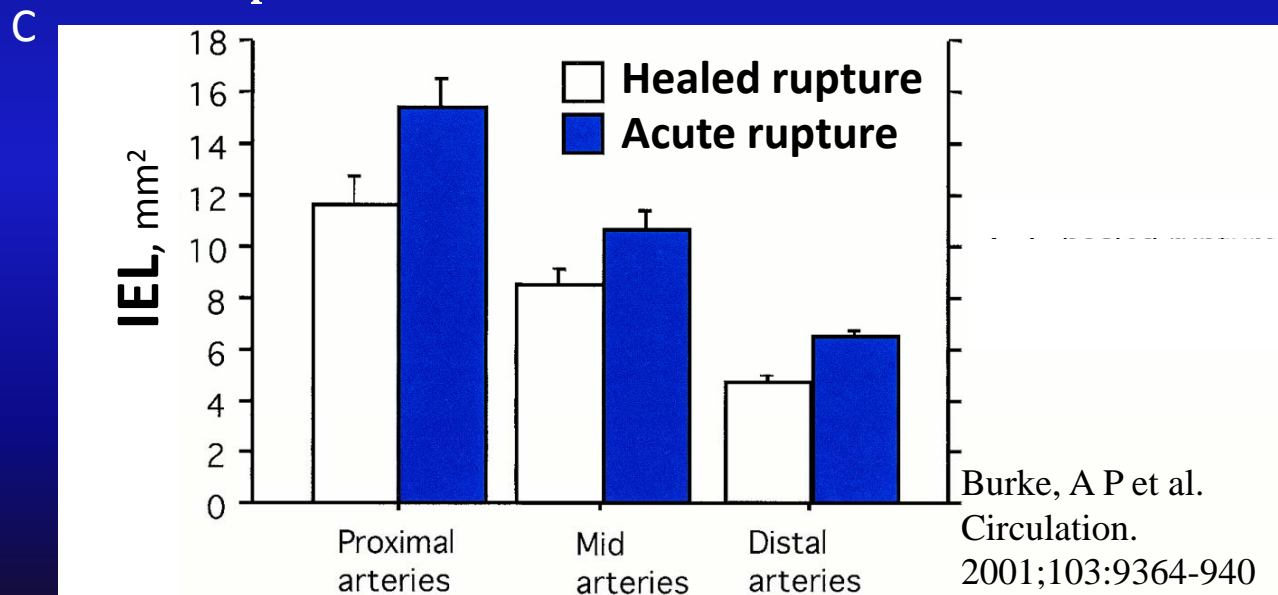
# Healed Rupture Causes “Luminal Narrowing” and “Negative Remodeling”



A  
Number of prior ruptures,  
healed rupture sites

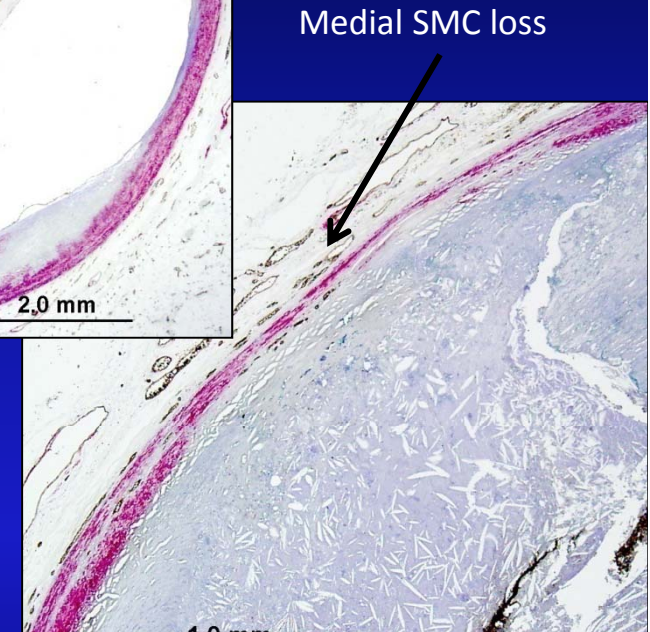
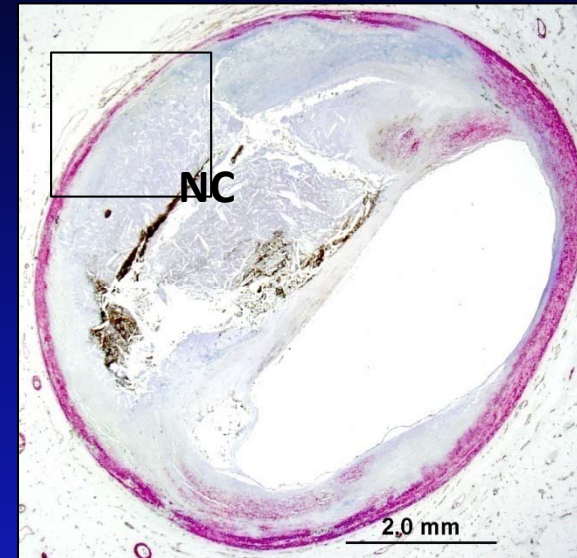
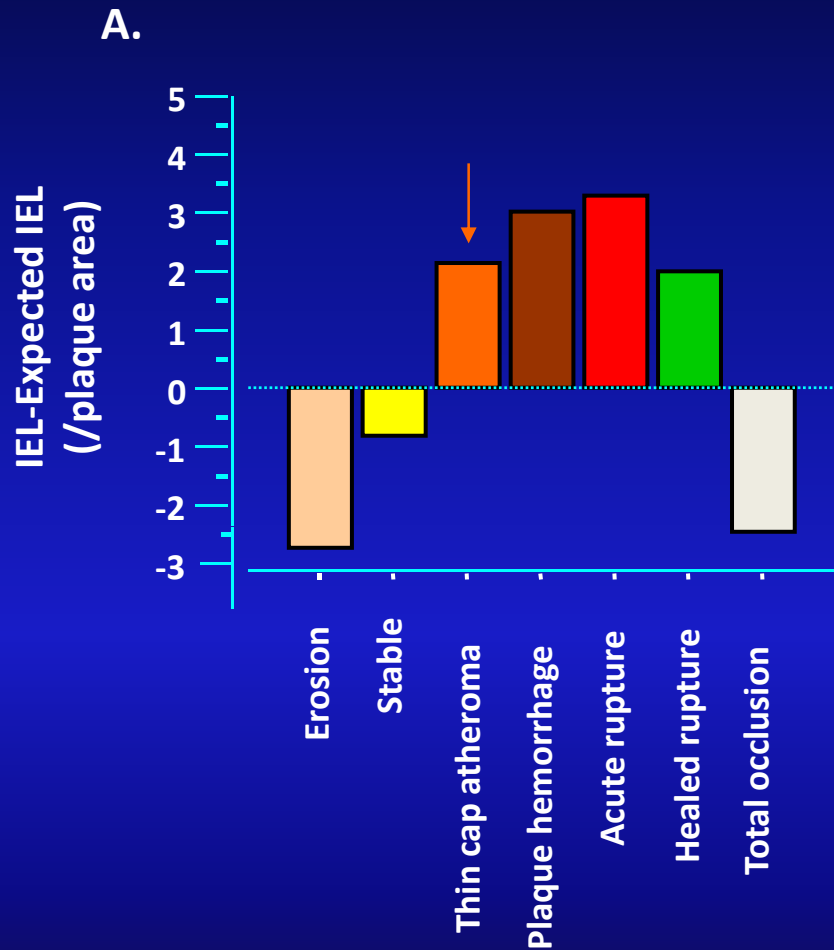


B  
Number of prior ruptures,  
acute rupture sites

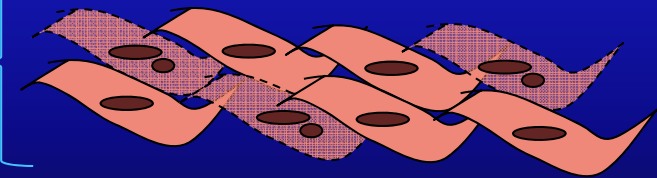


Burke, A P et al.  
Circulation.  
2001;103:9364-940

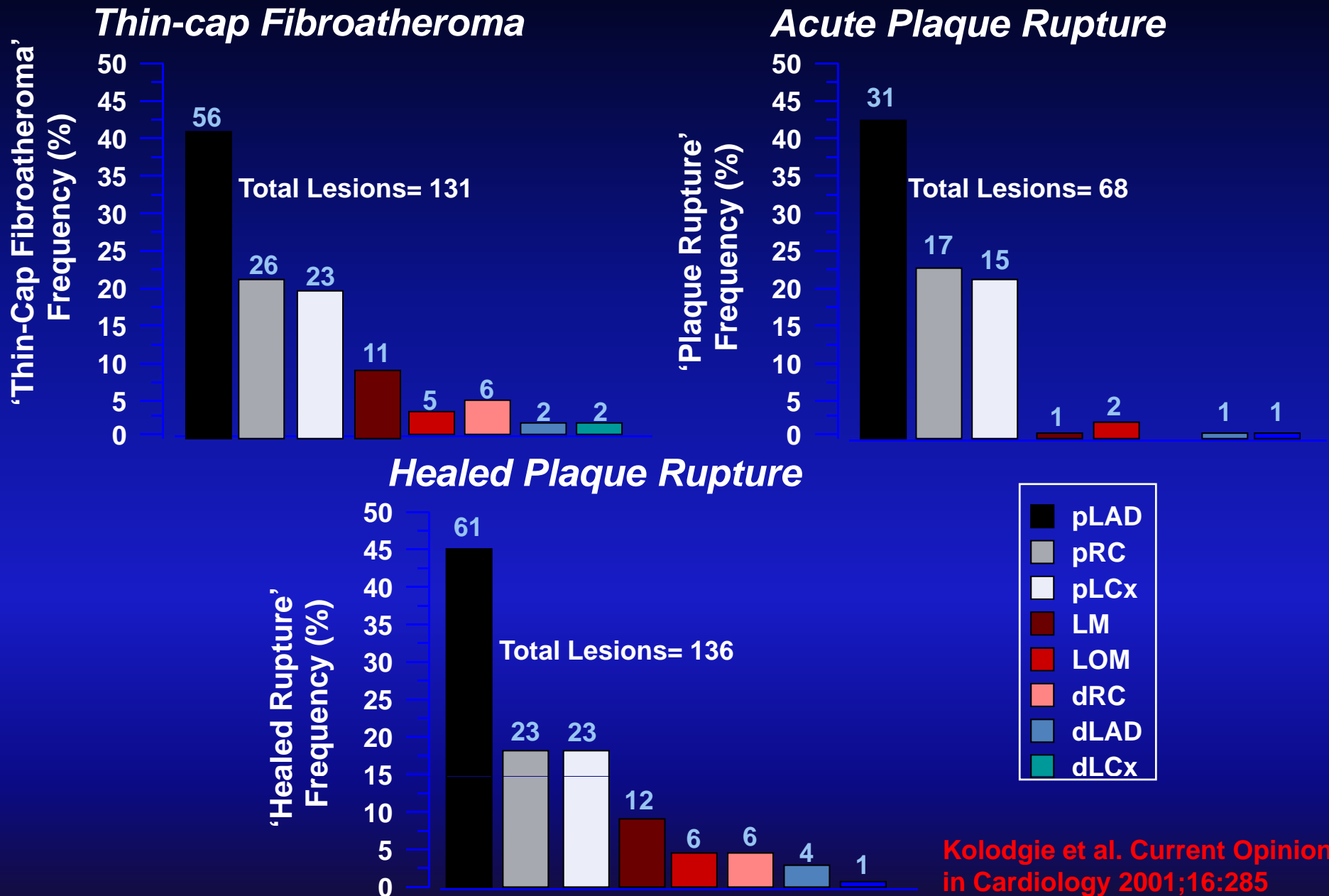
# Remodeling in Varying Coronary Lesion Morphologies



Medial SMC apoptosis

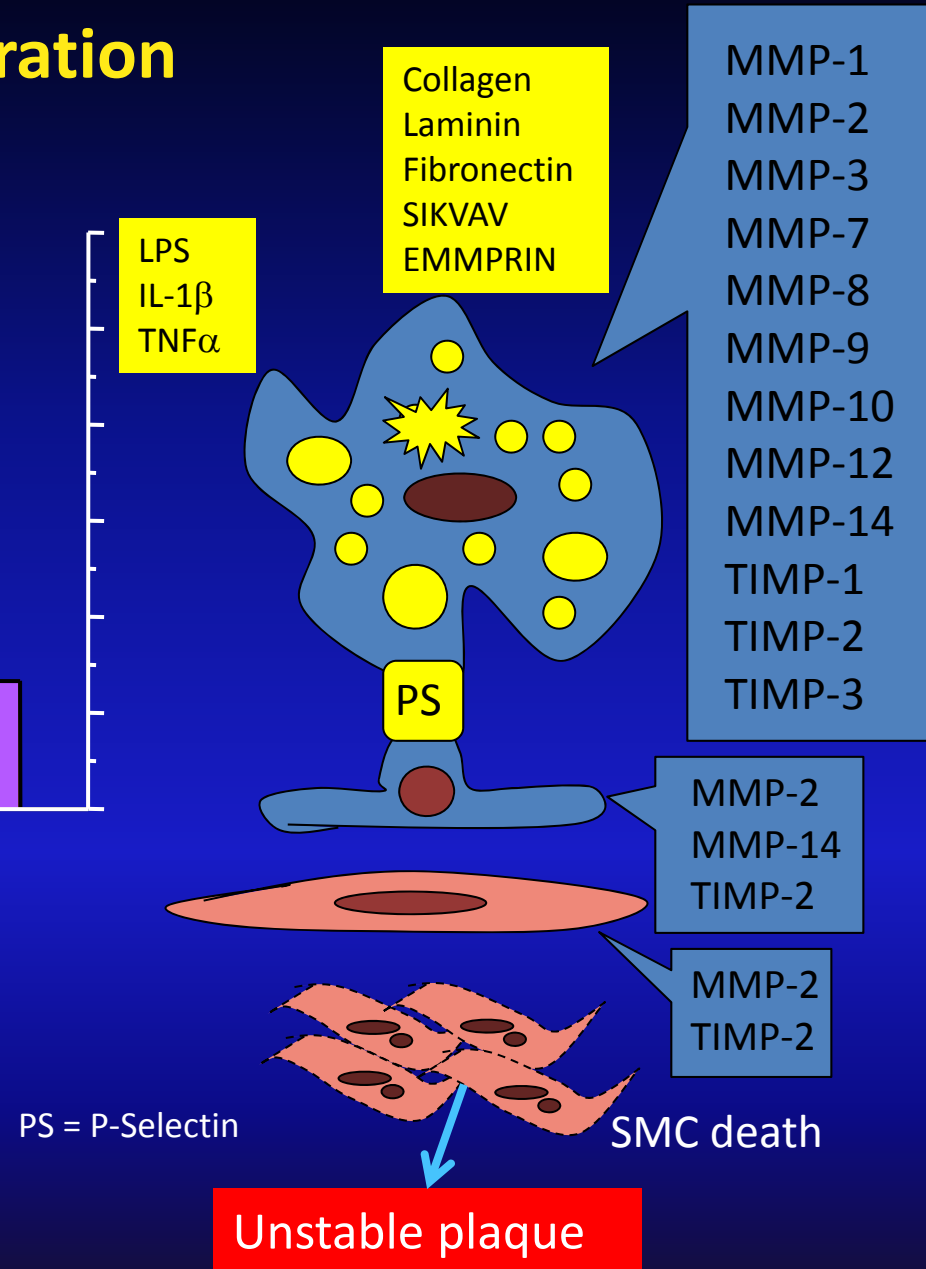
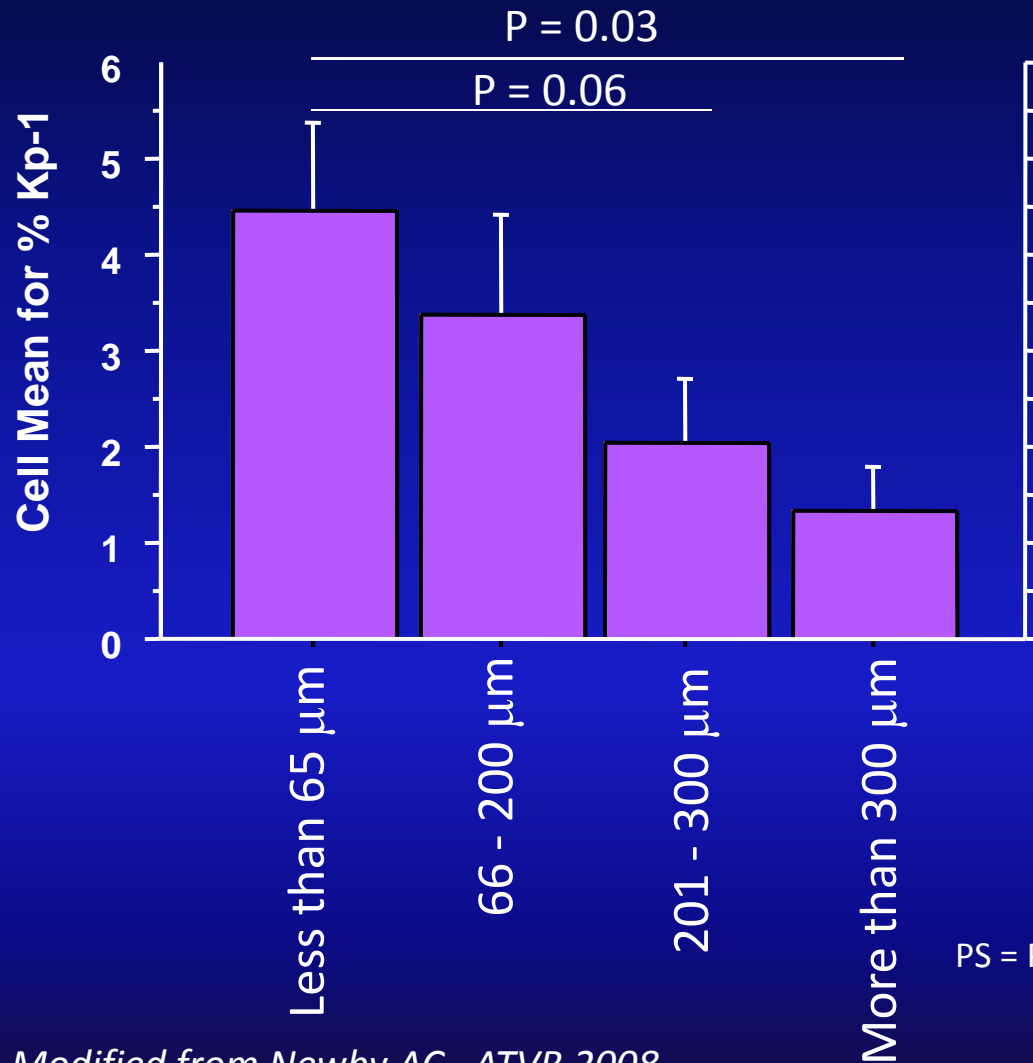


# Frequency and Location of Unstable Lesions: Thin-cap Atheromas, Acute and Healed Ruptures in the Coronary Circulation





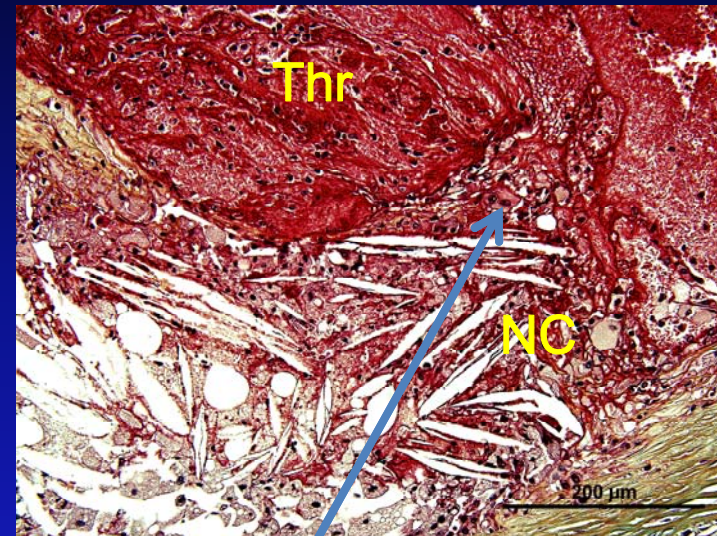
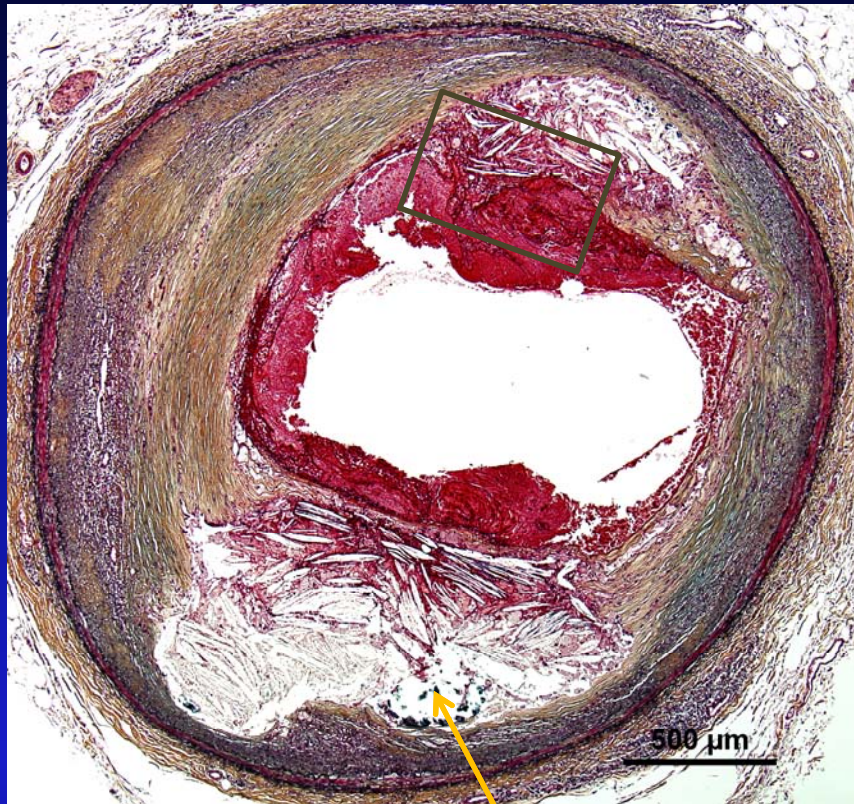
# Relationship of Fibrous Cap Thickness to Macrophage Infiltration



Modified from Newby AC. ATVB 2008

# Development of Necrotic Core

# The Necrotic Core “graveyard of dead Mφs”



Ruptured plaque at  
area of thinned  
fibrous cap

## Necrotic Core

inflammation

Coagulation  
thrombosis

proteases

stress on fibrous cap

# Adaptive Intimal Thickening

## Pathologic Intimal Thickening

Smooth muscle cell

- proliferation
- death (apoptosis)
- microcalcification

Extracellular lipid (lipid pool) ± luminal macrophages

Macrophage  
Infiltration into LP,  
apoptosis

Inflammation – T-cells

Fibroatheroma ( ± calcification)

Macrophage infiltration  
(proteolytic enzymes)

(early and late)

Hemorrhage (red cell membrane)

Thin cap fibroatheroma

Microcalcification  
of macrophages + iron

Flow disturbances

Plaque rupture

Lesion enlargement – asymptomatic or symptomatic

## Macrophages

“Fatty streak”

Associated with  
lesion regression

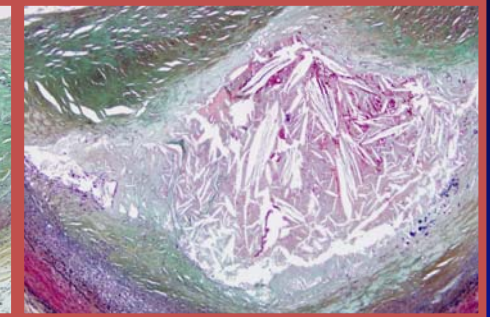
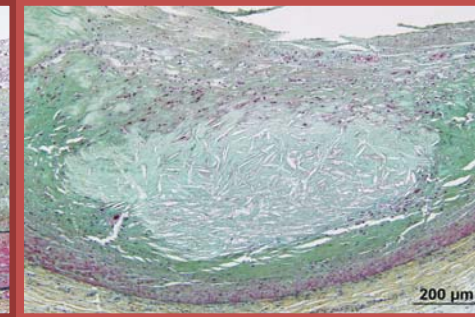
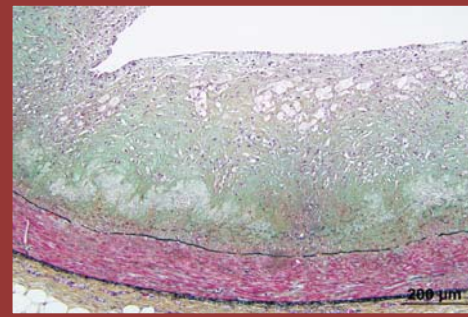
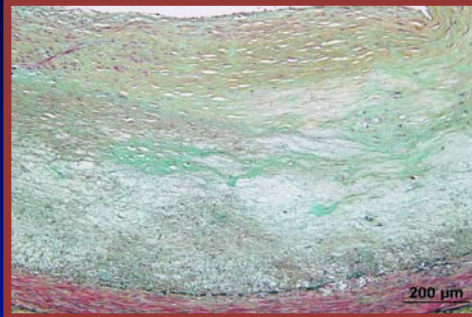
# Histomorphometric Analysis of Plaque Component

Pit (no Macs)

Pit (+ Macs)

Early FA

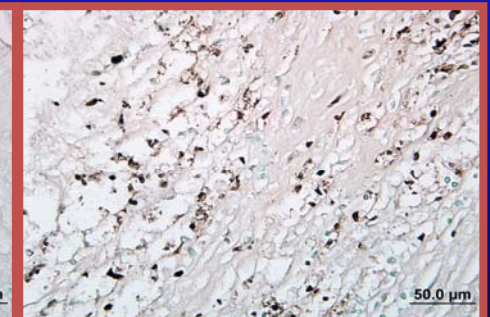
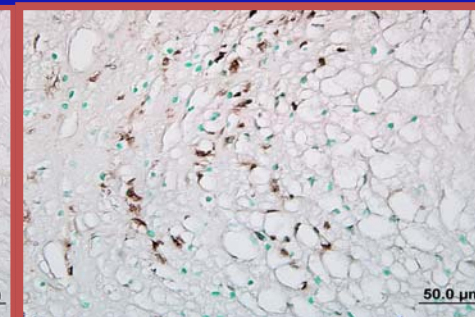
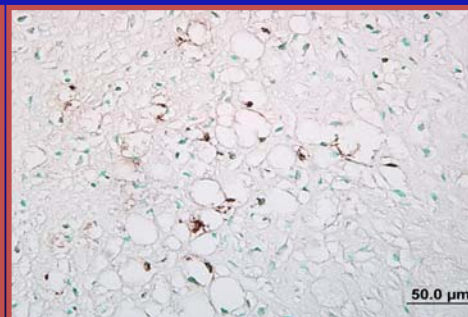
Late FA



Macrophage (KP-1.CD68)



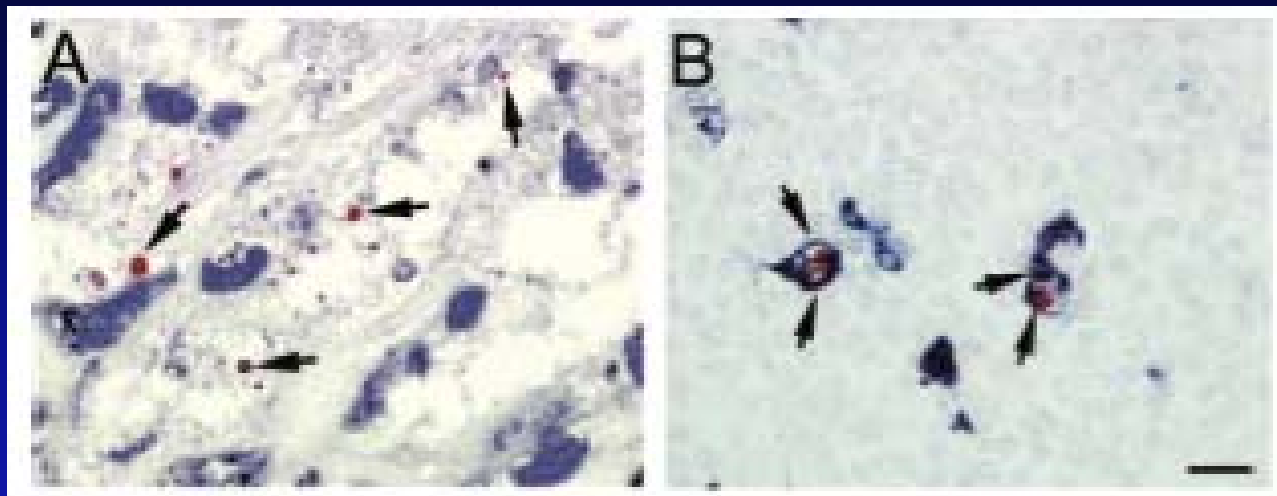
In-Situ End Labeling (DNA fragmentation, apoptosis)



# Phagocytosis efficiency of apoptotic cells (AC) in advanced atherosclerotic plaque and human tonsils

Carotid plaque

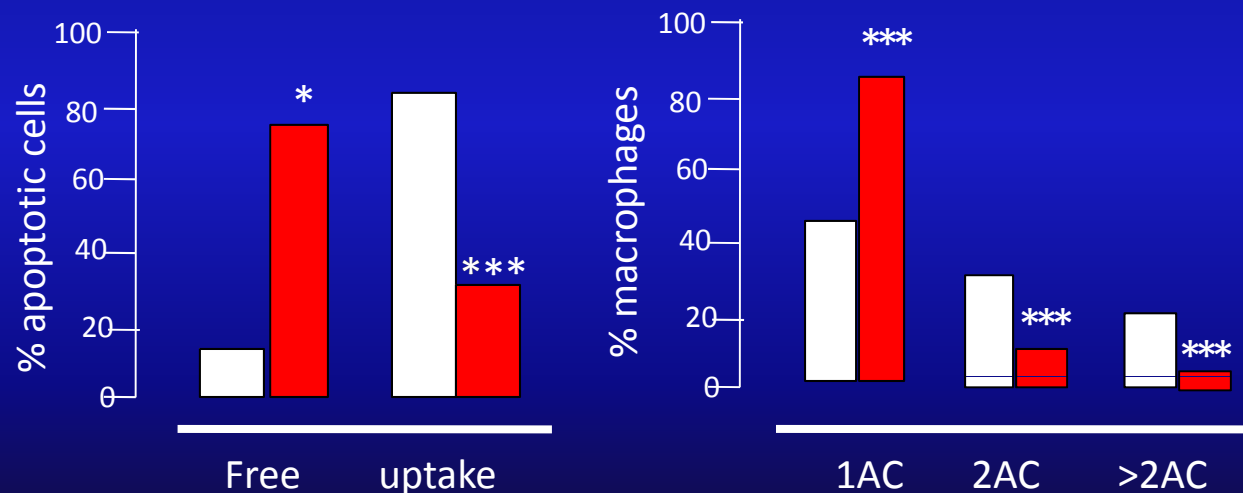
Tonsil



TUNNEL (AC, red)

CD 68  
(macrophages, blue)

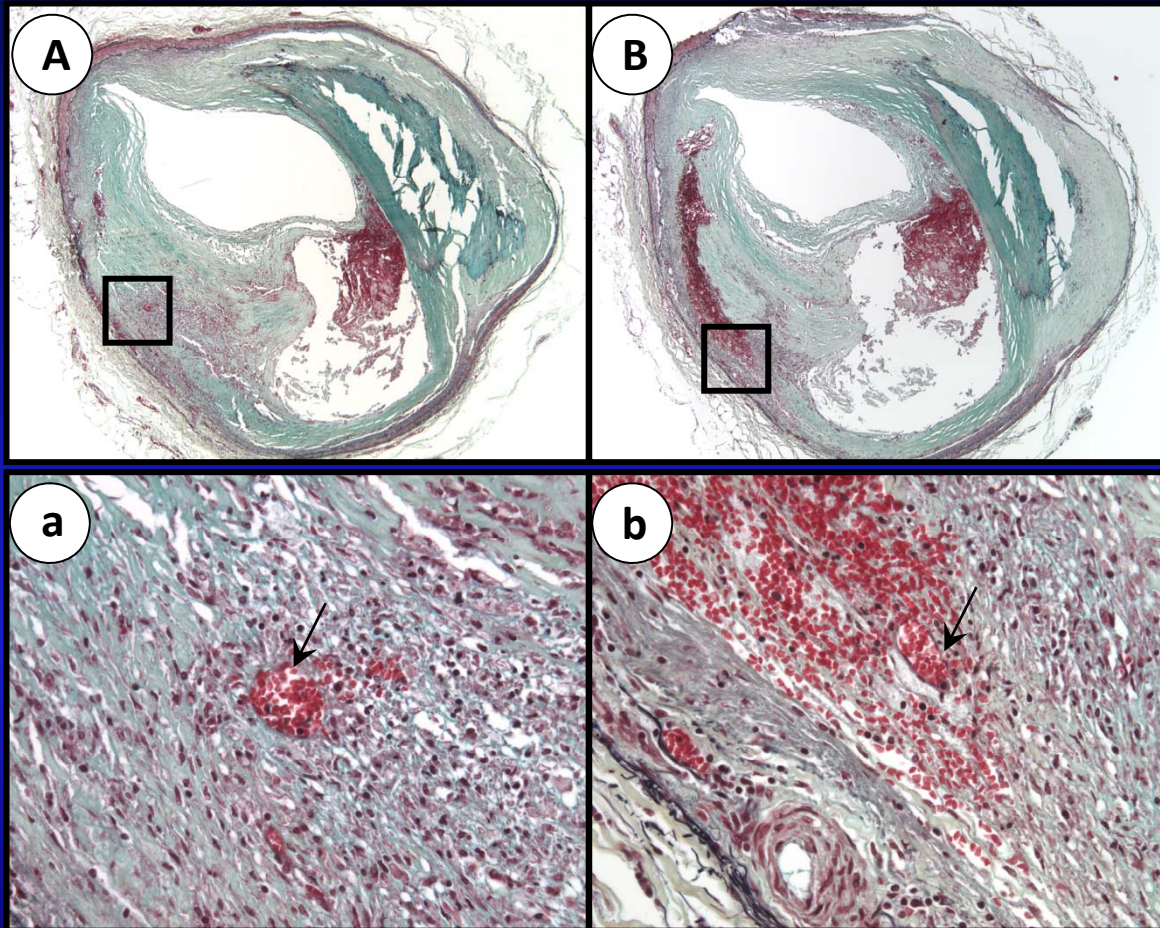
Tonsil  
 Atherosclerotic plaque



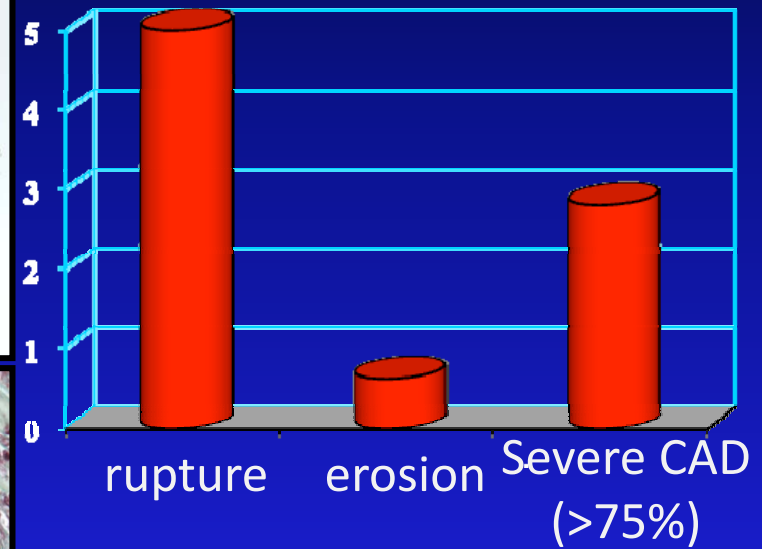
The ratio of free AC versus phagocytized AC was 19 times higher in atherosclerotic plaques as compared to human tonsil

# Thin-cap Fibroatheroma

*Recent Intraplaque Hemorrhage is seen at Multiple sites in Patients Dying SCD*

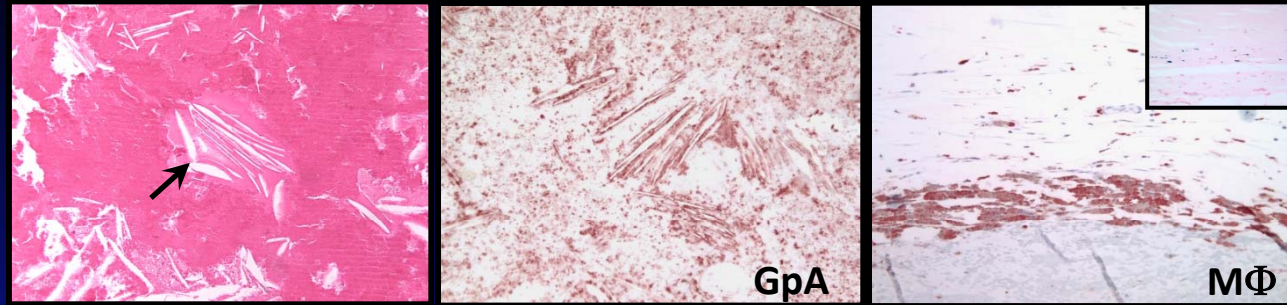


Frequency of Plaque Hemorrhage

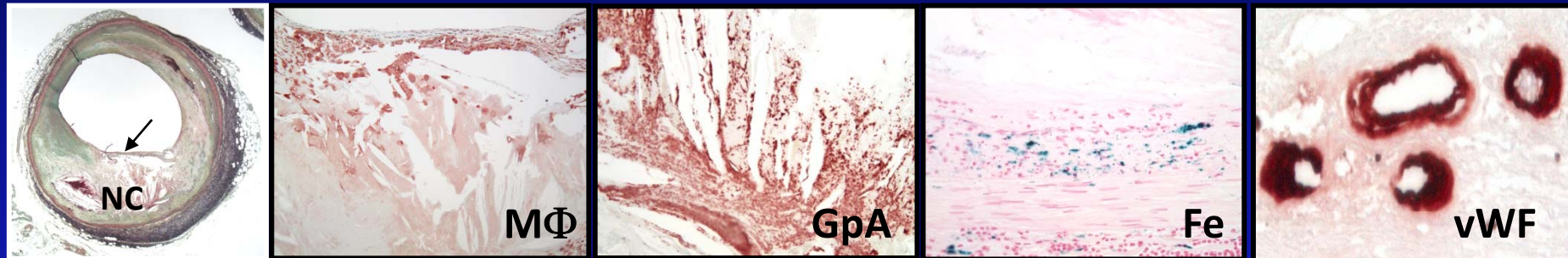


# Morphometric Analysis of Hemorrhagic Events in Human

Hemorrhagic Pericarditis



Vulnerable Plaque

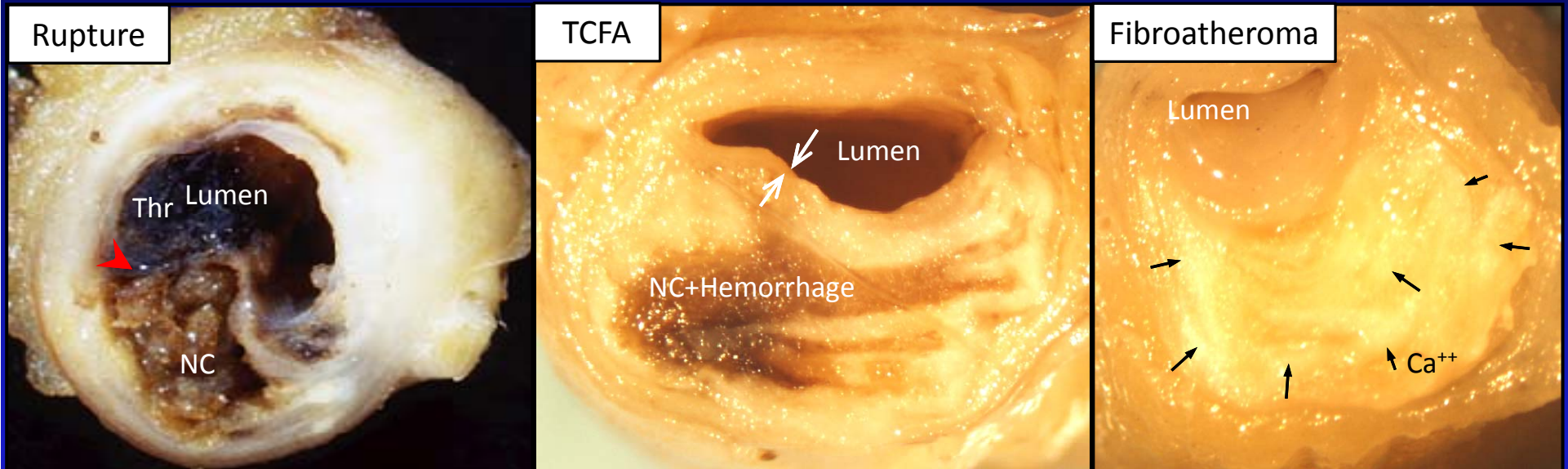


Plaque Type	GpA Score	Iron	Necrotic Core (mm <sup>2</sup> )	MΦ (mm <sup>2</sup> )
PIT <i>no</i> core (n=129)	0.09 ± 0.04	0.07 ± 0.05	0.0	0.002 ± 0.001
FA <i>early</i> core (n=79)	0.23 ± 0.07	0.17 ± 0.08	0.06 ± 0.02	0.018 ± 0.004
FA <i>late</i> core (n=105)	*0.94 ± 0.11	*0.41 ± 0.09	*0.84 ± 0.08	*0.059 ± 0.007
TCFA (n=52)	*1.60 ± 0.20	*1.24 ± 0.24	*1.95 ± 0.30	*0.142 ± 0.016

Values are reported as the means ± SE, \*p < 0.001 versus early core. The number in parenthesis represent the number of lesions examined; the total number = 365. MΦ = macrophages

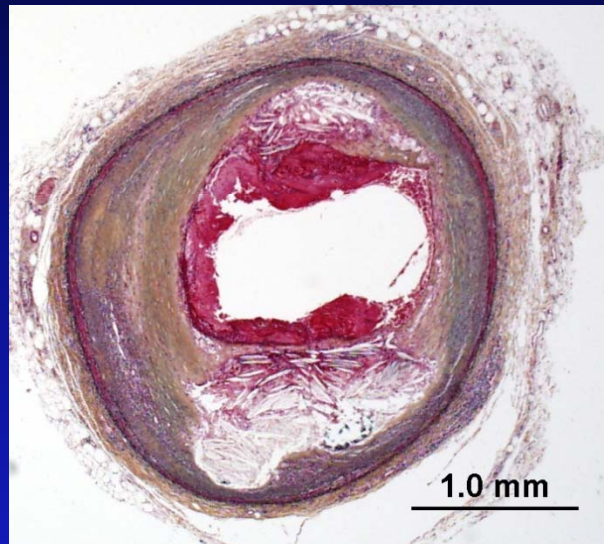


# Gross pictures of Plaque Rupture and TCFA

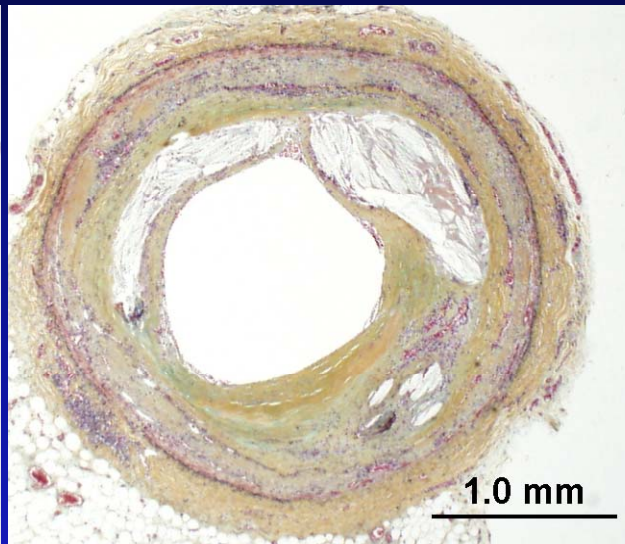


# Can we better characterize the differences between these three types of plaques?

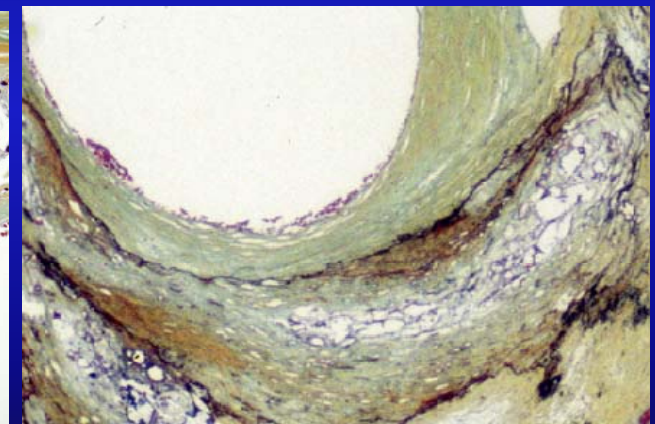
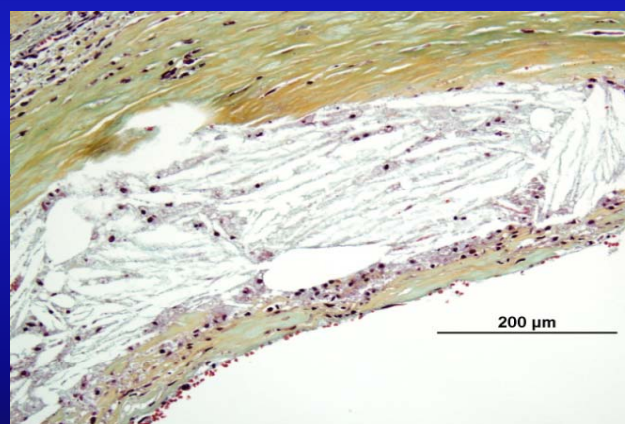
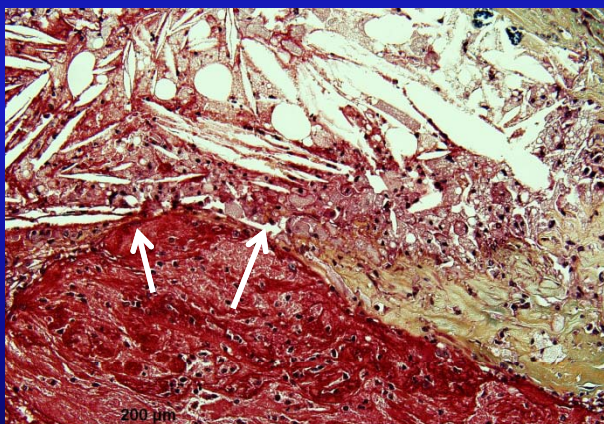
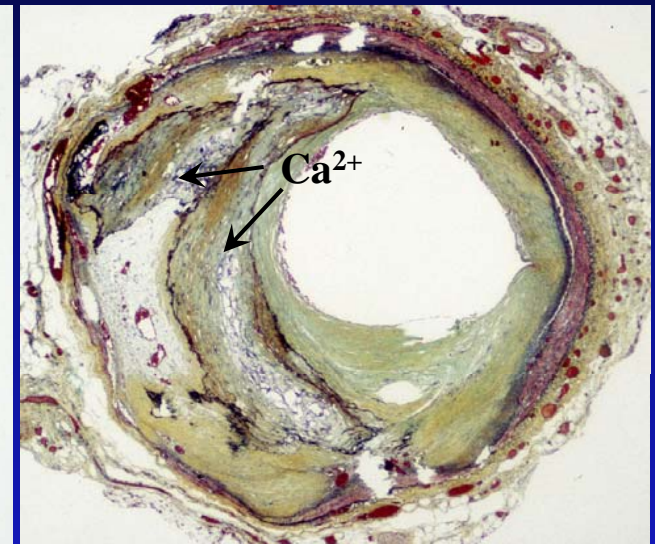
Plaque Rupture



Thin cap fibroatheroma



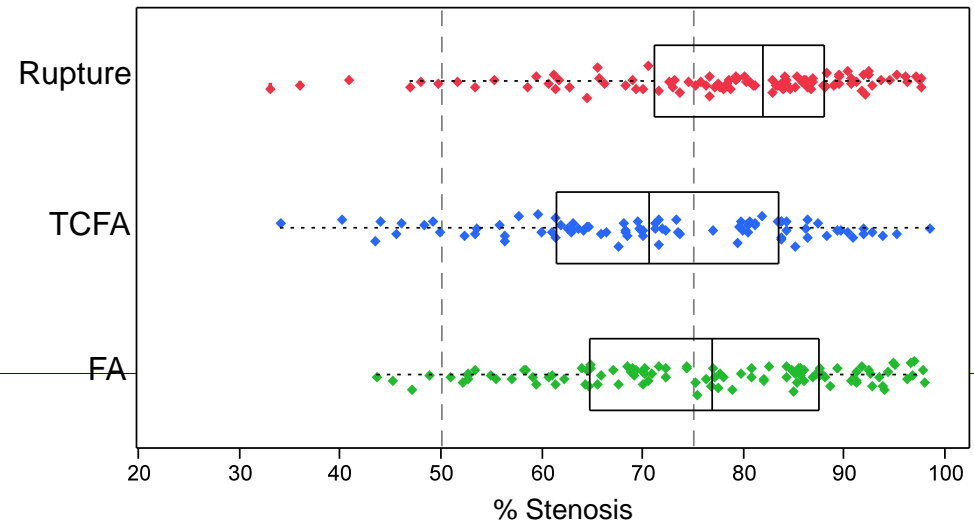
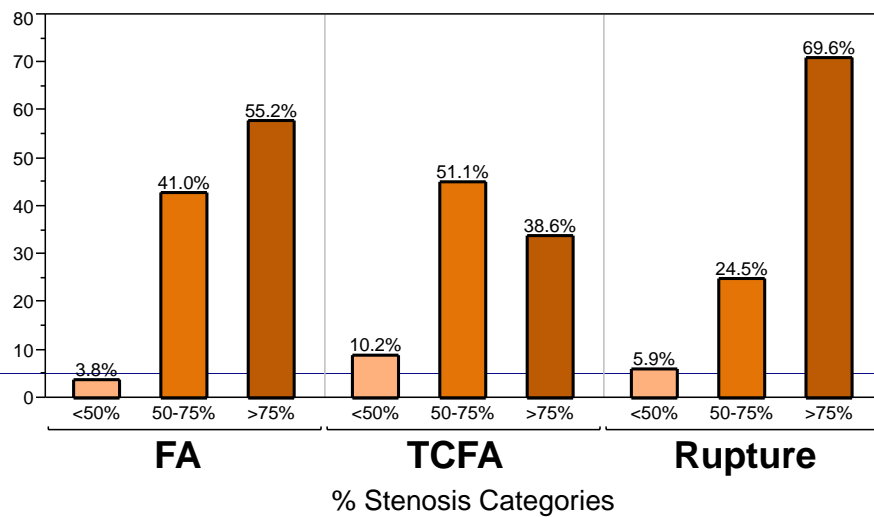
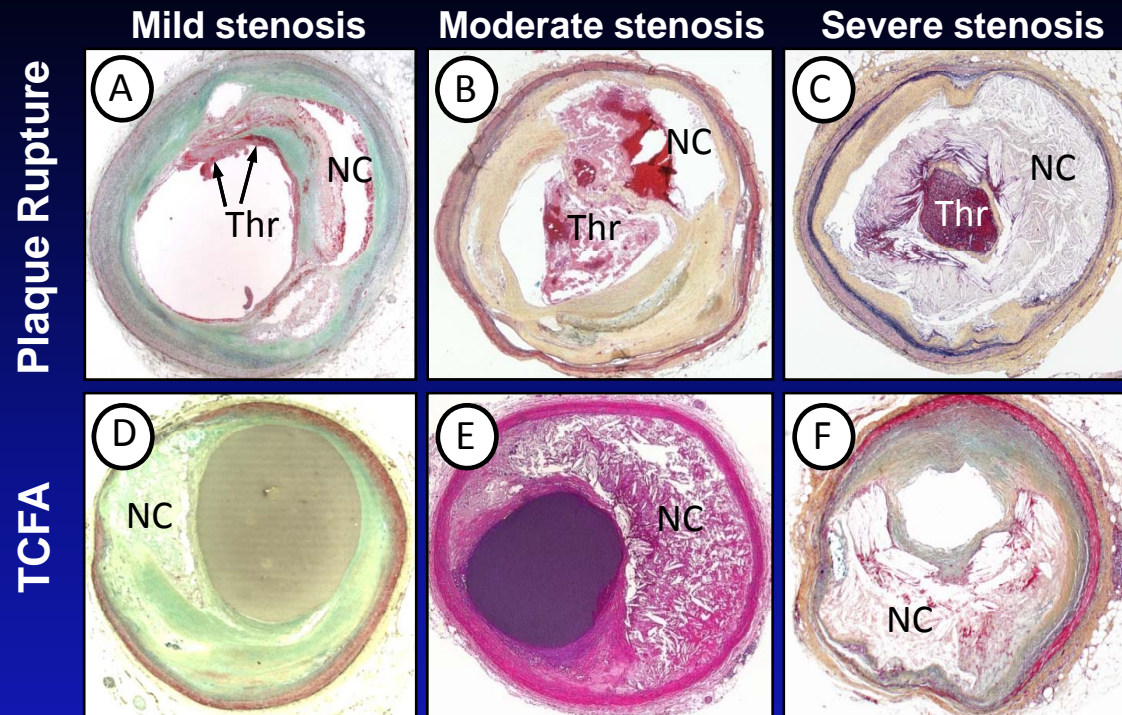
Fibroatheroma -SP



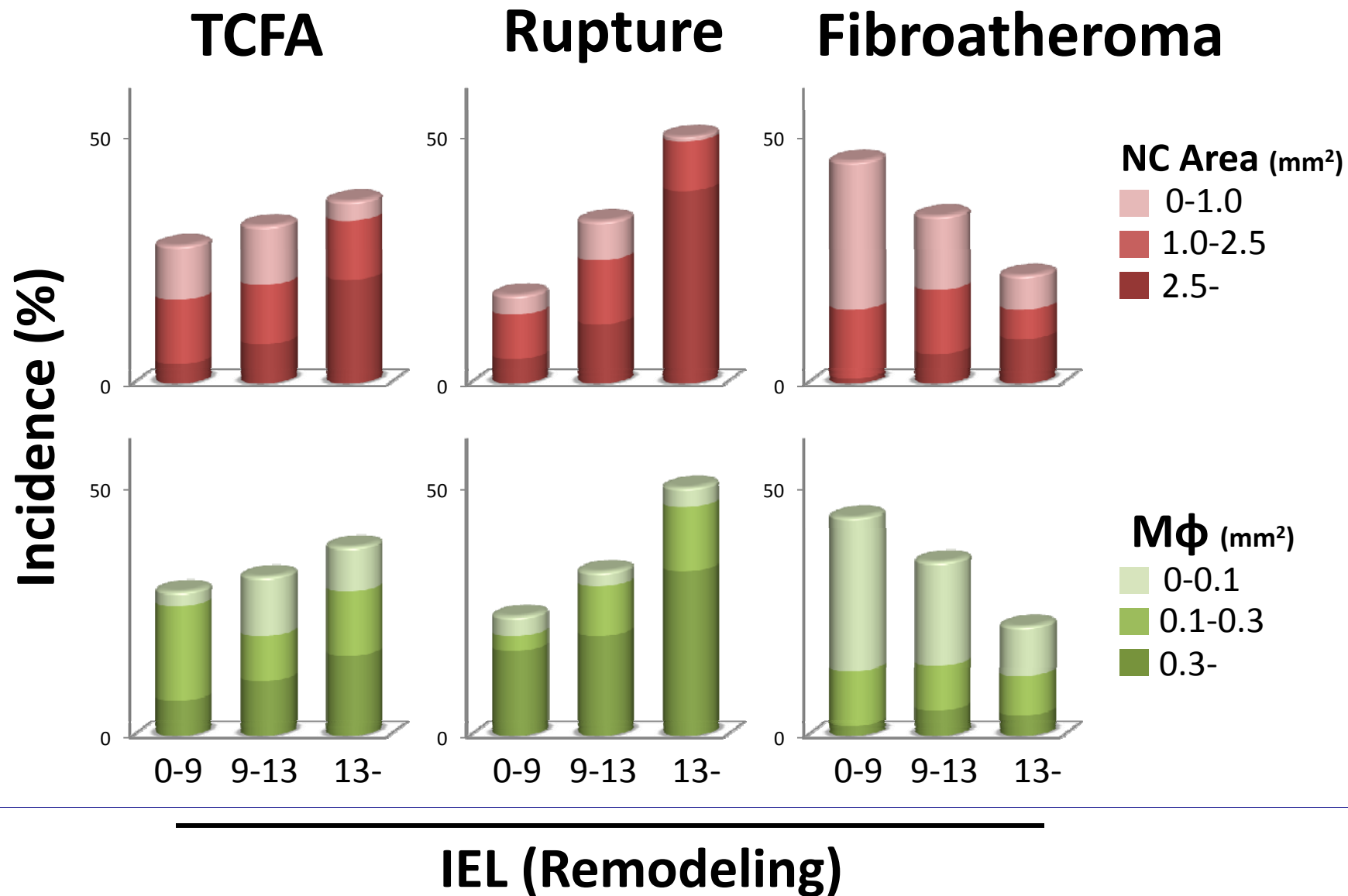
# Histomorphological Comparison of PR, TCFA and FA

	Rupture (N=100)	TCFA (N=101)	Rupture+TCFA	FA (N=105)	P value
Prox/Mid	66/34	68/33	<u>134/67</u>	70/35	0.98
EEL, mm <sup>2</sup>	16.0 ± 6.1	14.0 ± 5.9	15.2 ± 6.3	11.6 ± 4.5	<0.0001
IEL, mm <sup>2</sup>	14.2 ± 5.9	12.4 ± 5.5	13.5 ± 6.0	10.1 ± 4.0	<0.0001
Lumen, mm <sup>2</sup>	3.2 ± 2.7	3.6 ± 2.4	<u>3.5 ± 2.9</u>	2.5 ± 1.8	0.0014
Plaque Area, mm <sup>2</sup>	11.0 ± 5.0	8.8 ± 4.4	10.0 ± 4.9	7.6 ± 3.3	<0.0001
%Stenosis	78 ± 14	71 ± 14	<u>75 ± 15</u>	76 ± 14	0.50
Total NC Area, mm <sup>2</sup>	4.37 ± 4.09	2.26 ± 1.98	3.38 ± 3.43	1.33 ± 1.00	<0.0001
Total Cal Area, mm <sup>2</sup>	0.58 ± 0.99	0.50 ± 0.94	<u>0.54 ± 0.97</u>	0.46 ± 0.81	0.46
Total Mφ Area, mm <sup>2</sup>	0.53 ± 0.44	0.31 ± 0.36	0.43 ± 0.42	0.12 ± 0.16	<0.0001
Cap thickness, mm	0.03 ± 0.01	0.04 ± 0.02	0.03 ± 0.02	0.40 ± 0.19	<0.0001

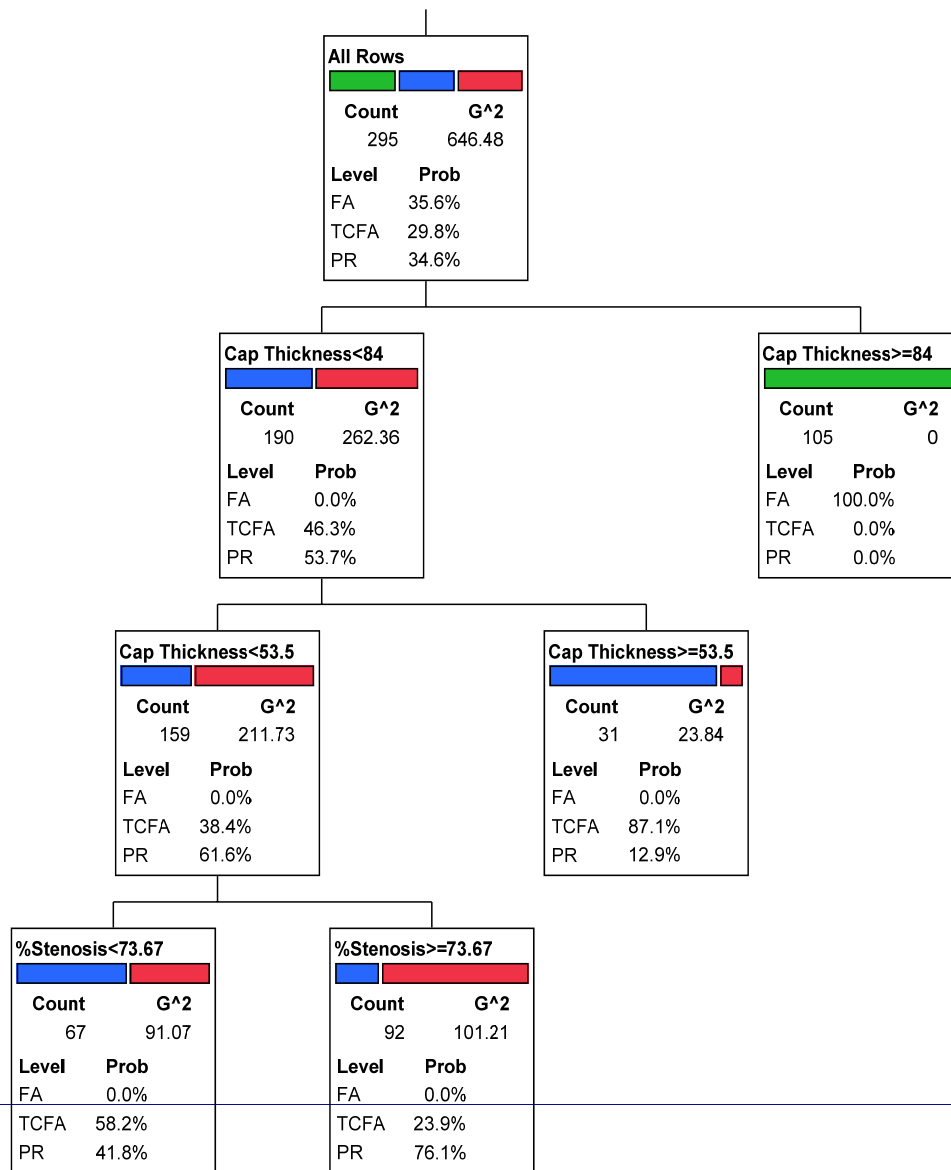
# Plaque Rupture and TCFA with Varying Luminal Stenosis






# Incidence of TCFA, Rupture, Stable Plaque Stratified by Remodeling (IEL)



# Recursive Partitioning Analysis (RPA) of Coronary arteries by Fibrous cap thickness and % Stenosis

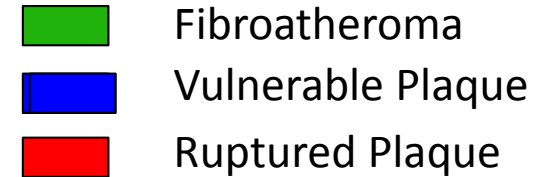
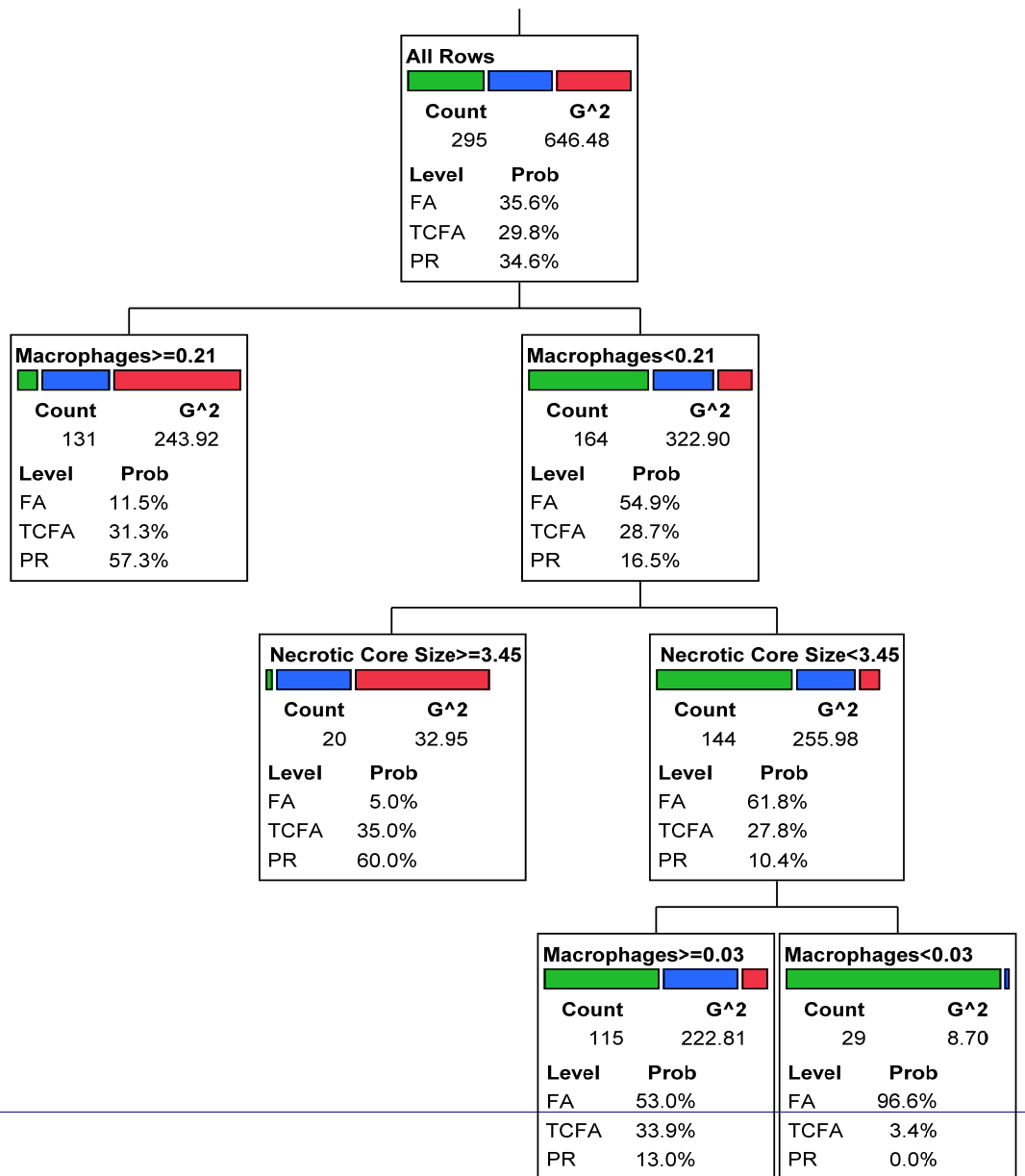


	Fibroatheroma
	Vulnerable Plaque
	Ruptured Plaque

Narula J, Nakano M, et al. Submitted JACC




# Recursive Partitioning Analysis (RPA) of Coronary arteries by

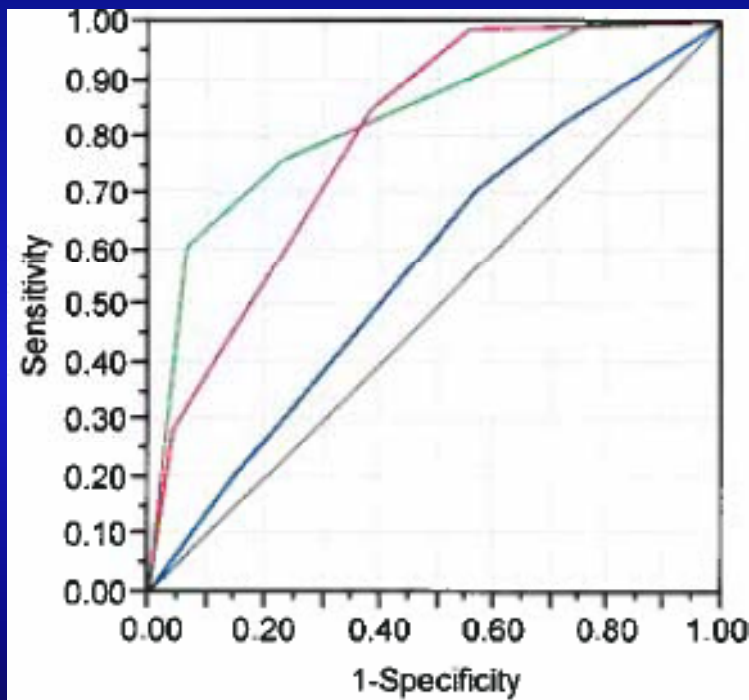
## Macrophage Infiltration and Necrotic core



## Partitioning




Analysis : %Stenosis  
 $\geq 75\%$

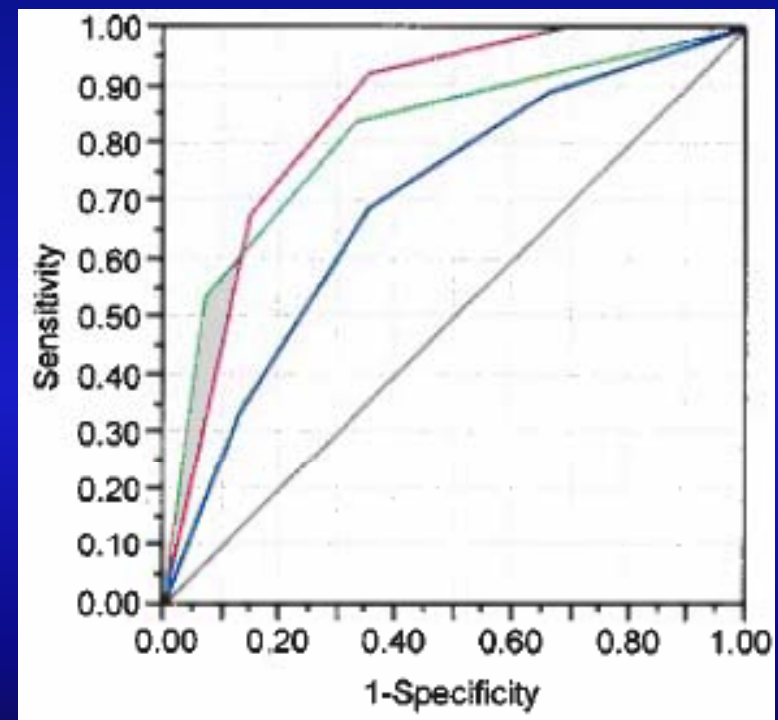
	Plaque Type	Area
	Rupture	0.7977
	TCFA	0.5790
	SP	0.8363



## Partitioning

Analysis : %Stenosis 50-  
75%

	Plaque Type	Area
	Rupture	0.8484
	TCFA	0.6979
	SP	0.8133

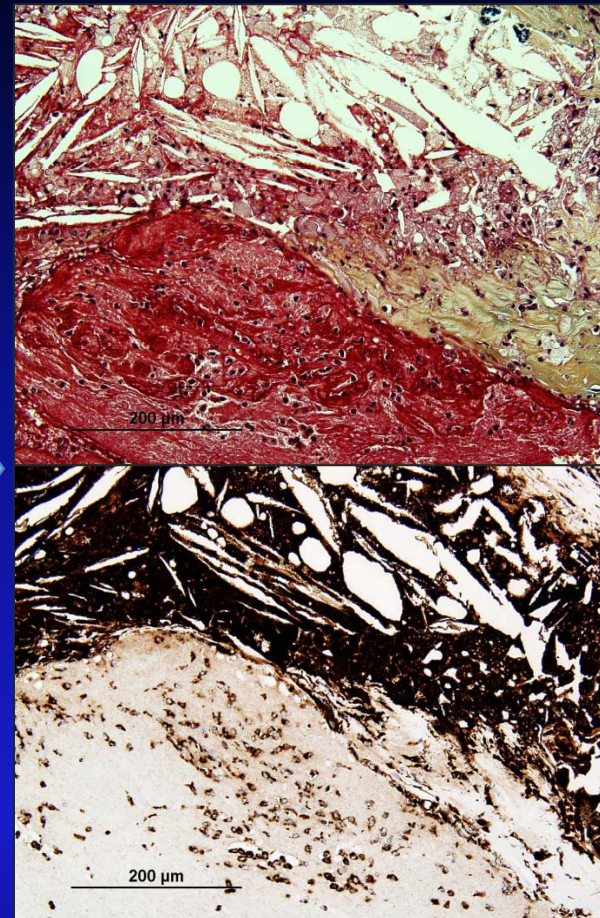
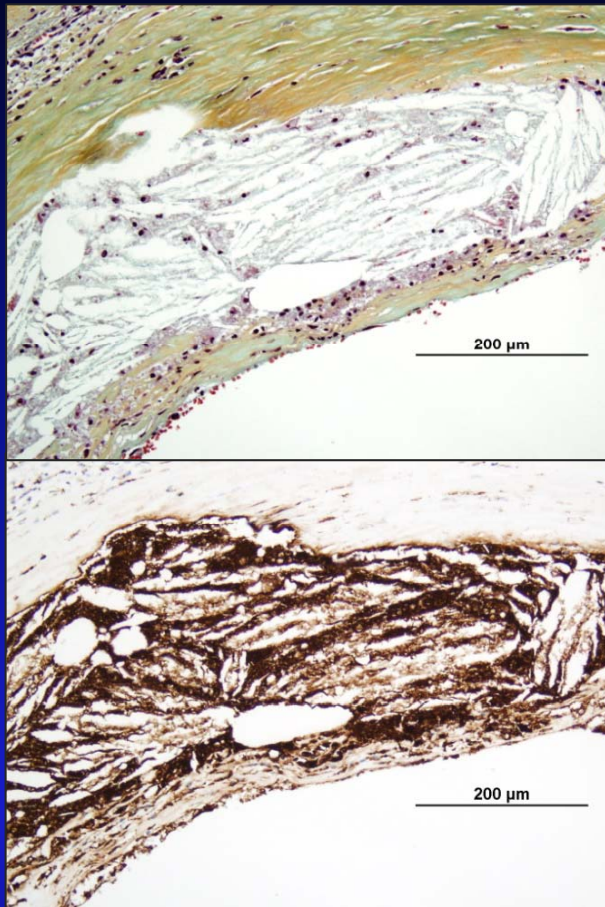




# Independent Morphological Predictor of Rupture

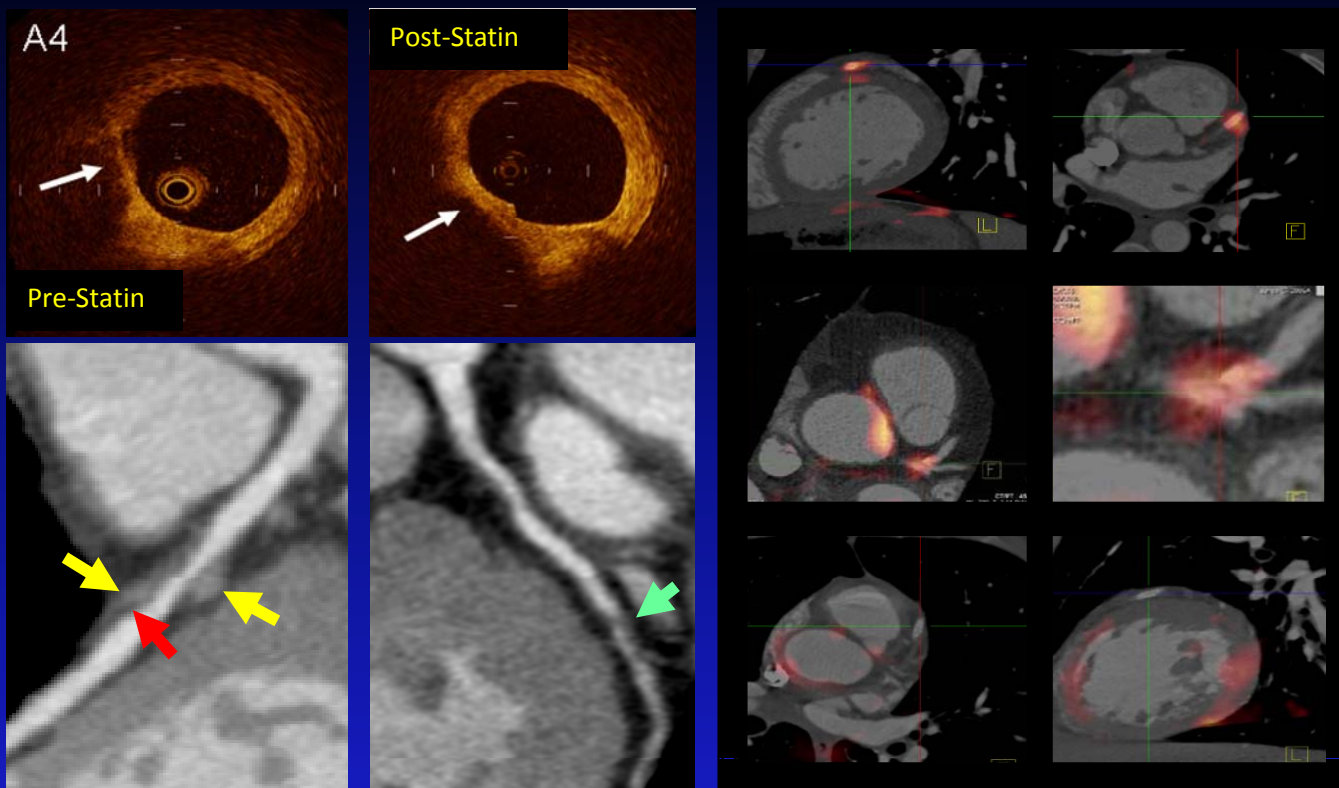
Independent risk factors for "rupture"  
**50-75% cross-sectional stenosis**

Movat  
 CD68  
 (Macrophage)



	P Value	Odds Ratio	95% CI
<b>Cap thickness</b>	0.005	0.35	0.16 – 0.69
<b>%NC</b>	0.02	2.0	1.1 – 3.7
<b>%Macrophage</b>	0.052	1.8	0.99 – 3.2

# Imaging Strategies for the Assessment of High-Risk Plaque Characteristics, including Cap Thickness (OCT), Necrotic Core (CT- low attenuation plaque [LAP]), and Inflammation (FDG-PET)



	ACS in 0-12 mo	ACS in 13-24 mo	No ACS in 24mo	<i>p</i>
Remodeling Index (%)	131±5	121±6	113±2	=.005
Plaque volume (mm <sup>3</sup> )	167±18	93±20	58±6	<.001
max LAP area (mm <sup>2</sup> )	5±0.5	1±0.6	0.5±0.2	<.001
%LAP/plaque area	32±5	8.1±5.2	8±1	<.001

Motoyama S, et al JACC 2009; Courtesy Jagat Narula, MD, PhD

# Summary: Atherosclerosis

- Plaque rupture is a main cause of thrombosis (65-70%), while other minor causes include erosion (30%) and calcified nodule (2-5%).
- Risk factors are predictive of specific plaque types
- Diabetes and metabolic syndrome play an important role in CAD
- Vulnerable plaques (TCFA) is a likely precursor lesions of rupture.
- Fibrous cap thickness is the best discriminator of vulnerable plaque and plaque rupture from stable lesions
- Macrophage infiltration, necrotic core, and positive remodeling are important parameters to identify if we are to recognize these lesion prior to clinical manifestation.

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