

Pathogenesis of Vulnerable Plaque 2013: What's New?

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Natural History of Atherosclerosis

- **Systemic factors –**

Dyslipidemia, diabetes mellitus, smoking, hypertension, age and gender, hsCRP, Lp-PLA₂, etc.

- **Local factors –**

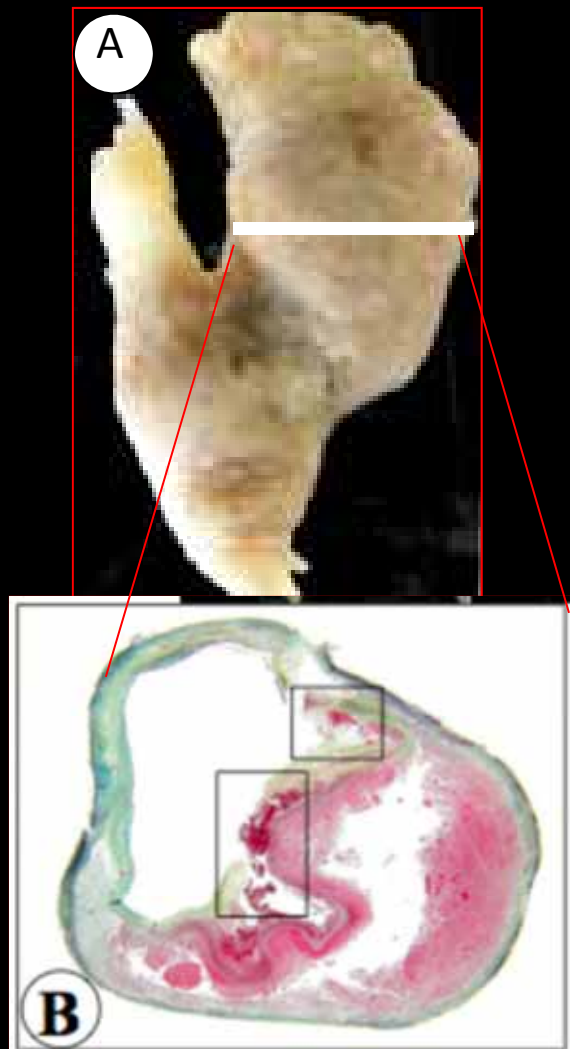
Branch points, e.g. carotid bifurcation, abdominal aorta just above bifurcation, coronary branch point, and arch vessels at take off, are the sites of early atherosclerosis .

- **Thrombosis –**

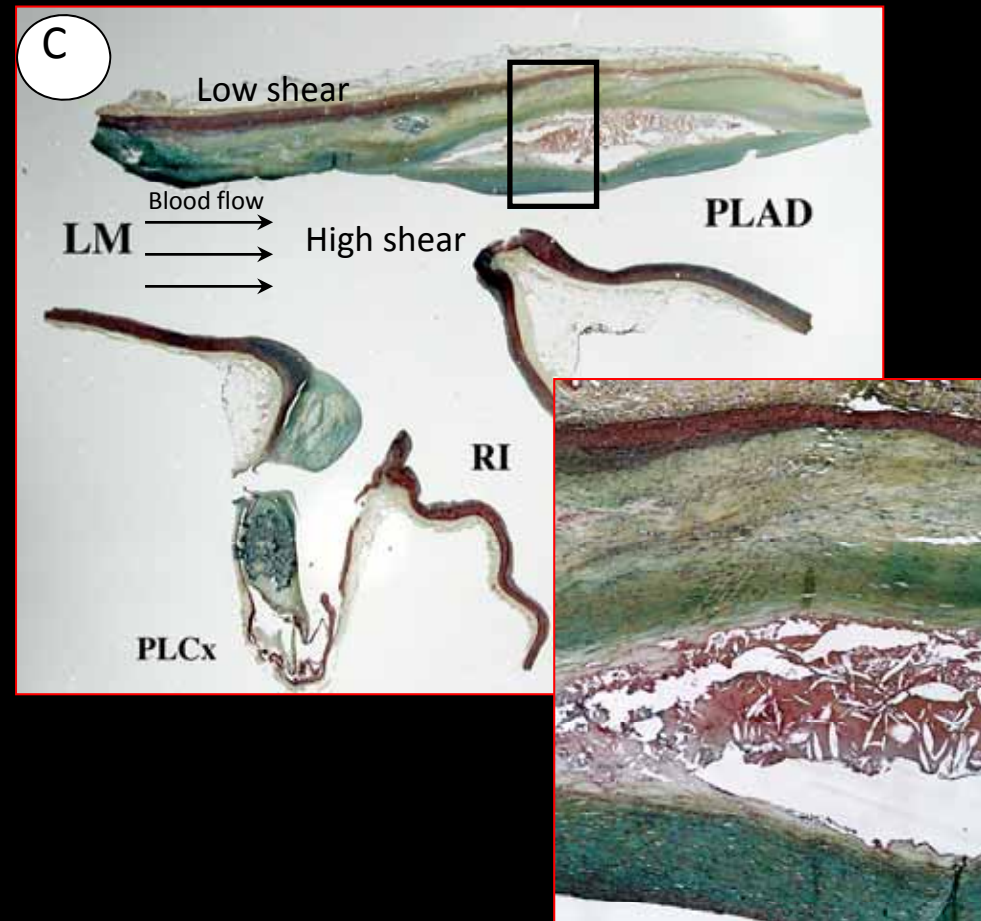
Occurs in the coronary arteries at focal points and is most often seen in the proximal segments of the three main coronary arteries (systemic coagulation factors play a role), and occur at sites where there are underlying plaque characteristic that result in thrombosis.

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

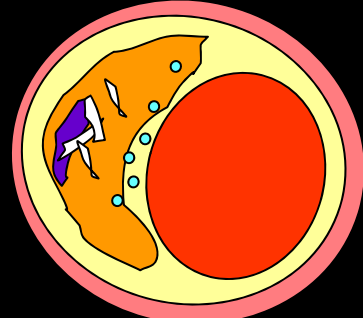
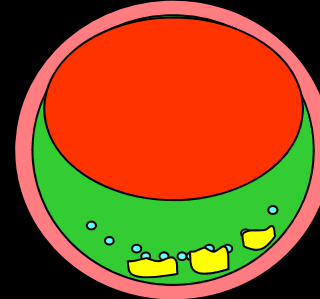
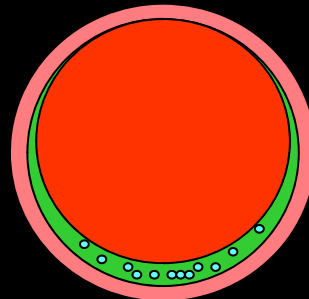
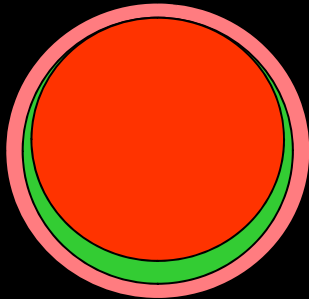
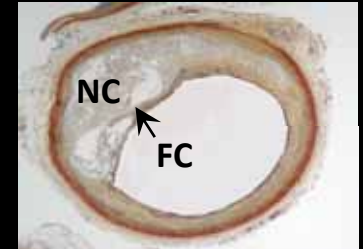
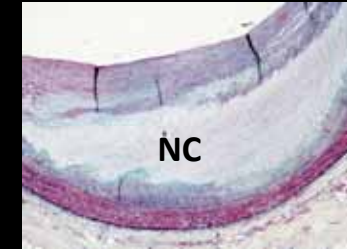
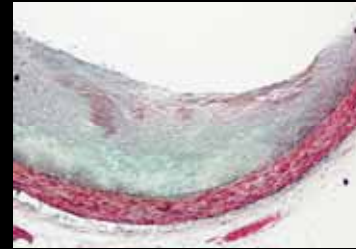
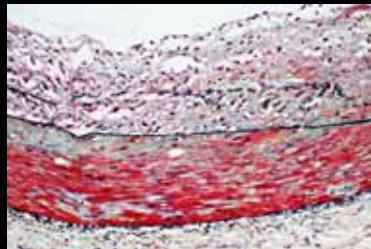
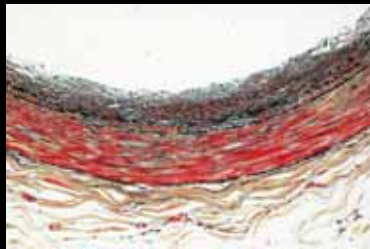
adaptive intimal thickening

Intimal xanthoma

pathologic intimal thickening

fibroatheroma

thin-cap fibroatheroma



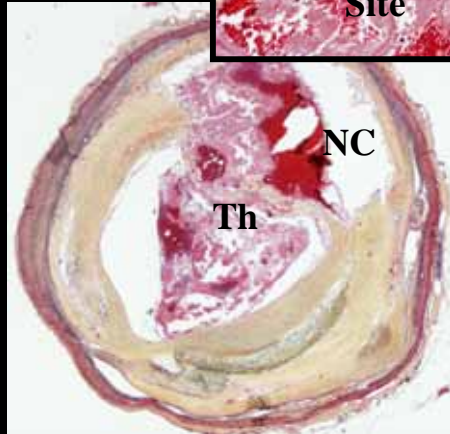
lipid pool

necrotic core

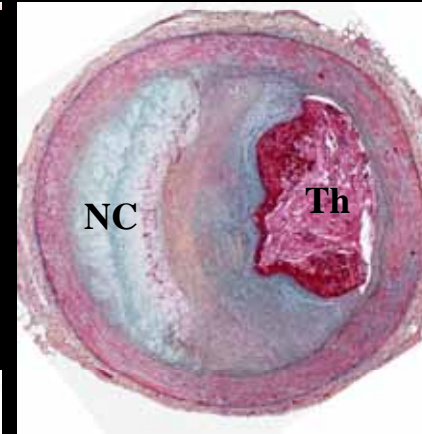
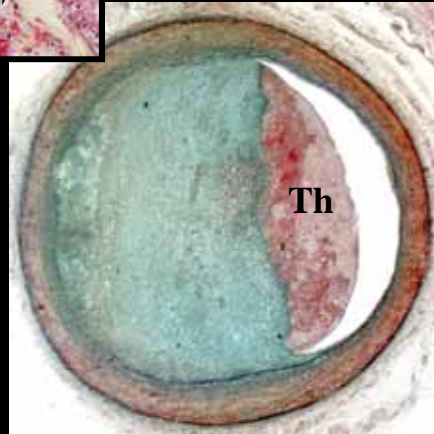
early → late necrosis

Causes of Coronary Thrombosis

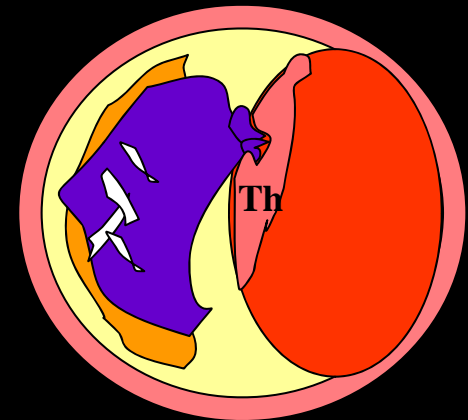
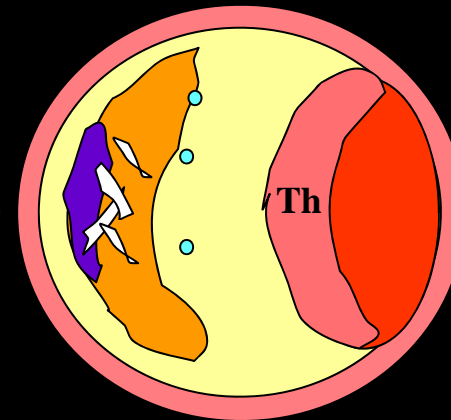
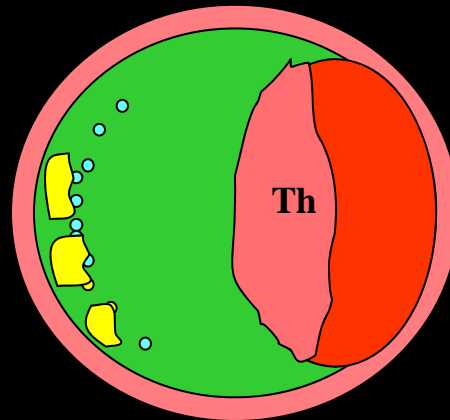
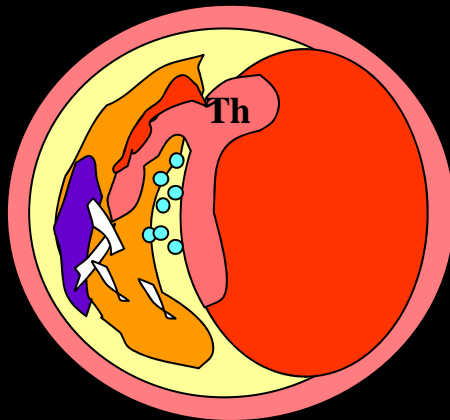
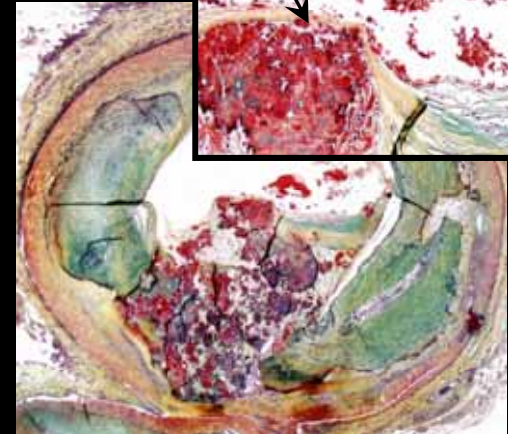
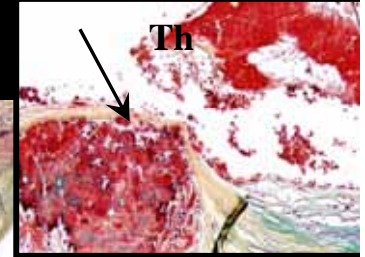
Rupture
60 to 75%

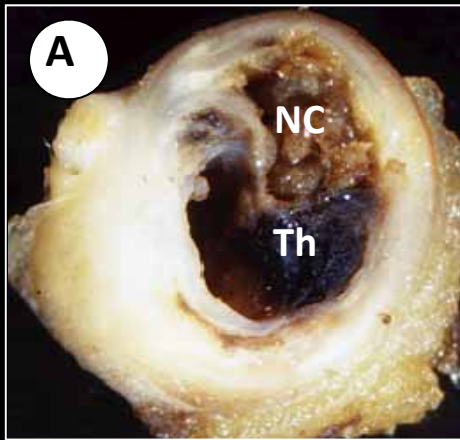


Erosion 30-35%



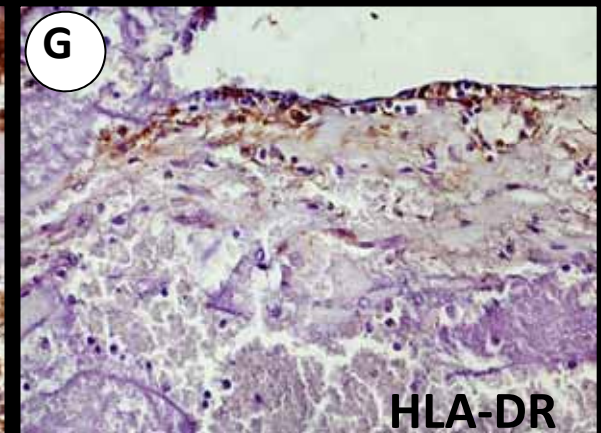
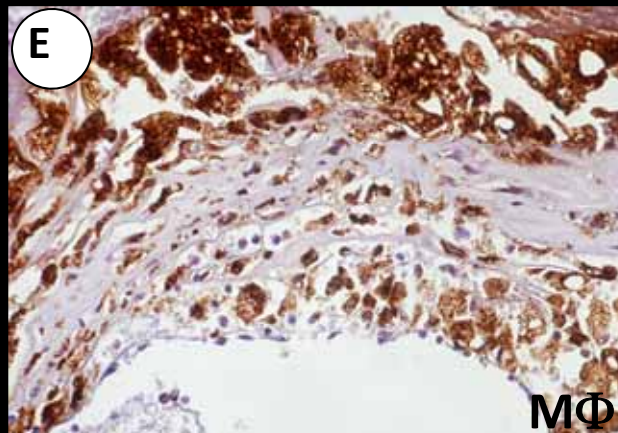
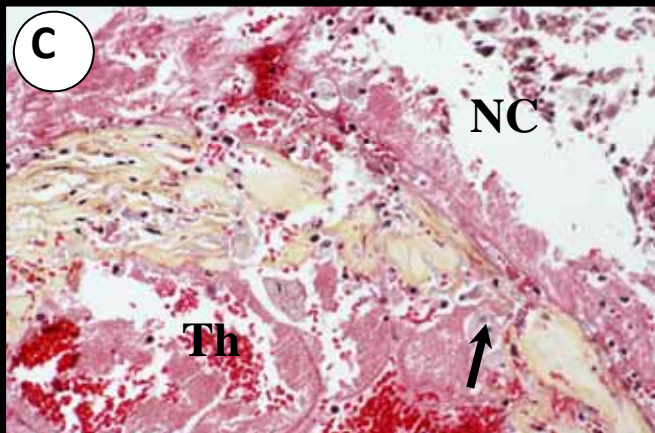
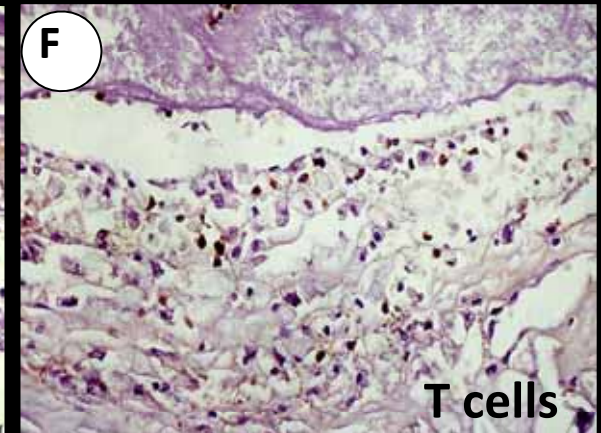
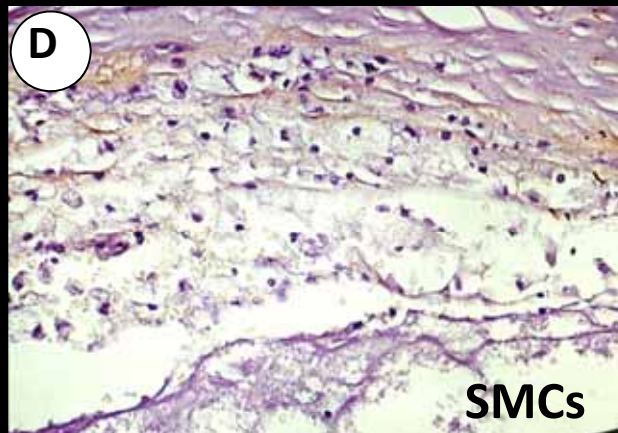
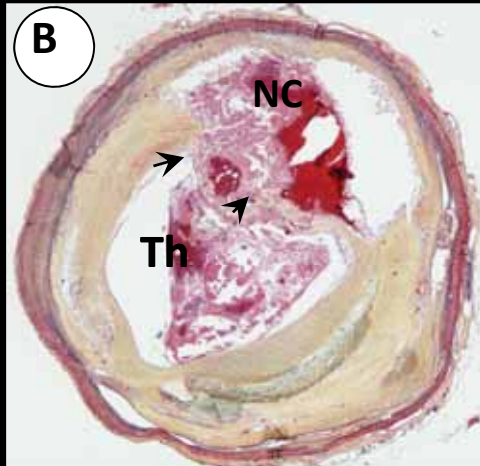
Calcified nodule (2 to 7%)





Gross and Light Microscopic Features of Plaque Rupture

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



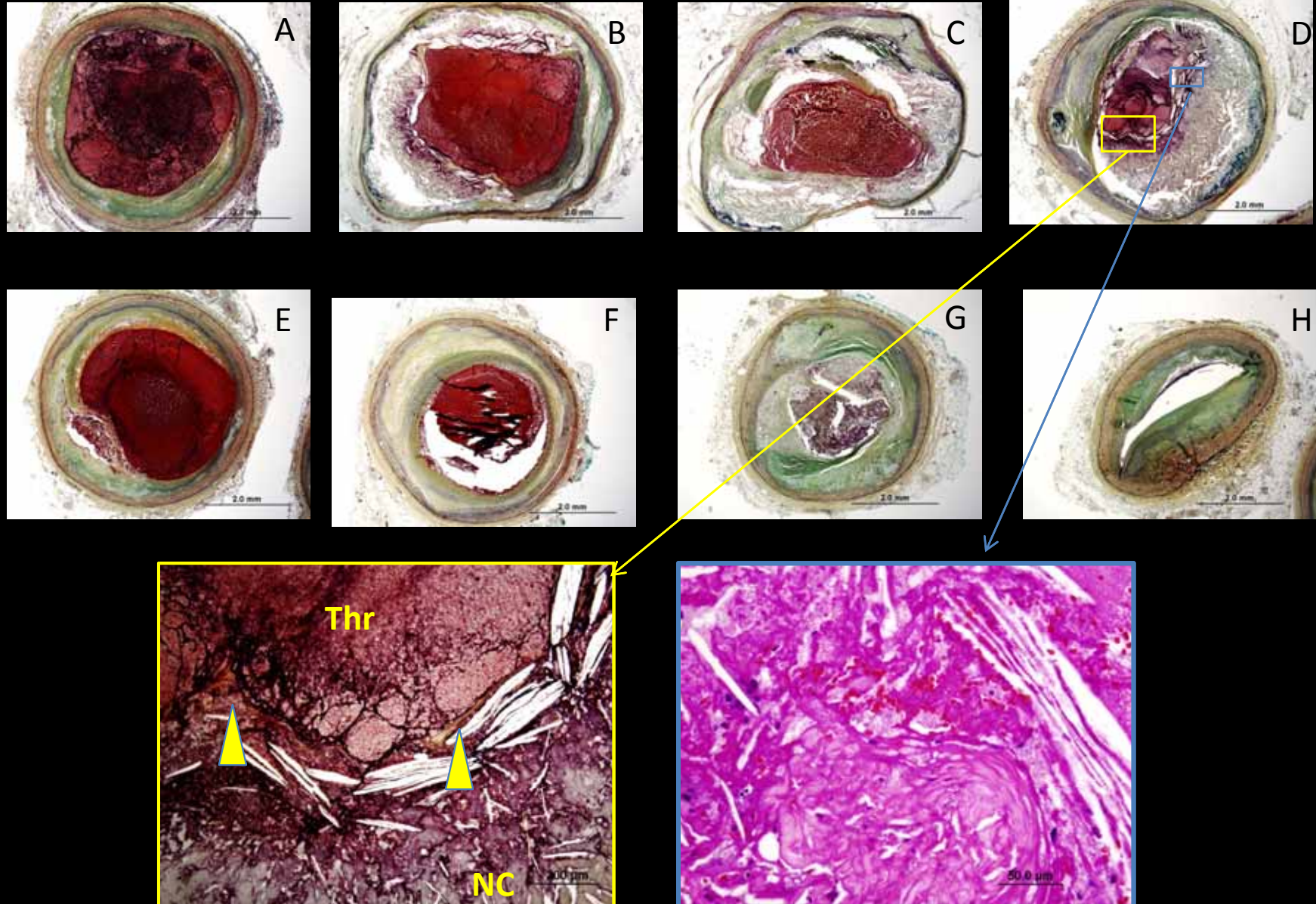
-----Features of ruptured plaques

- Thrombus
 - Large necrotic core (>30% of plaque)
 - Fibrous cap covering the necrotic core
 - thin (thickness usually <65 μm)
 - many macrophages (inflammation)
 - few smooth muscle cells (apoptosis)
 - Expansive remodeling preserving the lumen
 - Neovascularization from vasa vasorum
 - Plaque hemorrhage
 - Adventitial/perivascular inflammation
 - “Spotty” calcification
-

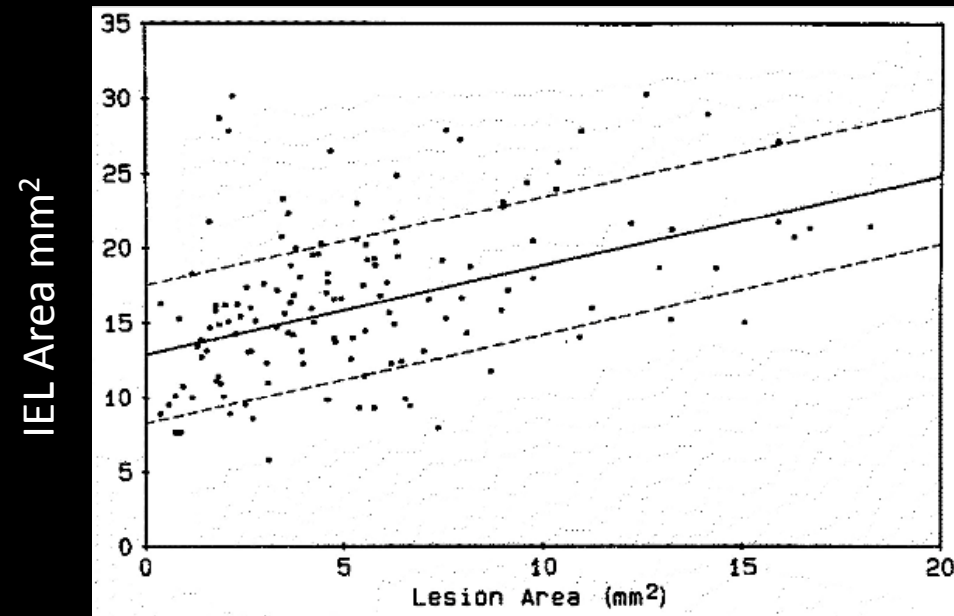
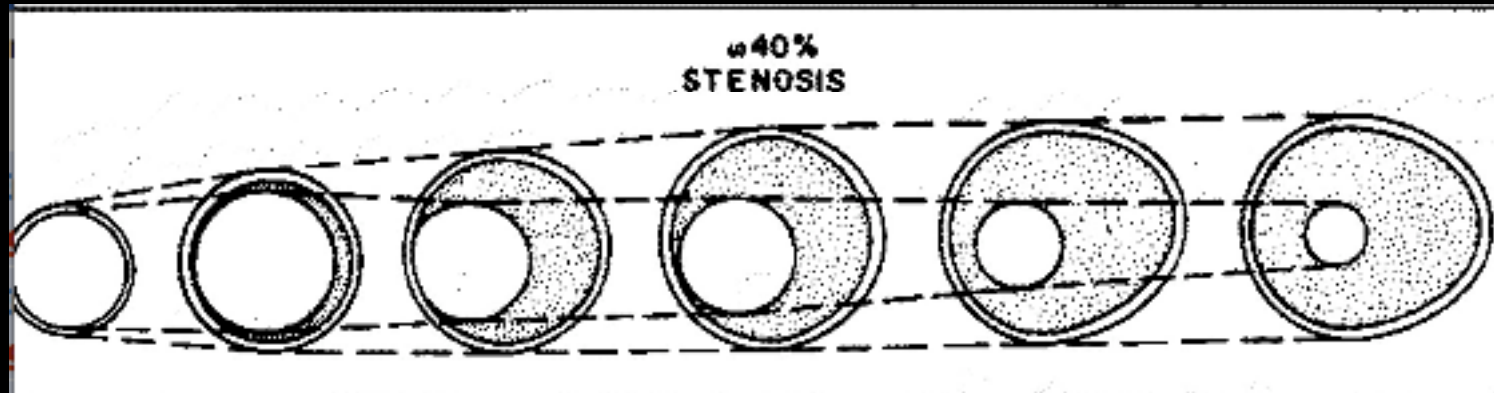
Serial Sections of Plaque Rupture

59M, with unknown medical history, died suddenly.

Proximal RCA

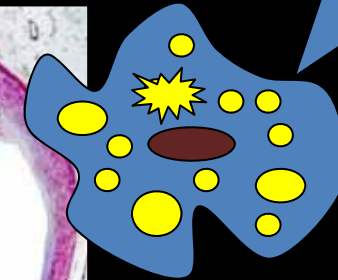
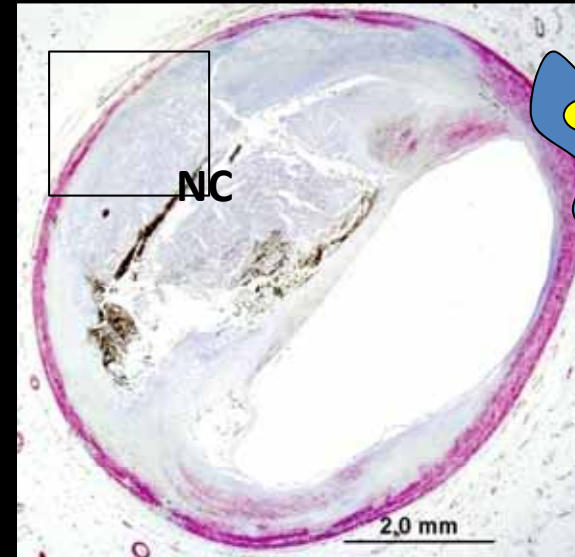
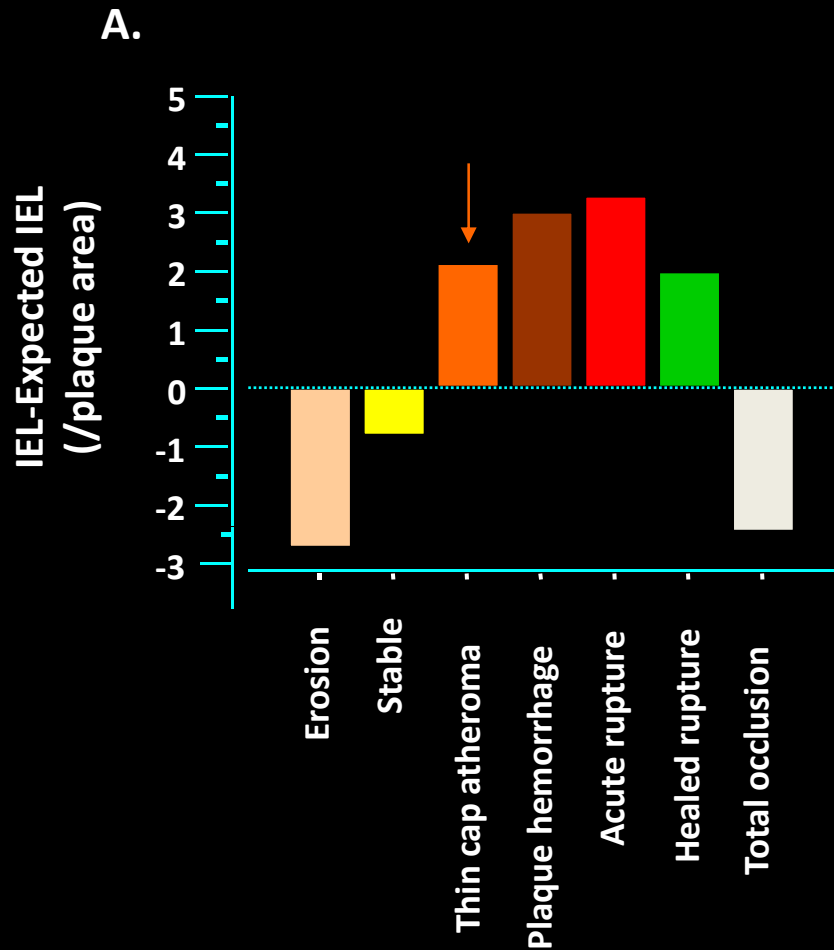


Arterial Remodeling



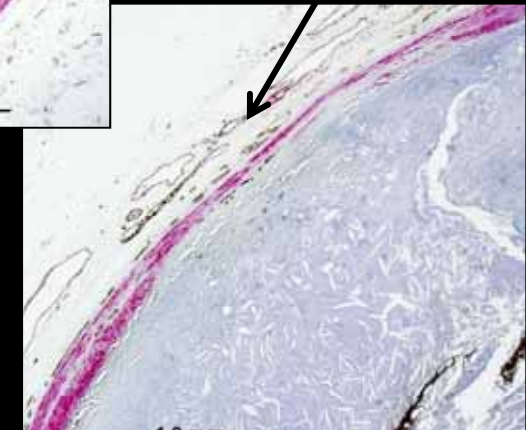
Glagov S. New Engl J Med 1987

Remodeling in Varying Coronary Lesion Morphologies

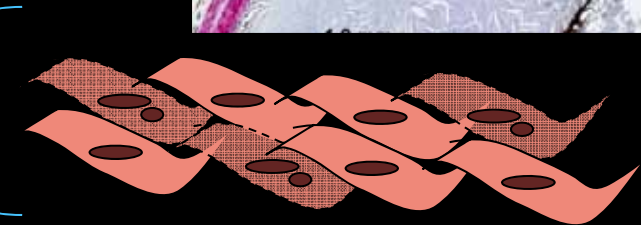


MMP-1
MMP-2
MMP-3
MMP-7
MMP-8
MMP-9
MMP-10
MMP-12
MMP-14
TIMP-1
TIMP-2
TIMP-3

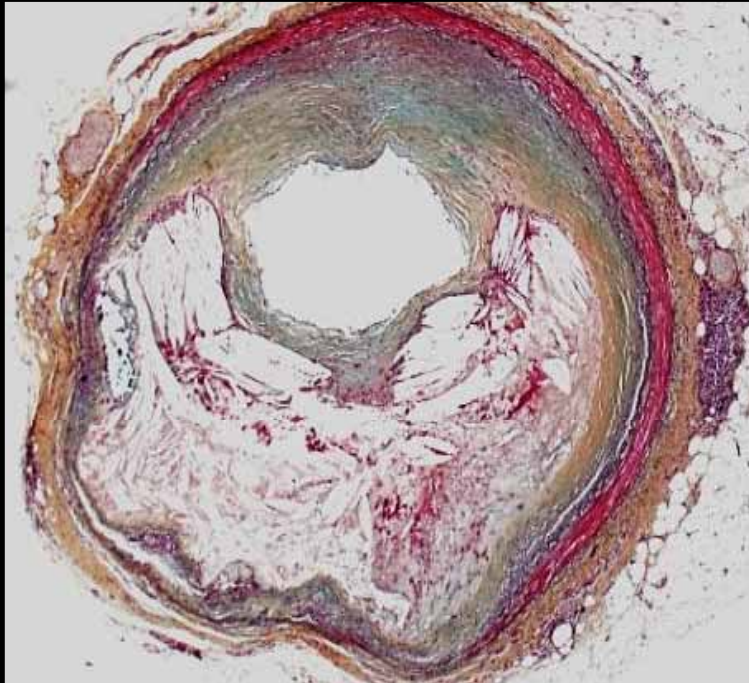
Medial SMC loss



Medial SMC apoptosis

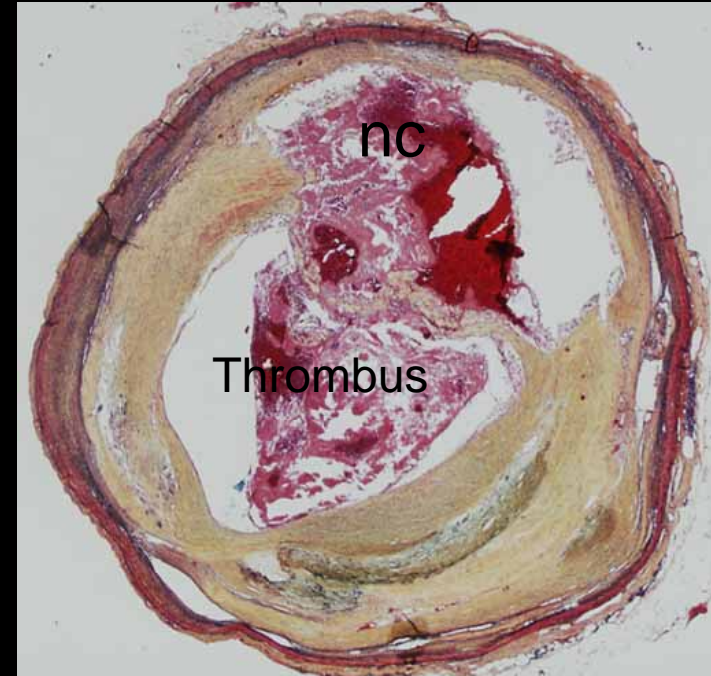


Do thin cap fibroatheromas (vulnerable plaques) go on and Rupture?



Thin cap fibroatheroma

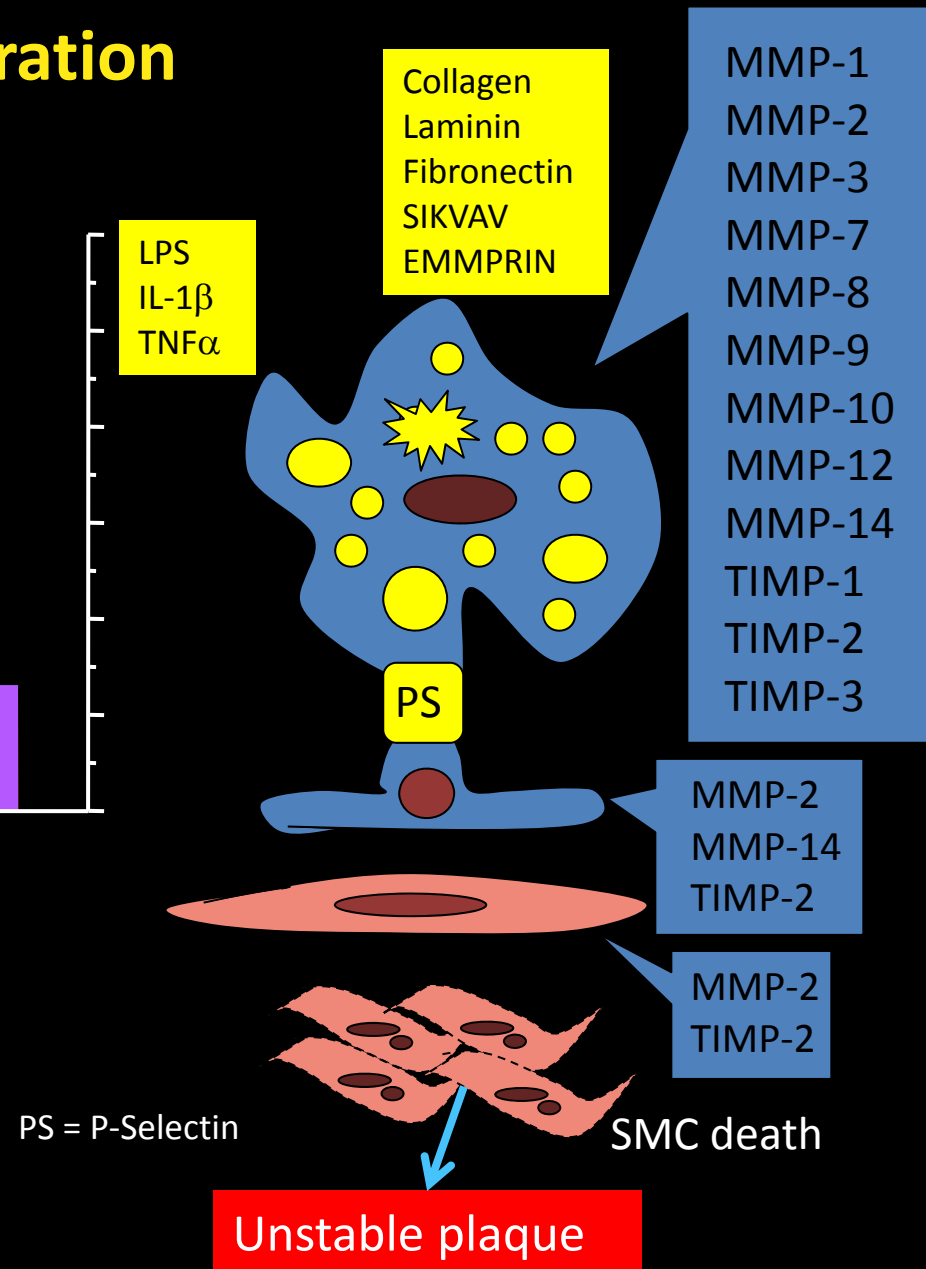
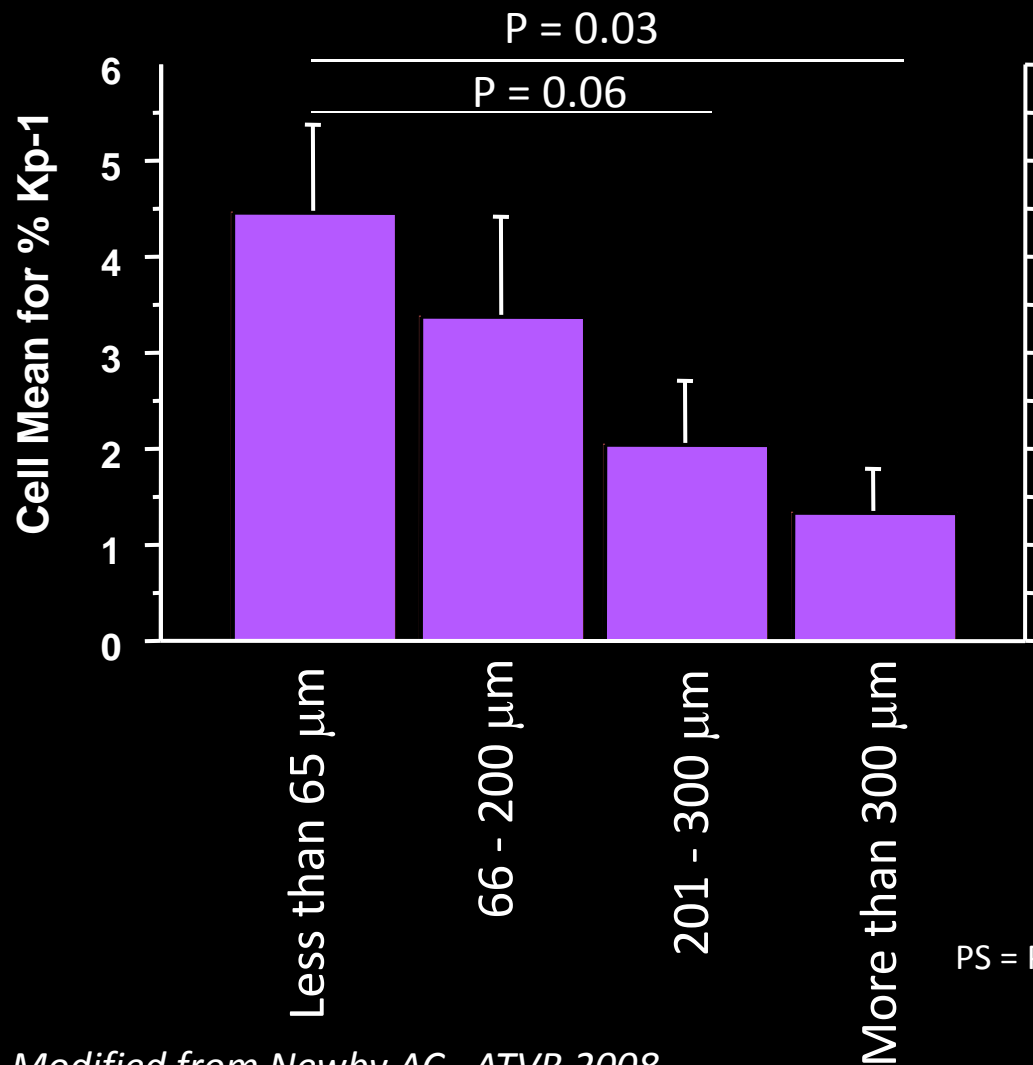
- Necrotic core ($21.6 \pm 23.7\%$)
- Thin fibrous cap ($< 65 \mu\text{m}$)
- Cap infiltrated by macrophages and lymphocytes
- Cap composition – type 1 collagen with few or absent smooth muscle cells



Plaque Rupture

- Discontinuous fibrous cap ($23 \pm 19 \mu\text{m}$)
- Underlying necrotic core ($29.0 \pm 19.0\%$)
- Luminal thrombus

Relationship of Fibrous Cap Thickness to Macrophage Infiltration

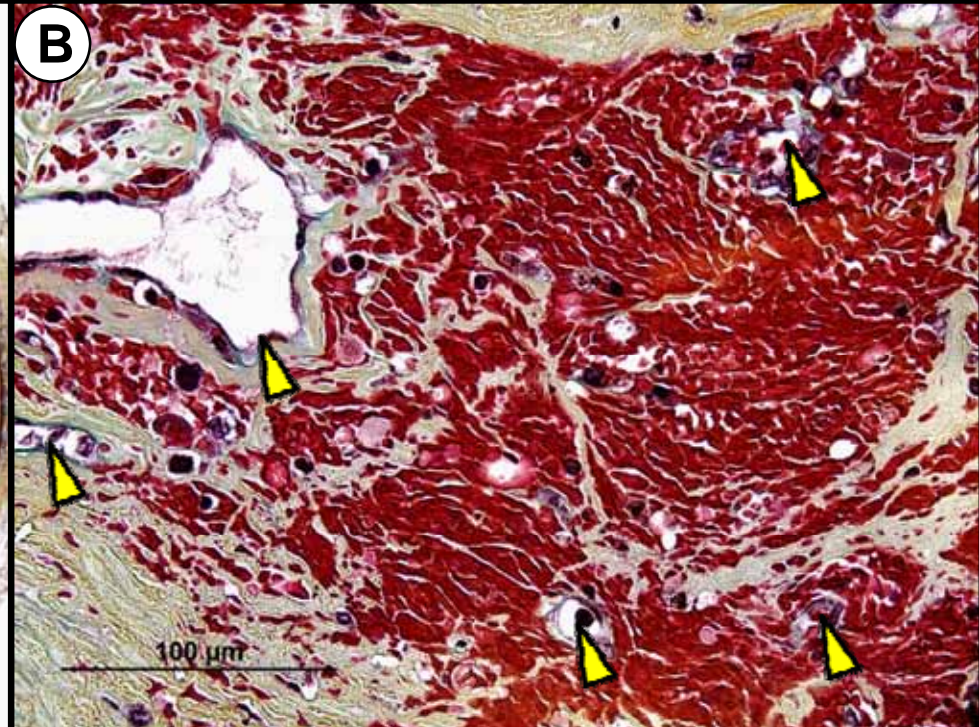
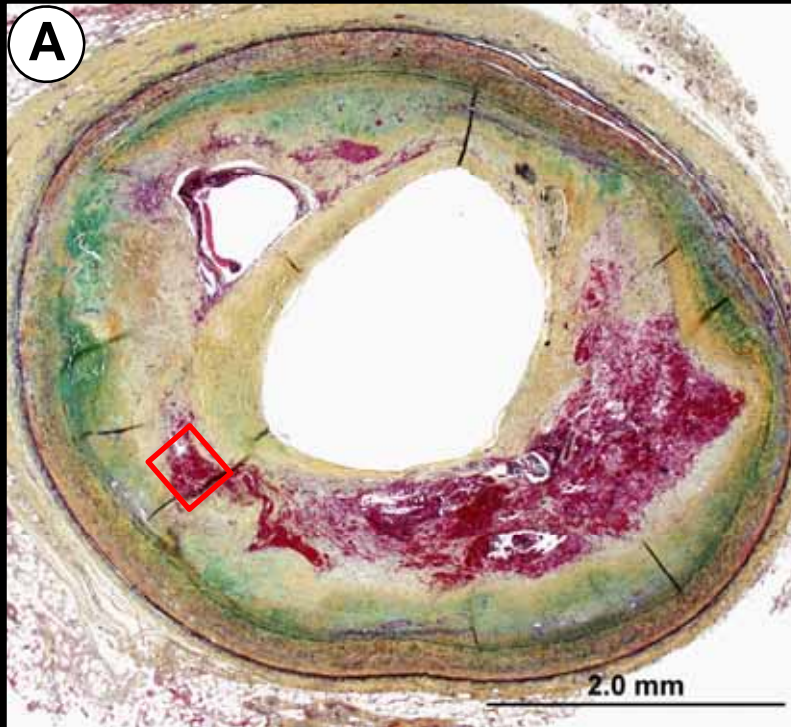


Modified from Newby AC. ATVB 2008

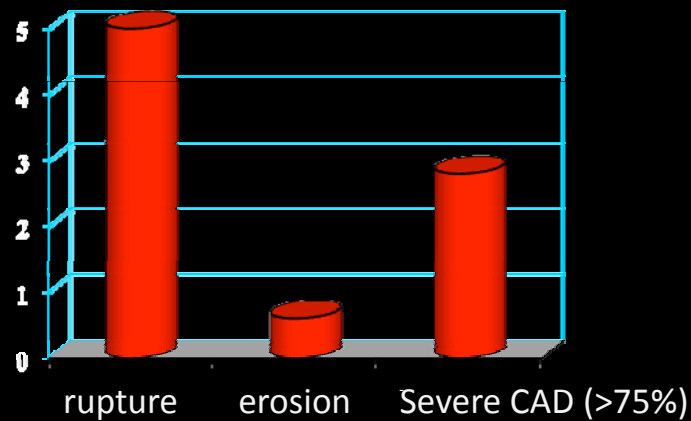
Macrophage Diversity around Angiogenesis, Plaque Hemorrhage and Iron deposits

Interplaque Hemorrhage

▲ Angiogenesis

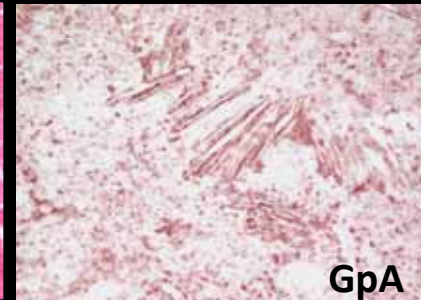


Frequency of Plaque Hemorrhage

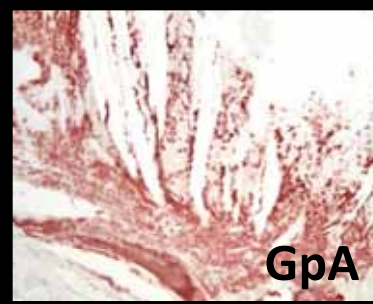
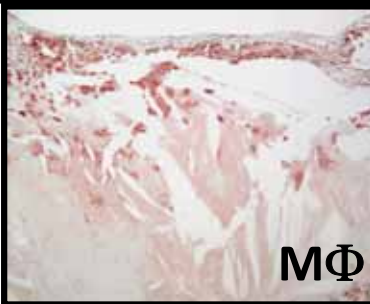
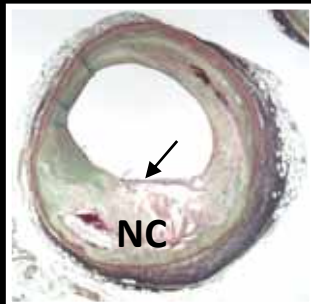


Morphometric Analysis of Hemorrhagic Events in Human

Hemorrhagic
Pericarditis



Vulnerable Plaque

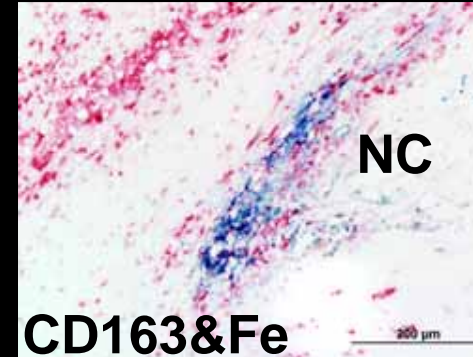
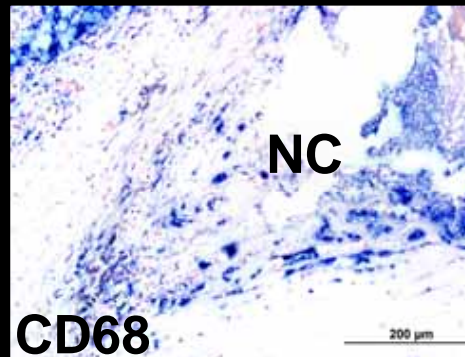
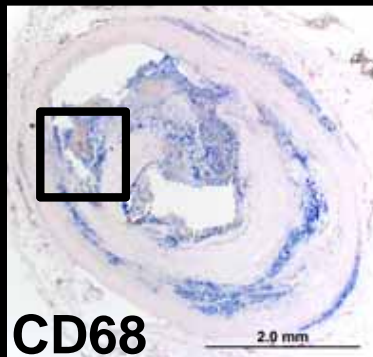
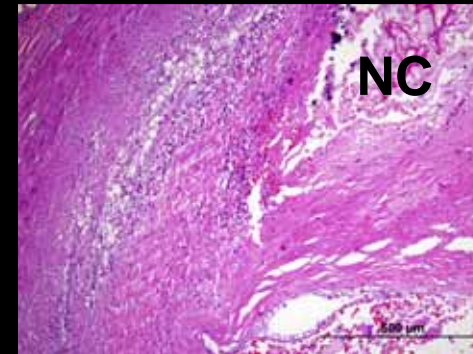
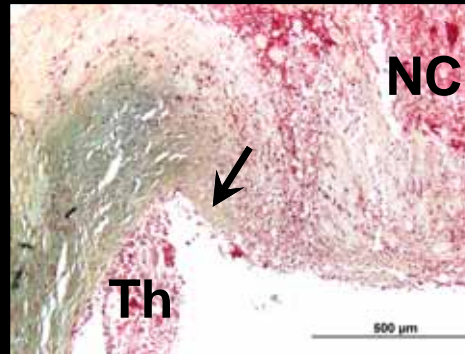
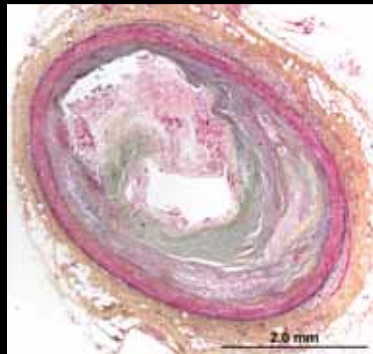
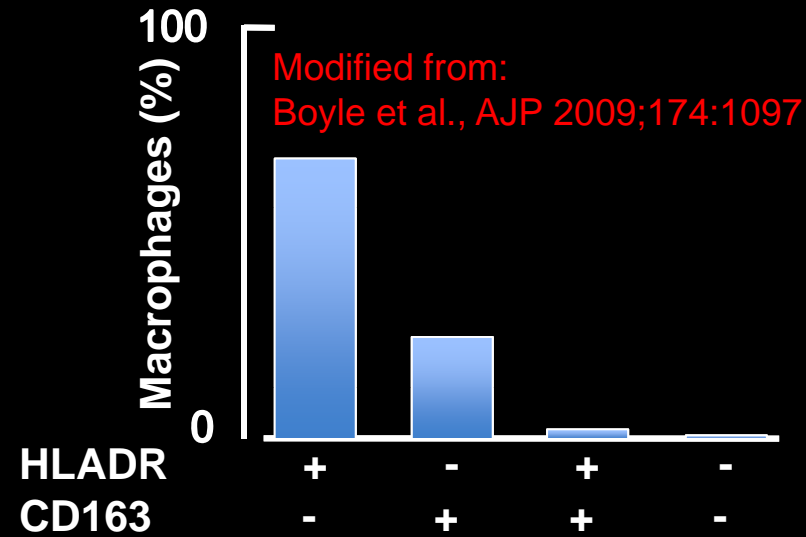


Plaque Type	GpA Score	Iron	Necrotic Core (mm ²)	MΦ (mm ²)
PIT <i>no</i> core (n=129)	0.09 ± 0.04	0.07 ± 0.05	0.0	0.002 ± 0.001
FA <i>early</i> core (n=79)	0.23 ± 0.07	0.17 ± 0.08	0.06 ± 0.02	0.018 ± 0.004
FA <i>late</i> core (n=105)	*0.94 ± 0.11	*0.41 ± 0.09	*0.84 ± 0.08	*0.059 ± 0.007
TCFA (n=52)	*1.60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

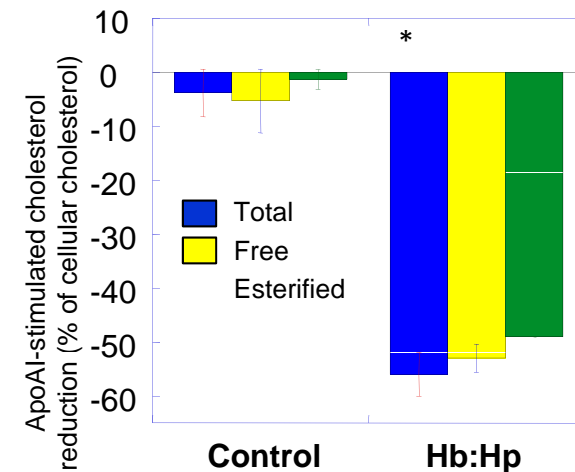
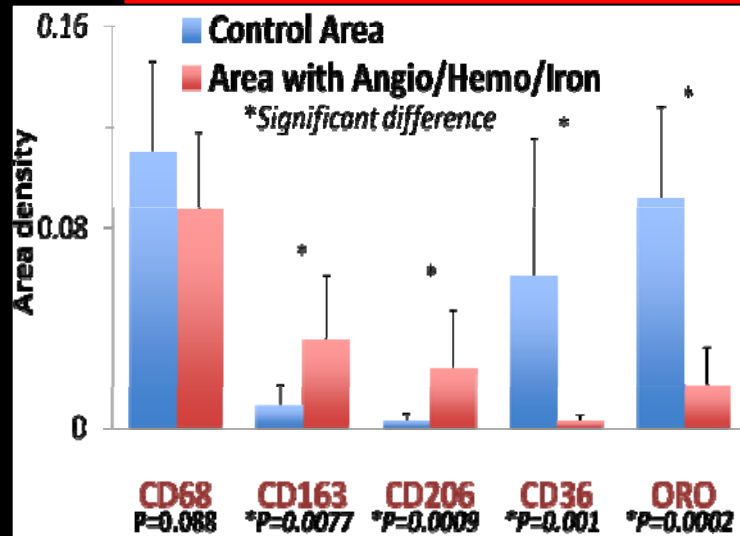
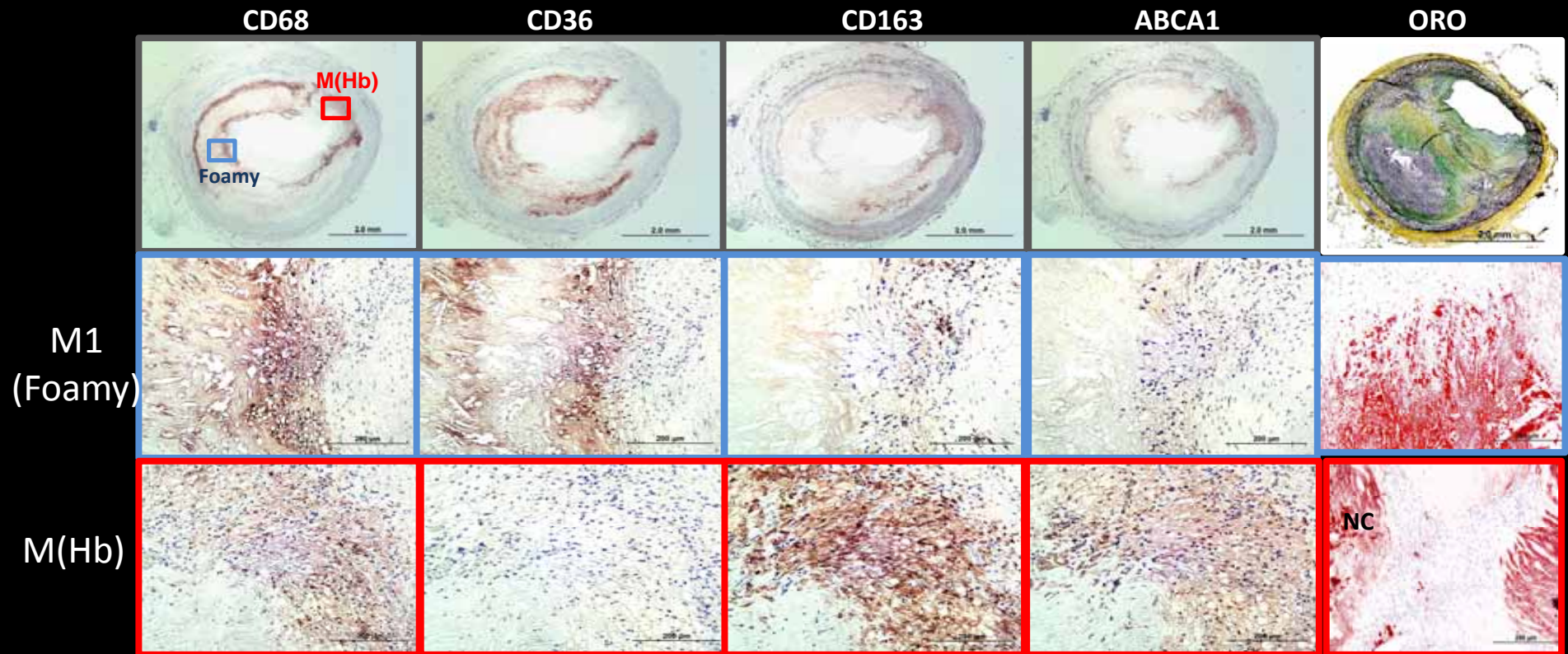
Values are reported as the means ± SE, *p<0.001 versus early core. The number in parenthesis represent the number of lesions examined; the total number= 365. MΦ = macrophages

Kolodgie FD, et al. *New Engl J Med* 2003

Expression of Haptoglobin Receptor (CD163) on a Subset of Macrophages in Human Coronary Plaque Rupture



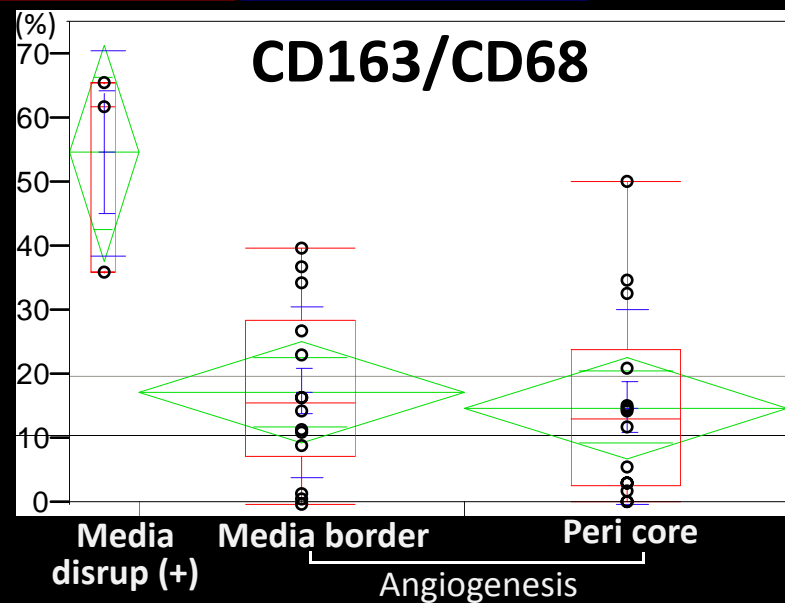
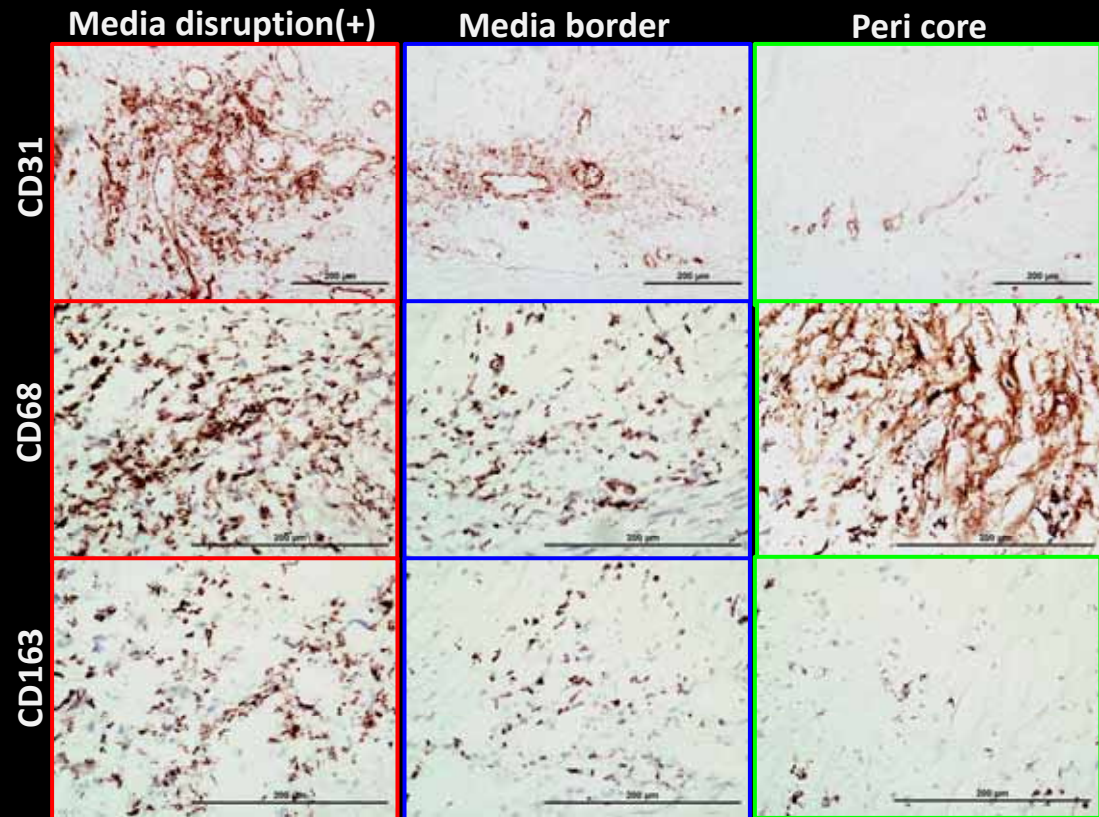
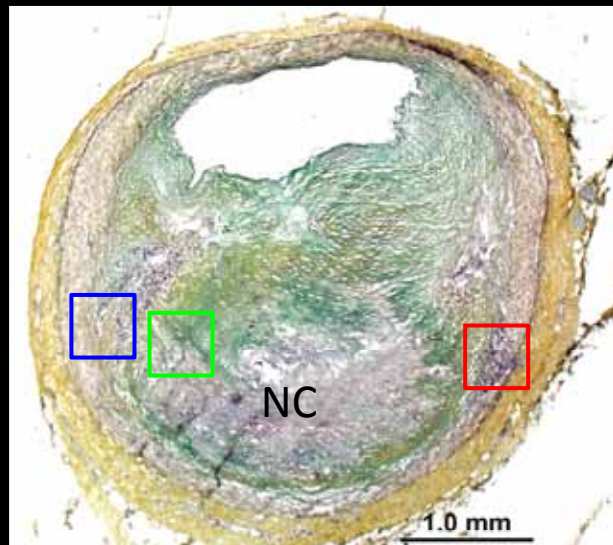
Different Phenotype of Macrophage Subclass



Finn AV, et al. JACC 2012;59:166-77

Distribution of Macrophage Sub-type

Human coronary plaque



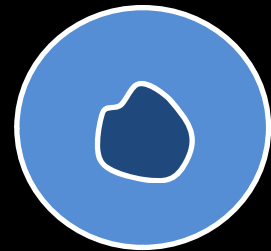
Macrophage Diversity

Classically activated macrophage

- + Pro-inflammatory cytokines production
- + Antigen presentation & microbicidal activity
- + Expression of MHC class II molecules

M1 Macrophage

IFN- γ , LPS



Hb:Hp

M (Hb)

MHC class II

Pro-inflammatory cytokines

- IL-6
- TNF
- IL-1

IL-10

Fe²⁺

FPN

LXR ABCA1/ABC

G1

Free cholesterol/sterols

↑ Mannose receptor

↑ CD163

HDL

M2 Macrophage

IL-4, IL-13

Activated PPAR γ

MHC class II

Mannose Receptor Upregulation

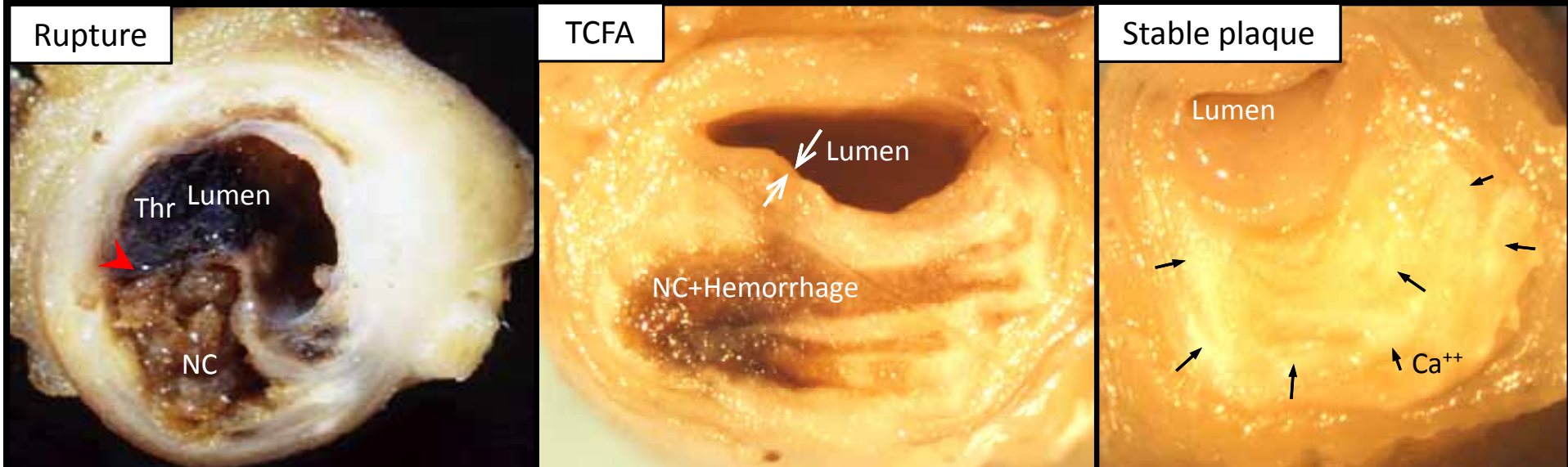
Anti-inflammatory cytokines

- IL-10
- IL-1Ra

Alternatively activated macrophage

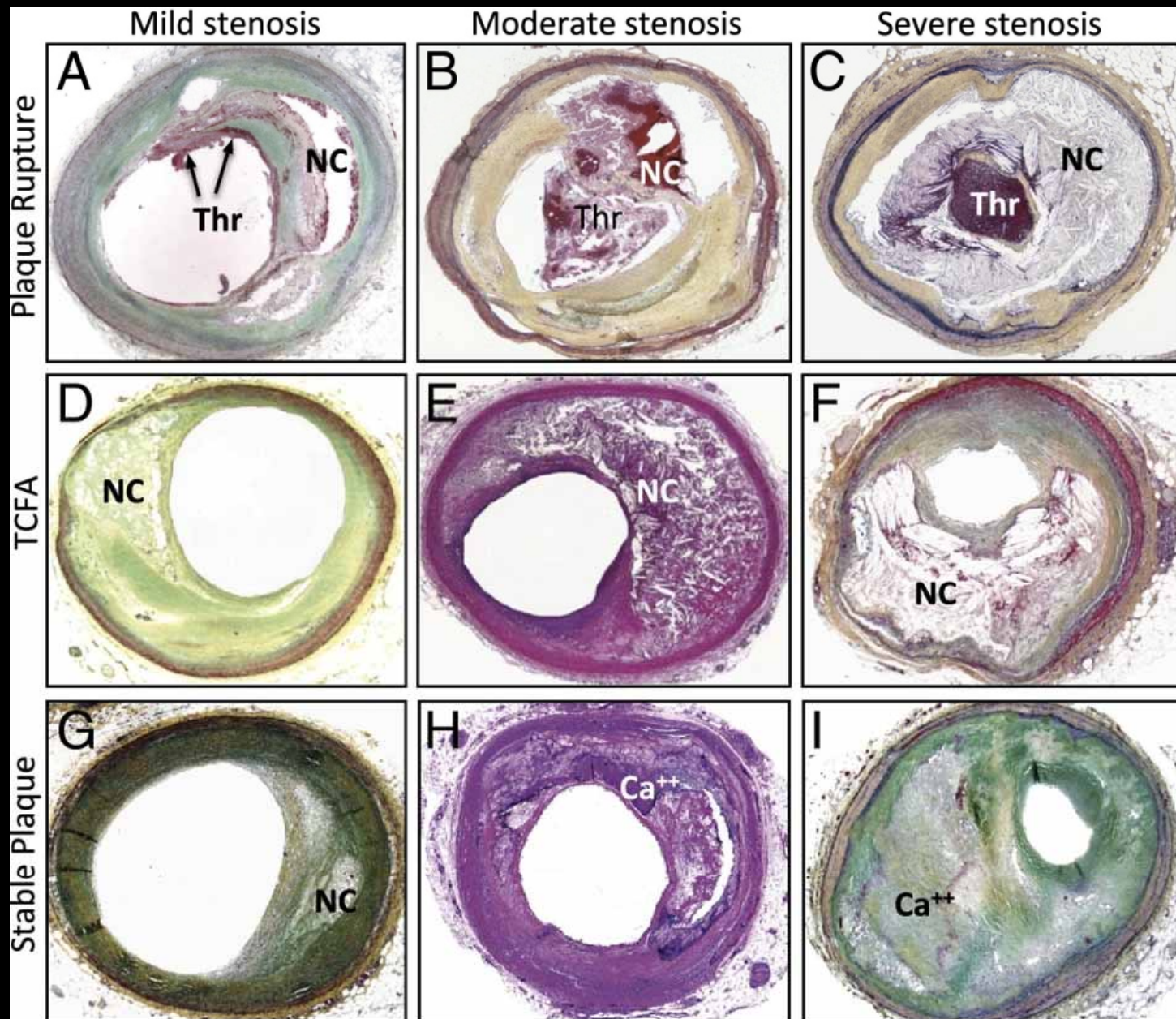
- + Anti-inflammatory cytokine production
- + Cell growth and tissue repair
- + Endocytic activity

Gross pictures of Plaque Rupture and TCFA



Narula J, Nakano M, et al. J Am Coll Cardiol 2013;61:1041-51.

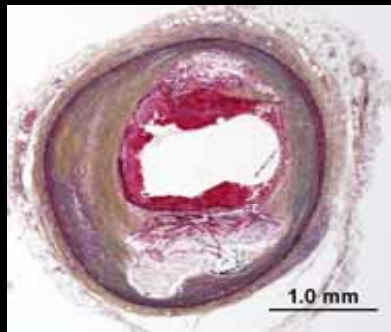
Plaque types: Rupture, TCFA, and Stable with varying degrees of stenosis



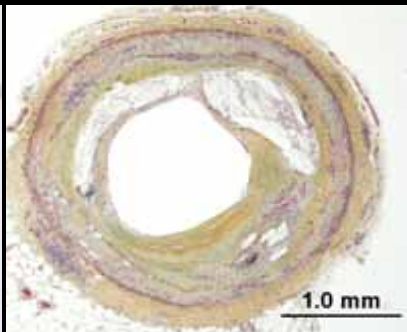
Narula J, Nakano M, et al. J Am Coll Cardiol 2013;61:1041-51.

Plaque Rupture and TCFA with Varying Luminal Stenosis

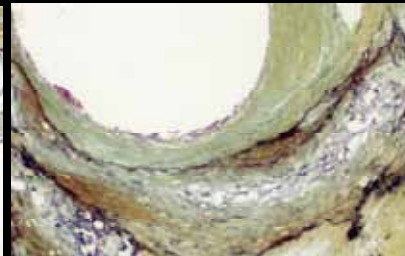
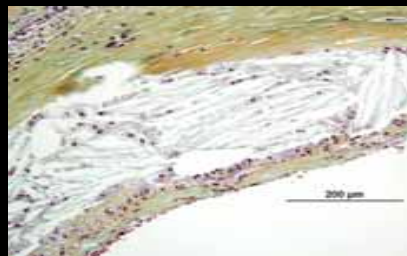
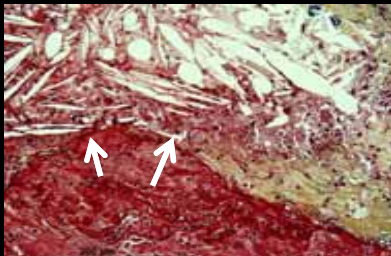
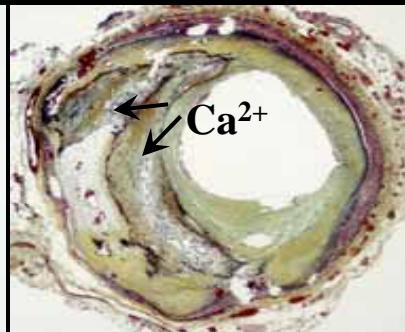
Plaque Rupture



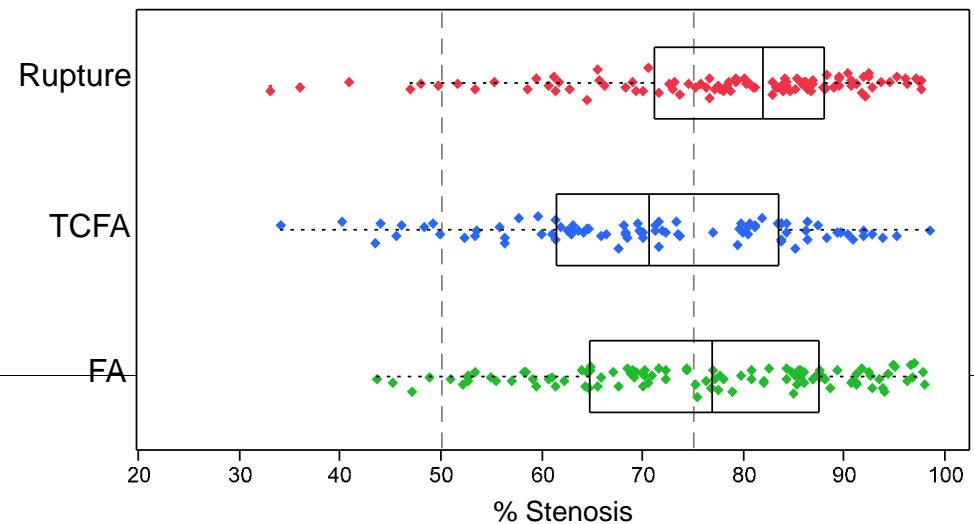
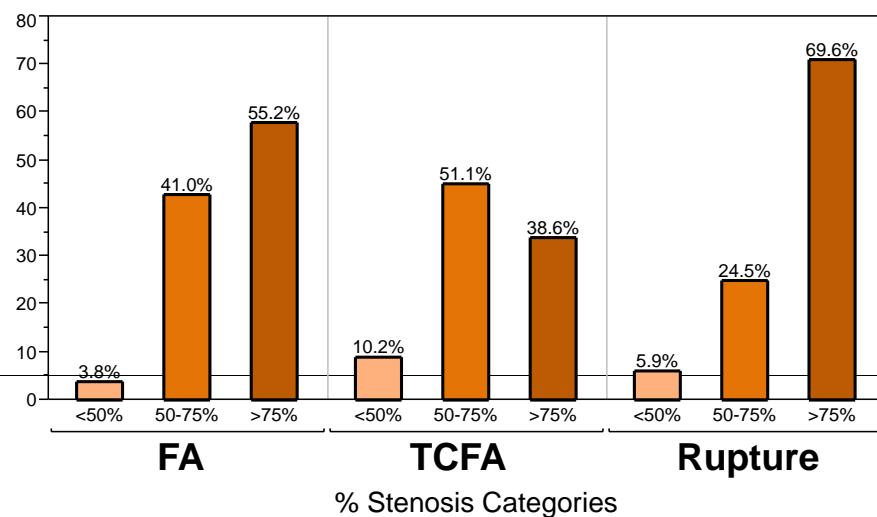
Thin cap fibroatheroma



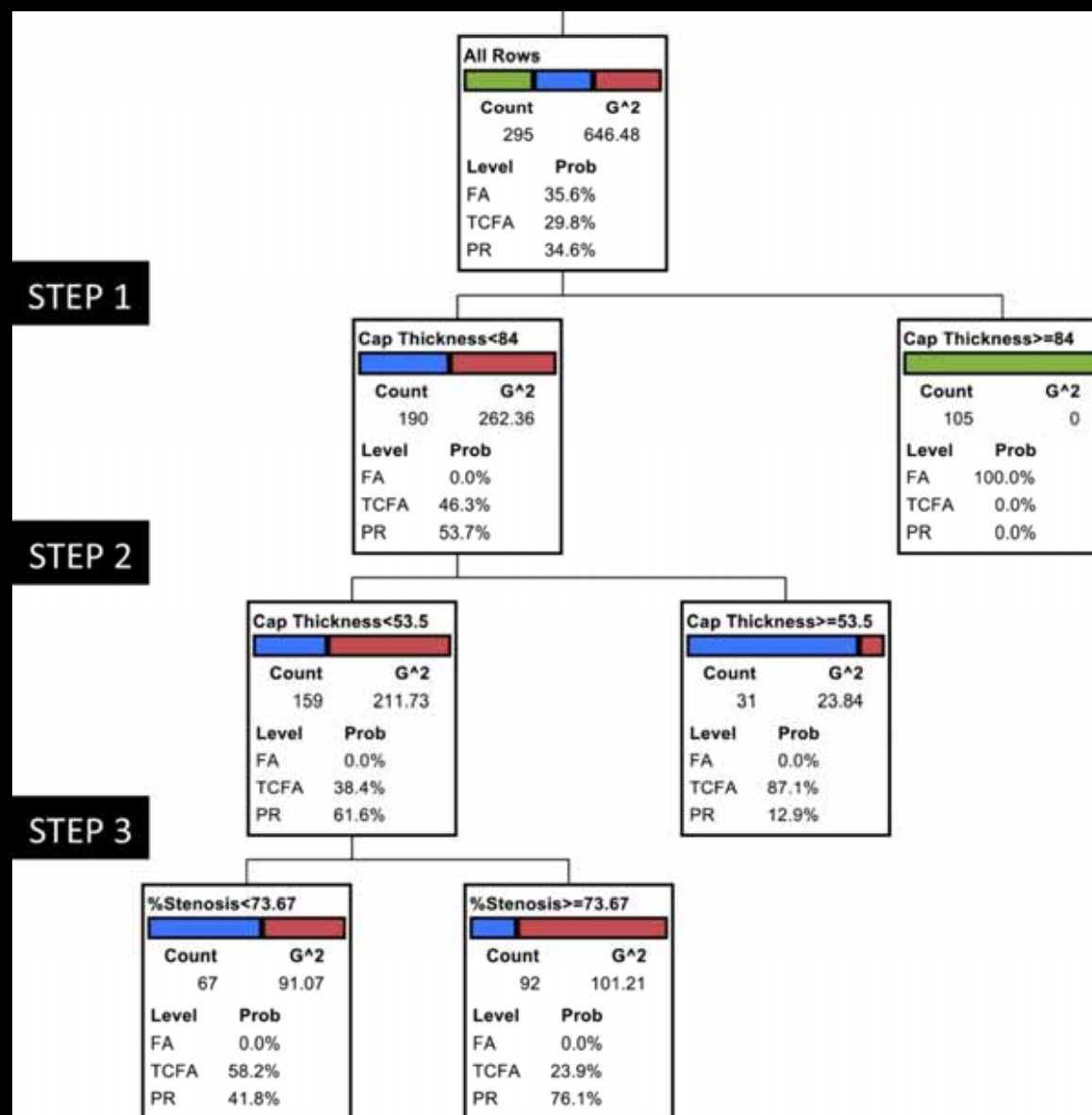
Fibroatheroma -SP



Narula J, Nakano M, et al.
J Am Coll Cardiol 2013;61:1041-51.



Multivariate Recursive Partitioning Analysis Model Including all Cases and all Candidate Variables



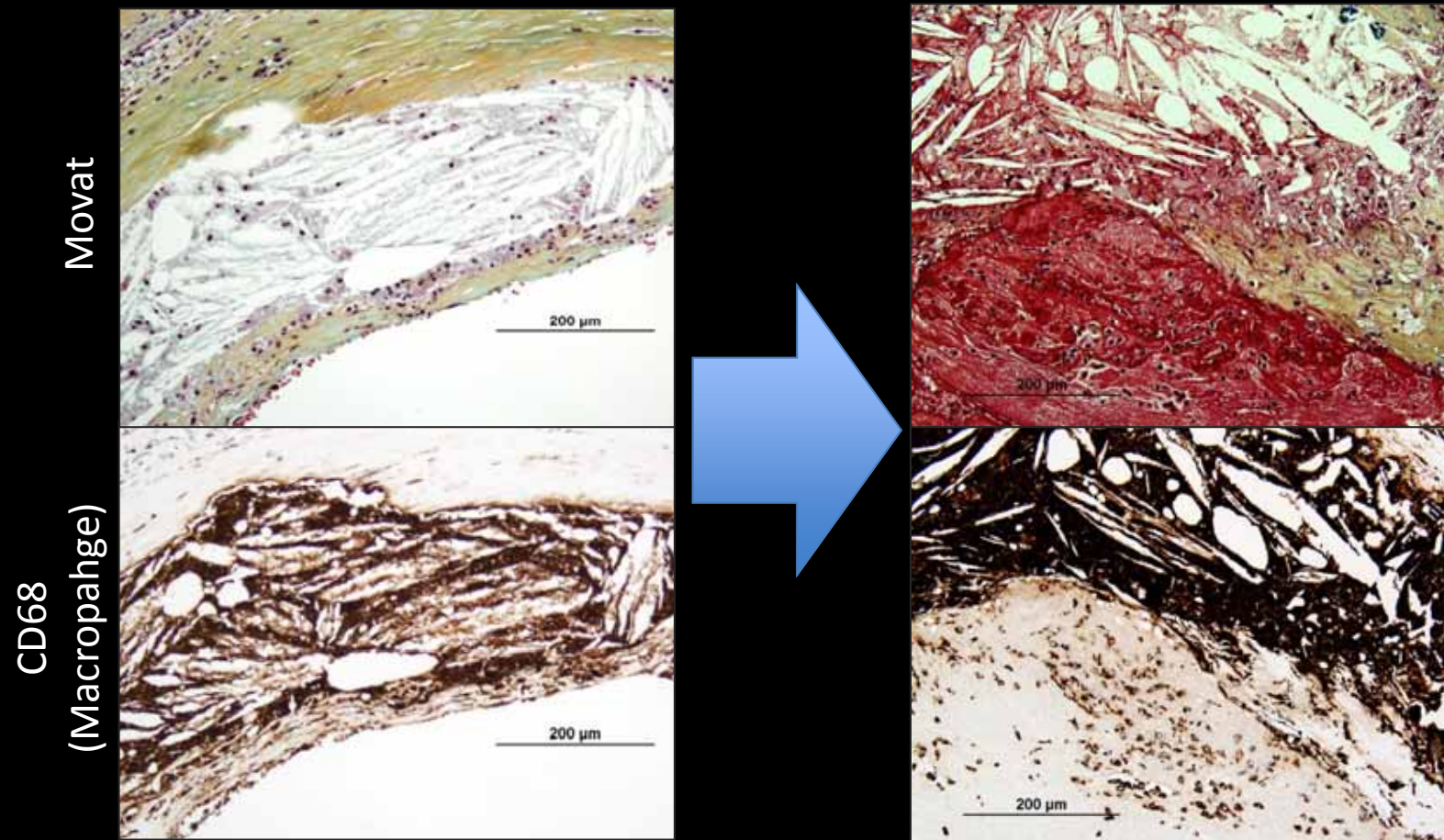
Narula J, Nakano M, et al. J Am Coll Cardiol 2013;61:1041-51.

Multivariate Recursive Partitioning Analysis Model Including all Cases but excluding Cap Thickness as Candidate Variable



Independent Morphological Predictor of Rupture

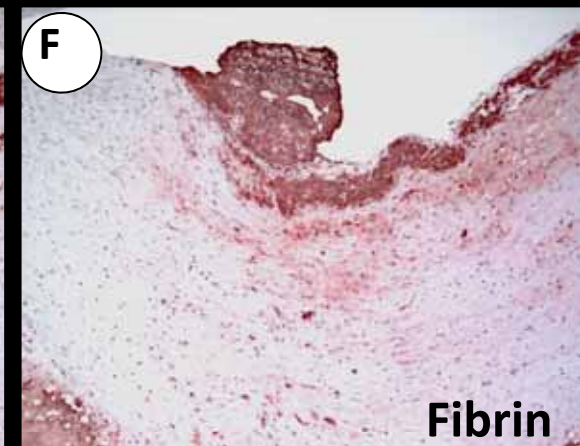
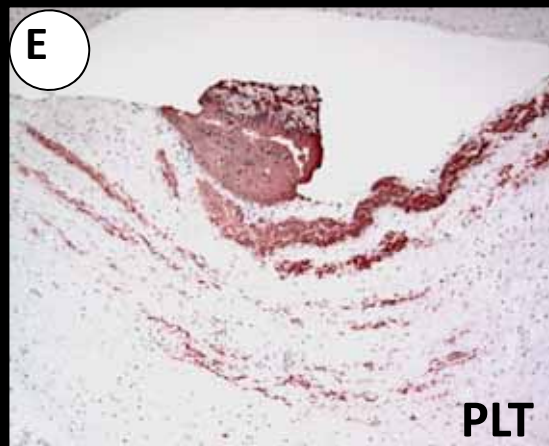
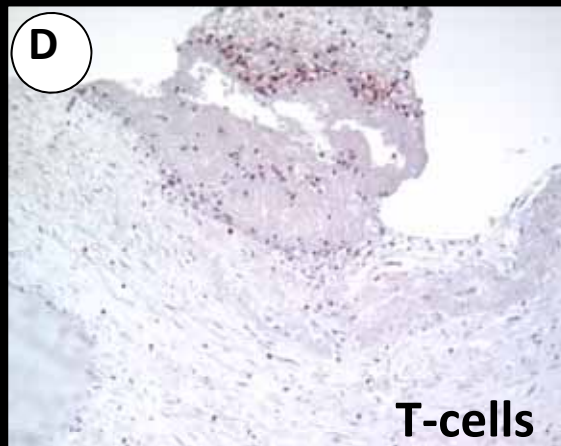
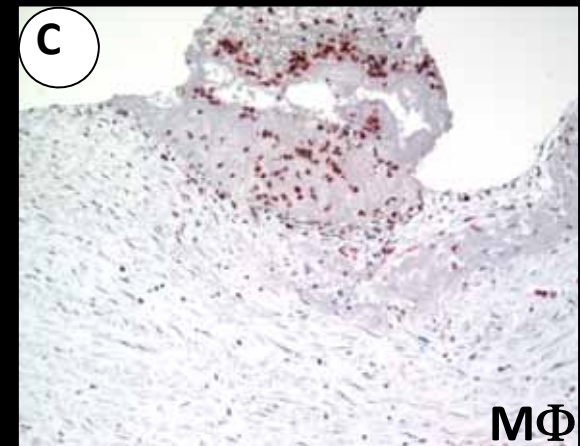
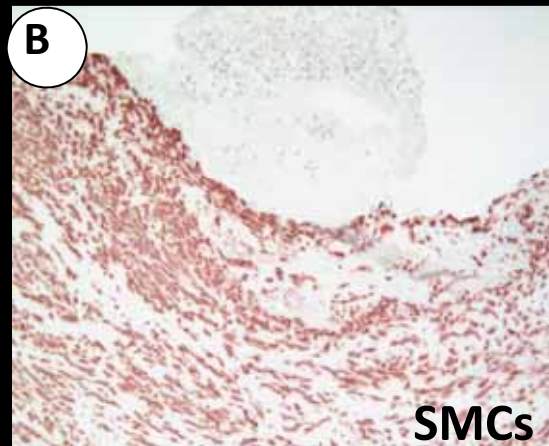
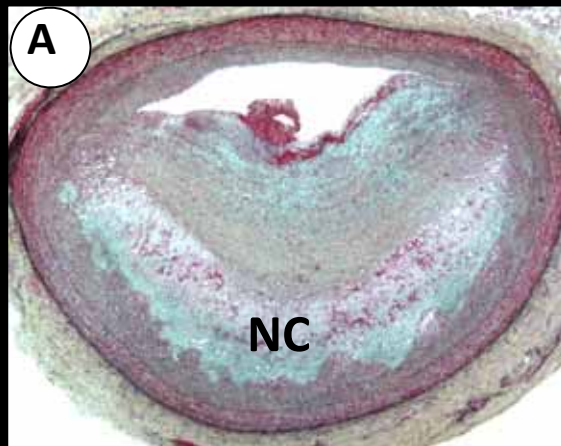
50-75% cross-sectional stenosis



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

Plaque Erosion: 30-35% of thrombi in SCD

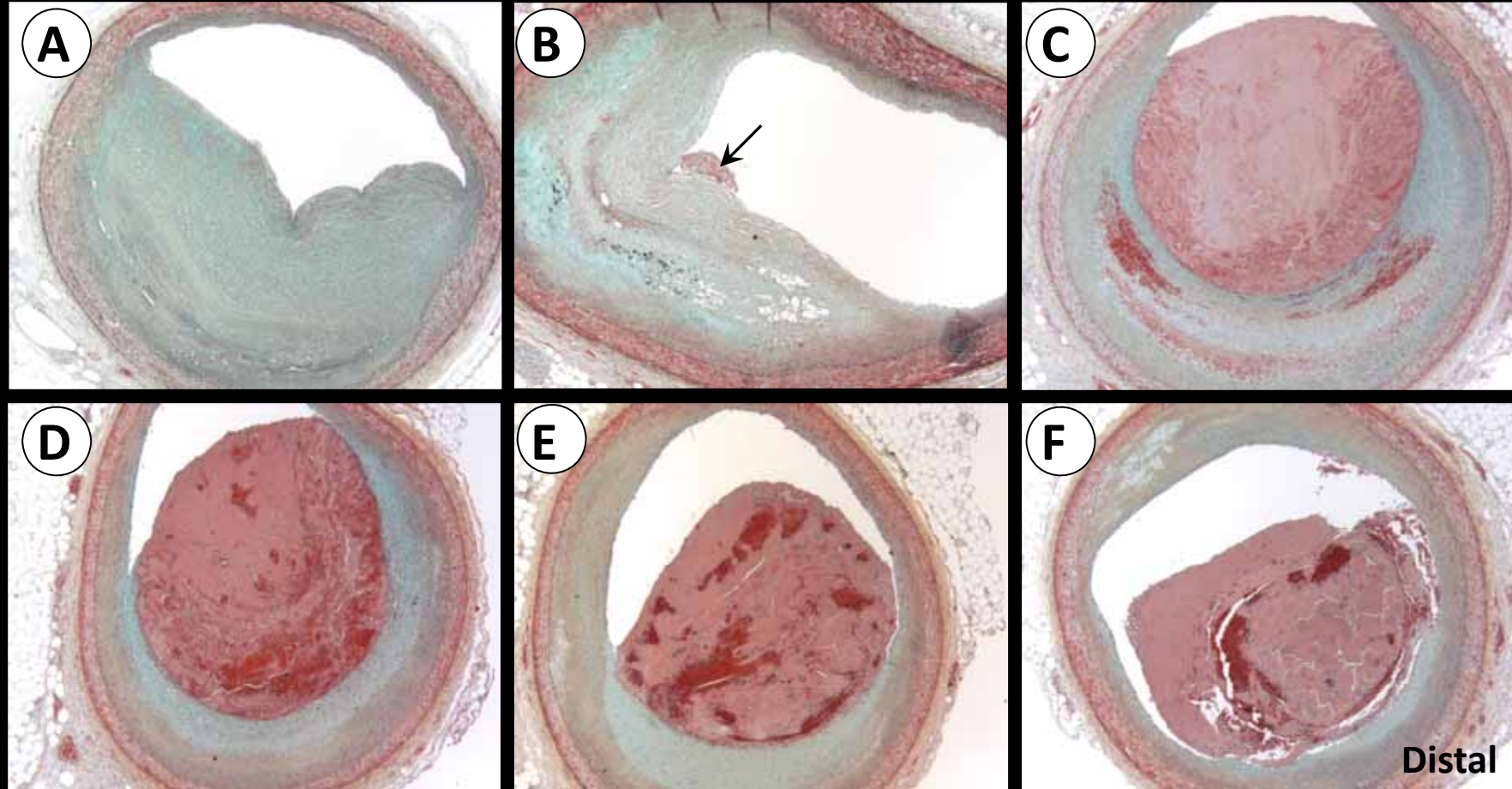
Plaque erosion in a 33 year-old female complaining of chest pain for two-weeks and discharged from the emergency room with a diagnoses of anxiety.



Serial Sections of Coronary Plaque Erosion

38F, Sudden Coronary Death Victim

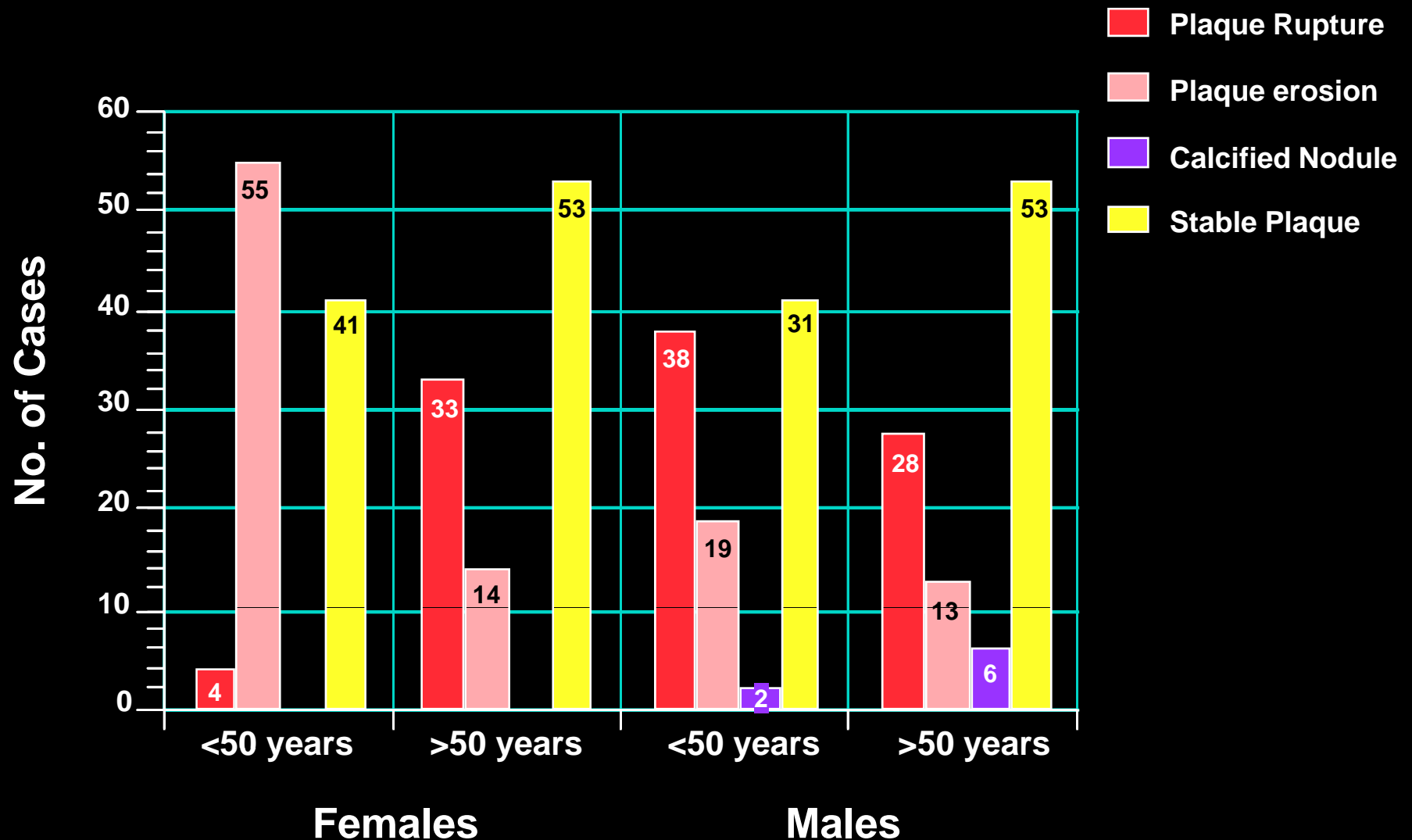
Proximal LAD →



Underlying plaque: PIT or fibroatheroma → rich in SMCs in a proteoglycan matrix, an absence of endothelial lining, and infrequently calcified.

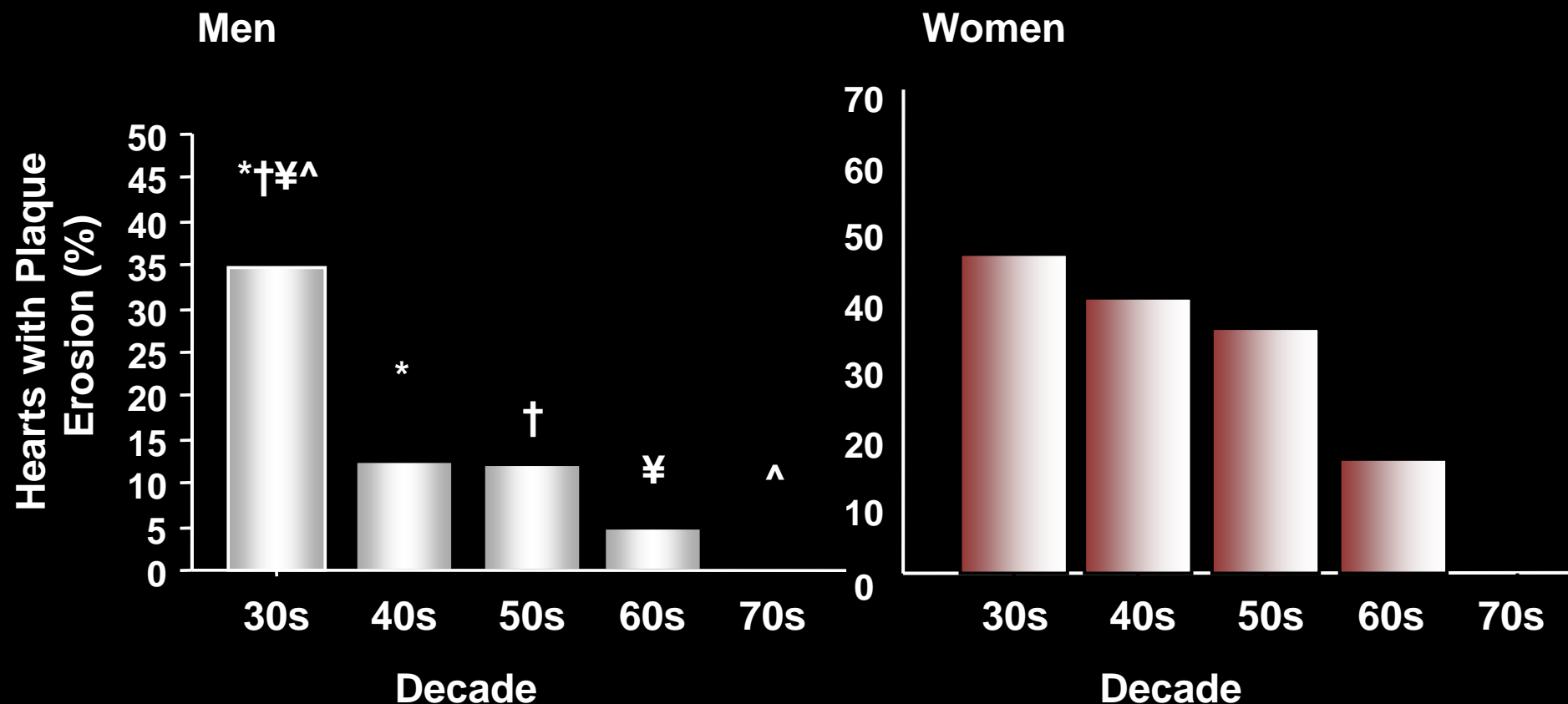
❖ Currently, no distinct morphological features of erosion-prone plaques have been identified.

Influence of Age on Coronary Thrombosis in Men and Women



Kolodgie FD, et al. Plaque erosion. 2008

Plaque Erosions in Men and Women Stratified by Age

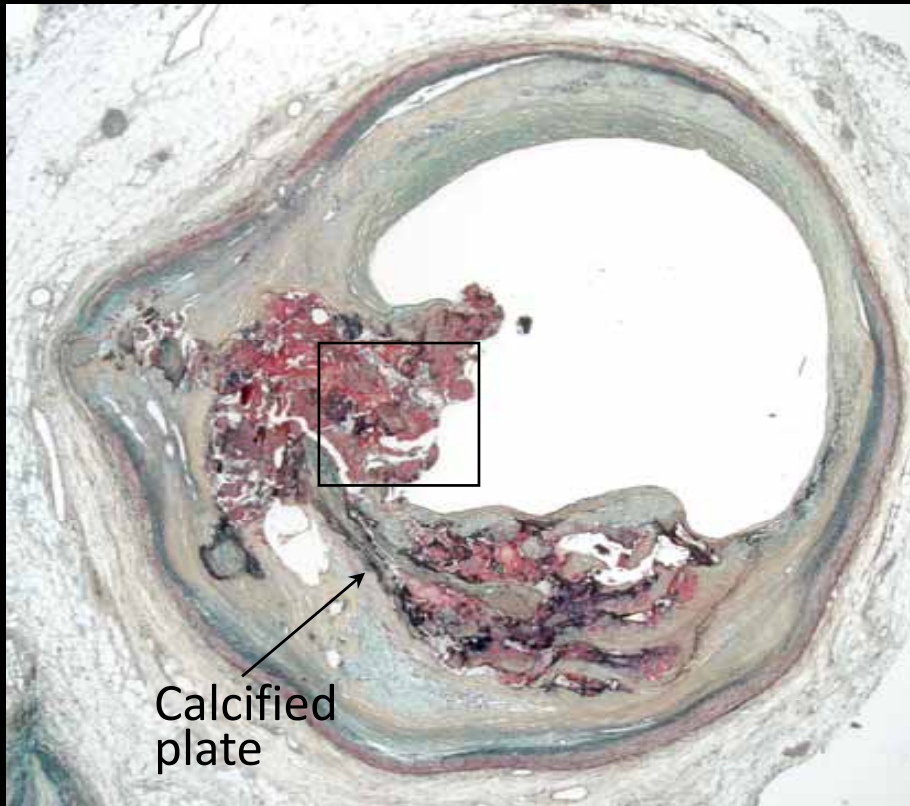


*P=0.01, †P=0.02, ¥p=0.01, ^P=0.03

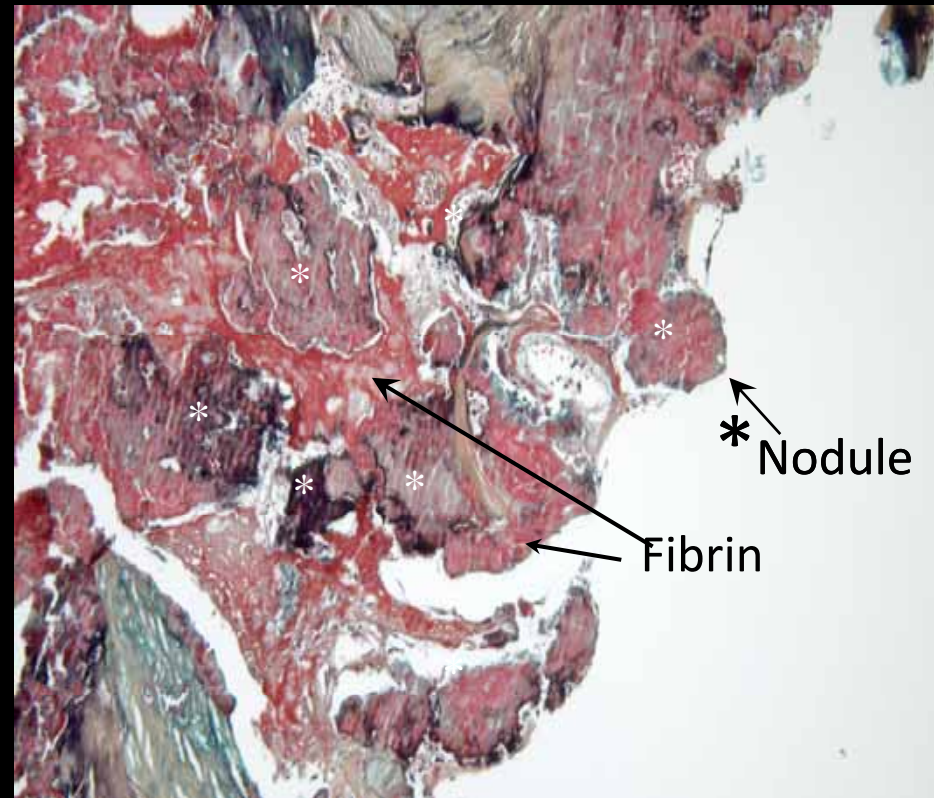
All P > 0.05

Calcified Nodule

A



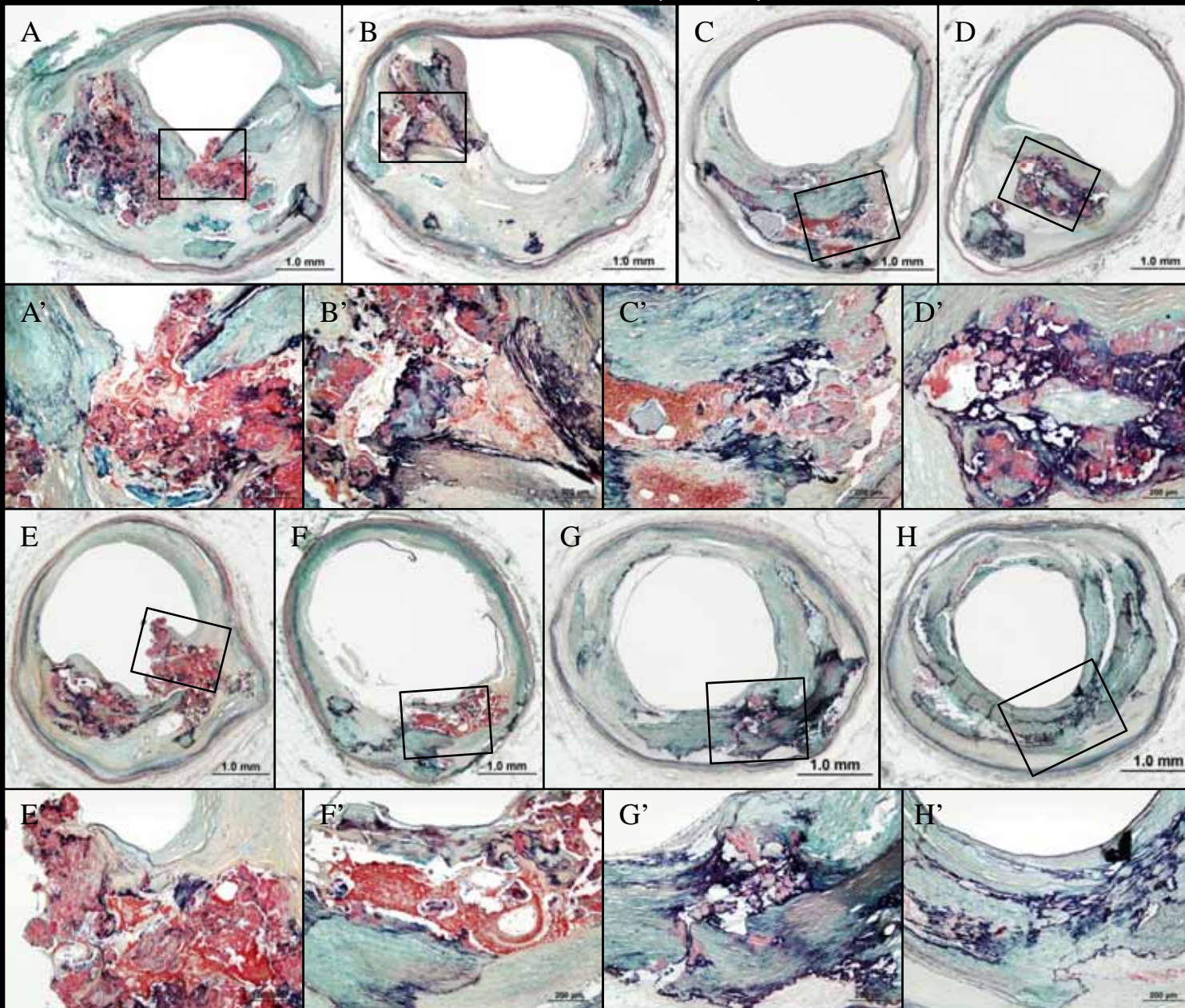
B



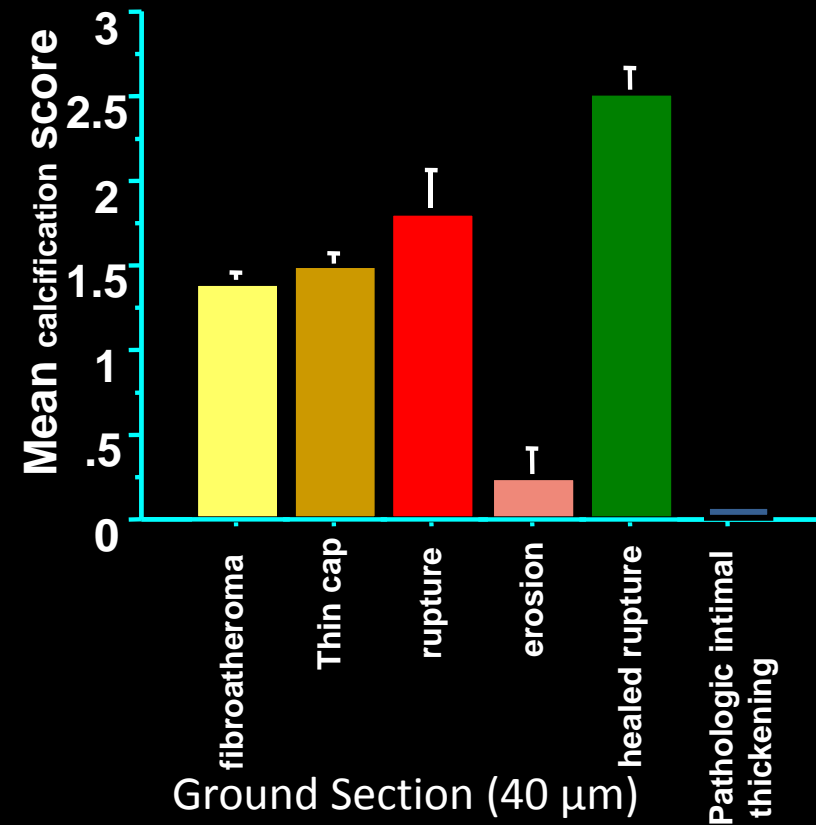
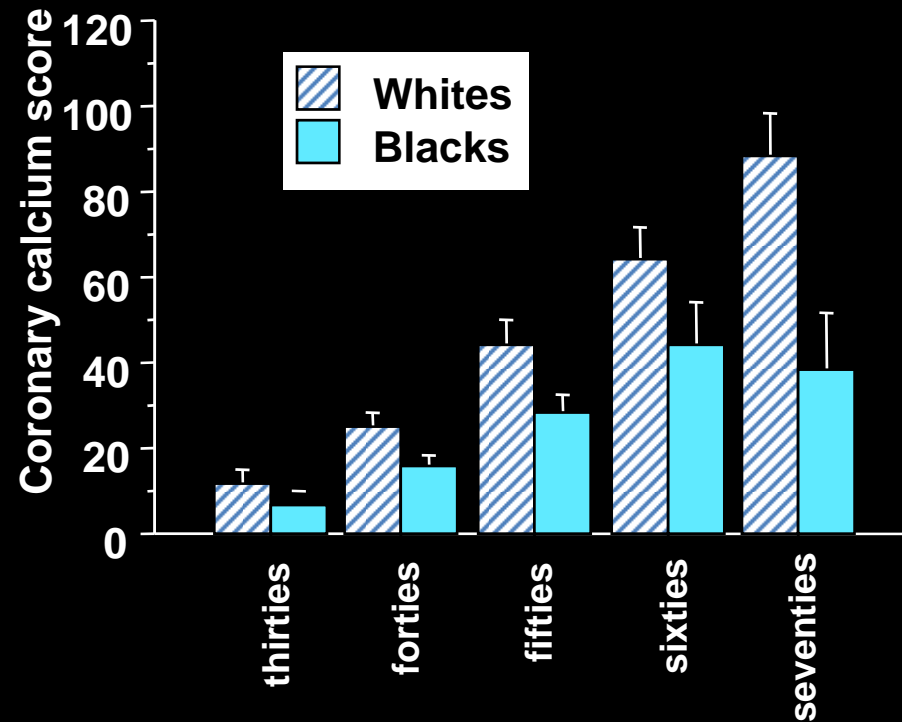
Frequency 2-7% of SCD, Older individuals, usually Men, equally common in tortuous right and left coronary arteries

Serial Sections of Calcified Nodule

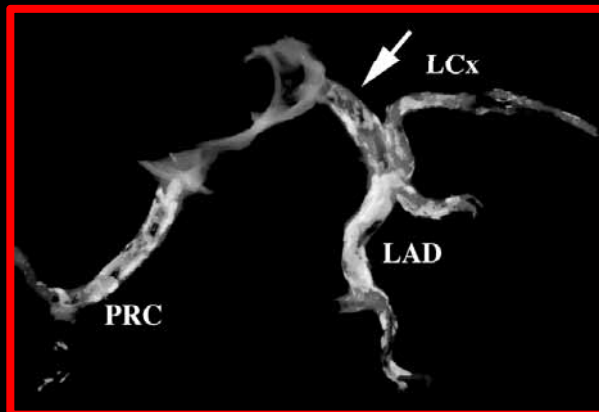
67M, Prediabetic and BMI 41.1, Mid RCA (A to H)



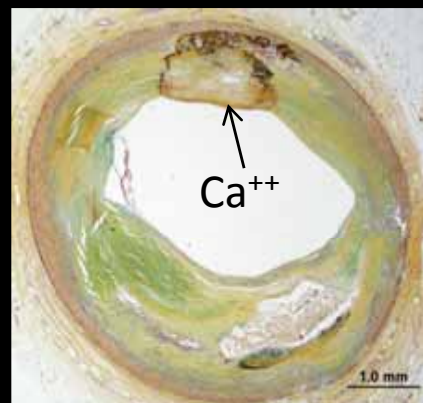
Patients dying from Sudden coronary Death: Extent of Coronary calcification by decades



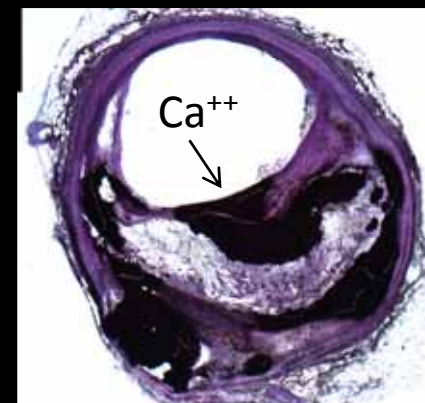
Radiograph



Movat Stain

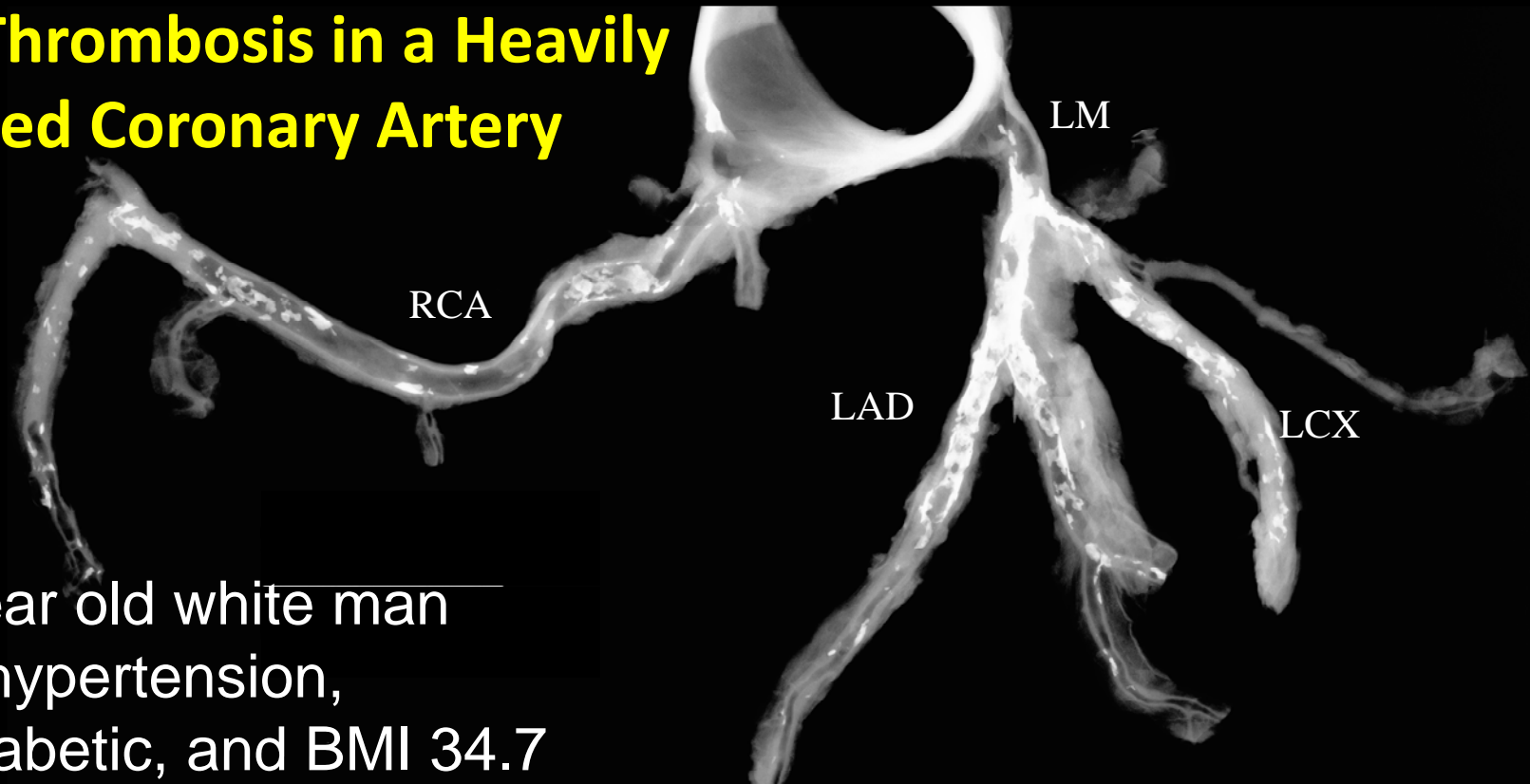


Ground Section (40 μm)

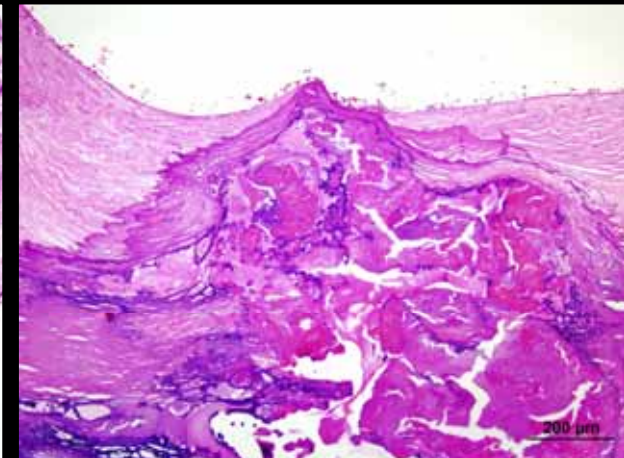
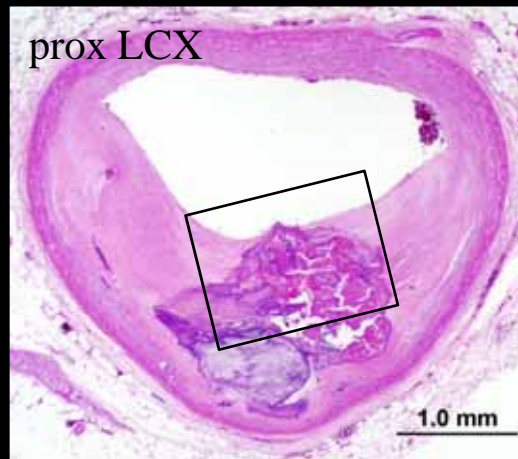
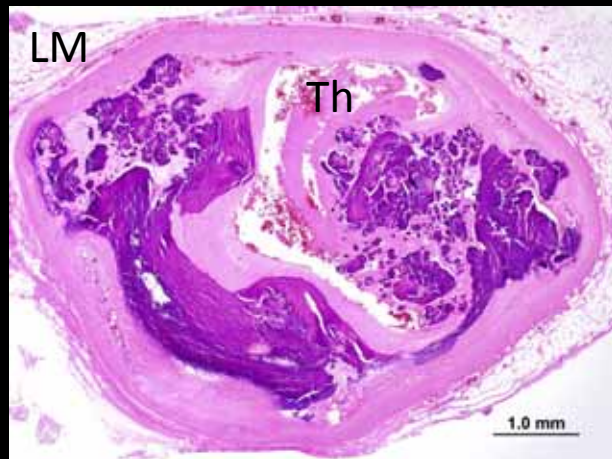


Pathologic intimal thickening

Eruptive Calcified Nodule with Thrombosis in a Heavily Calcified Coronary Artery



66 year old white man
H/O hypertension,
prediabetic, and BMI 34.7



The Role of Risk Factors in SCD patients

	Control N=163	Stable plaque n=131	Rupture n=84	Erosion n=45	Calcified nodules N=8
Age	46	54	49	45	57
Male	118 (72%)	102 (78%)	78 (90%)	29 (64%)	6 (88%)
Race %Black	75 (46%)	46 (35%)	21 (24%)	16 (36%)	2 (25%)
BMI	28.4	28.3	29.4	26.7	31.8
HbA1c	6.6	7.5	7.2	7.0	7.0*
Hx of HTN	35 (21%)	61 (47%)	27 (31%)	9 (20%)	5 (63%)
Smoker	64 (39%)	63 (48%)	53 (60%)	33 (73%)	7 (88%)
T. Chol	202	208	258	211	208
HDL	46	41	37	39	42
T.Chol/HDL	5.3	5.8	7.7	5.9	5.4
Healed MI	1 (1%)	76 (58%)	37 (42%)	11 (24%)	4 (50%)
Plaque Burden	---	232.4	248.1	178.9	258

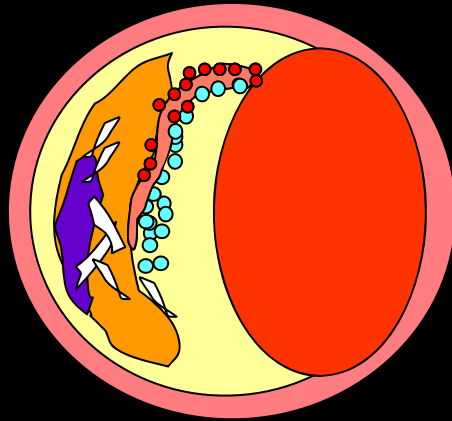
* Out of 8 case, 4 were DM, and 2 had Pre-DM.

The Role of Risk Factor

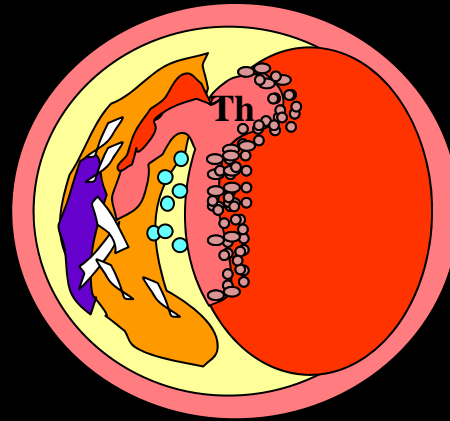
Multivariate logistic regression analysis

	Rupture			Erosion			Calcified Nodule		
Risk factor	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
Age (10 year increase)	1.09	0.86-1.38	0.48	0.75	0.53-1.05	0.10	2.14	1.24-3.69	0.01
Male sex	1.84	0.92-3.70	0.08	0.43	0.21-0.89	0.02	0.72	0.13-3.91	0.70
African American	0.66	0.37-1.16	0.15	0.73	0.36-1.48	0.39	0.23	0.03-1.99	0.18
BMI	1.02	0.98-1.06	0.30	0.96	0.91-1.02	0.17	1.07	0.97-1.18	0.18
Hb A1c	1.09	0.97-1.21	0.13	0.96	0.81-1.13	0.64	0.94	0.65-1.38	0.76
HTN	0.92	0.52-1.64	0.77	0.57	0.25-1.33	0.20	1.17	0.27-4.97	0.83
Smoker	1.89	1.12-3.17	0.02	3.42	1.61-7.28	0.001	2.71	0.61-11.99	0.19
T.Cho (10mg/dl increase)	1.12	1.07-1.16	<0.0001	0.98	0.94-1.03	0.53	0.95	0.85-1.08	0.44

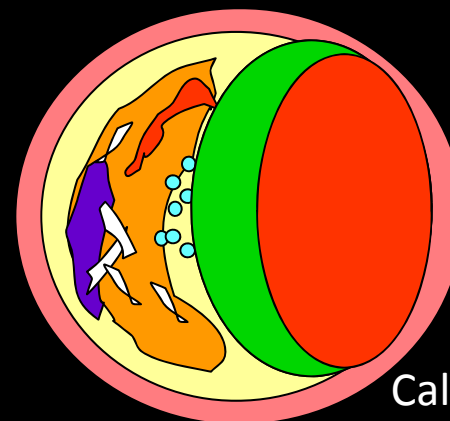
Plaque Fissure



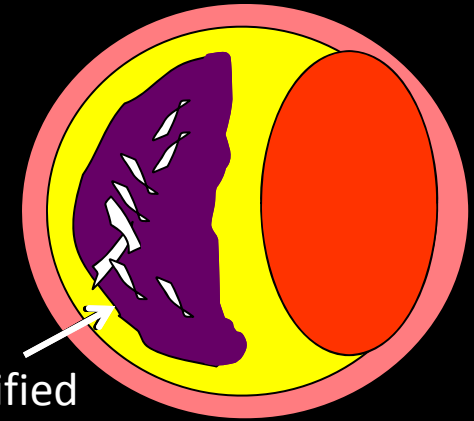
Plaque Rupture



Healed Plaque Rupture

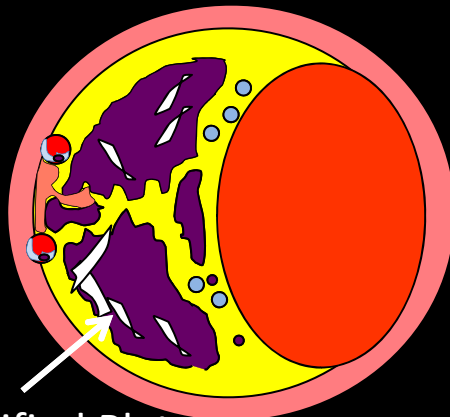


Fibrocalcific Plaque



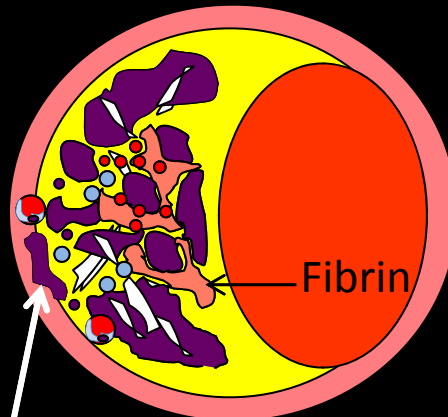
Calcified plate

Calcified Plate Fragmentation



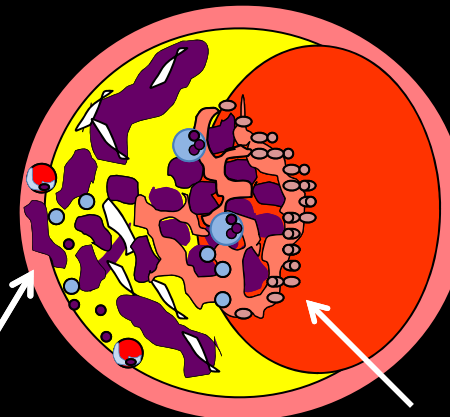
Calcified Plate fragmentation from artery tortuosity and beating heart

Nodular Calcification



Nodules of calcium Destroying the media

Calcified Nodule with luminal thrombus



Medial destruction

Luminal thrombus surrounded by Fibrin and platelet

Summary:

Pathogenesis of Vulnerable Plaque

- Plaque rupture is the main cause of thrombosis, 65-75%; while erosion occurs in 25-30%; and calcified nodule is uncommon, 2-7%, in ACS and sudden coronary death.
- Vulnerable plaques (TCFA) is a likely precursor lesions of rupture. Macrophage infiltration play an important role in modification of plaque vulnerability.
- Plaque erosion occur principally in younger individuals, especially women with a smoking history. The underlying plaque consists of PIT or fibroatheroma; however, distinct morphological features of erosion-prone plaques have not been identified.
- Calcified nodules is another substrate for thrombosis, especially in elderly male individuals with high plaque burden, tortuous arteries, diabetes or metabolic syndrome, hypertension, and smoking.
- Intraplaque hemorrhage from “leaky” vasa vasorum is an important contributor to necrotic core expansion and potential lesion instability.
- Macrophage subtypes may help us better understand the role of plaque hemorrhage and plaque stabilization vs. plaque rupture.

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