

Pathogenesis of Vulnerable Plaque 2015: What's New?

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Potential conflicts of interest

Speaker's name: Michael Joner, MD

I have the following potential conflicts of interest to report:

Consultant: Biotronik

Employment in industry: No

Honorarium: Orbus Neich, Biotronik

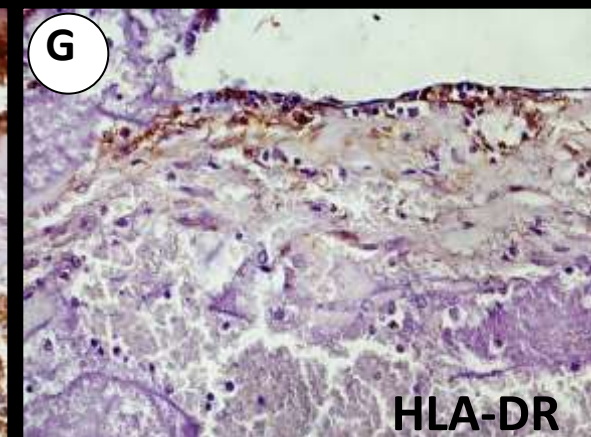
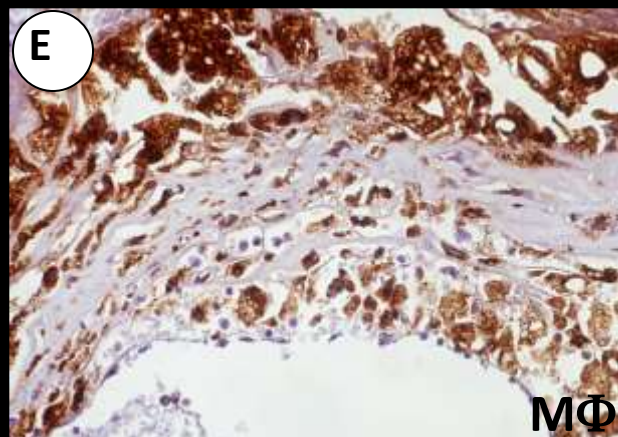
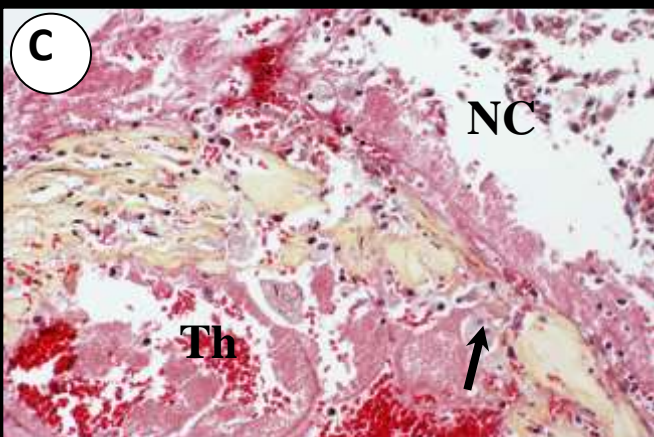
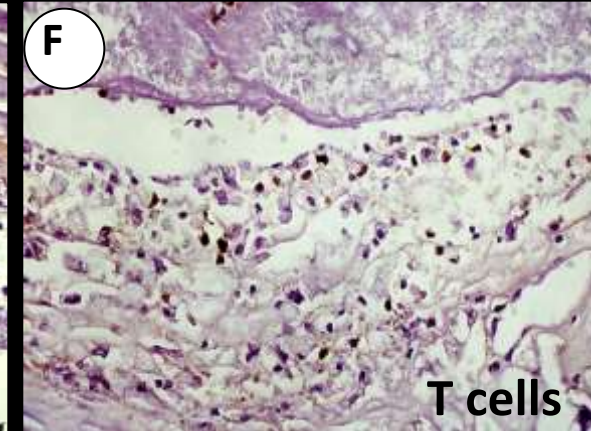
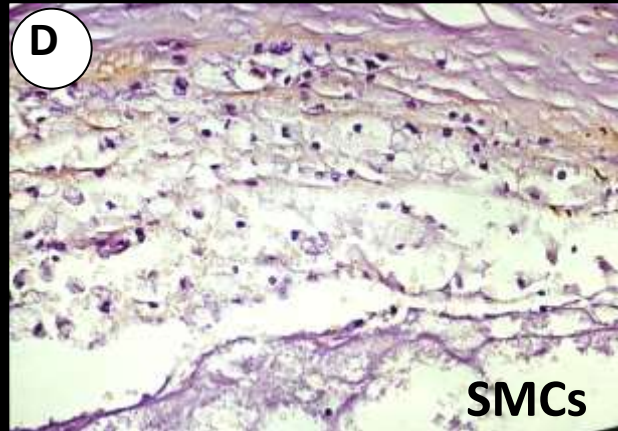
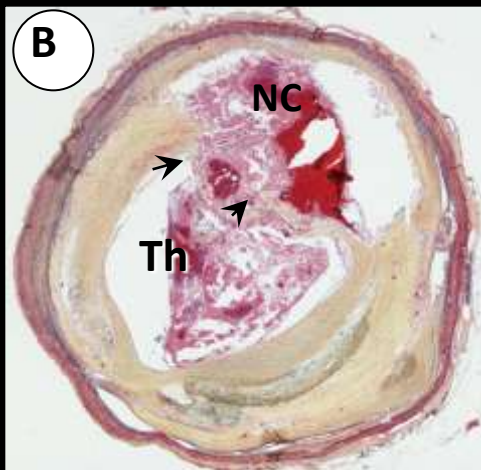
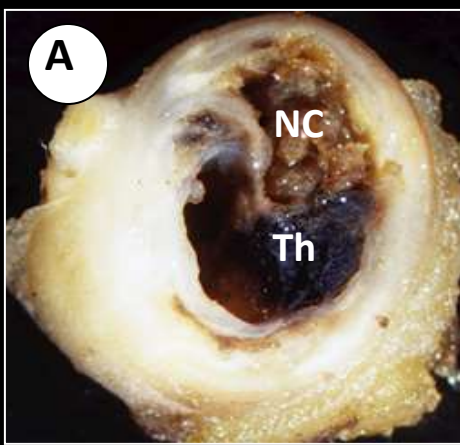
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Stockholder of a healthcare company: No

Gross and Light Microscopic Features of Plaque Rupture

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

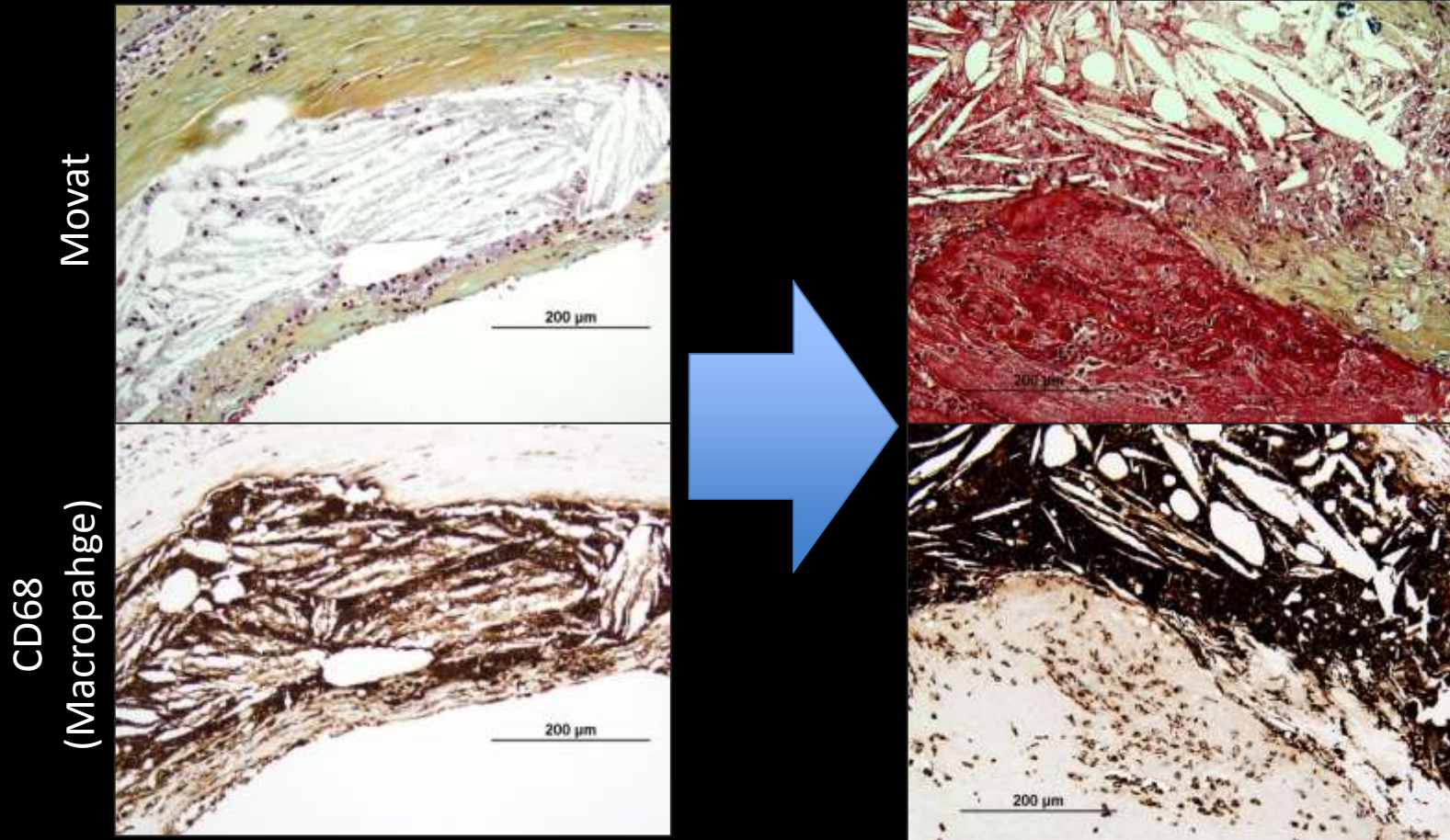


Features of Ruptured Plaques

- 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
-

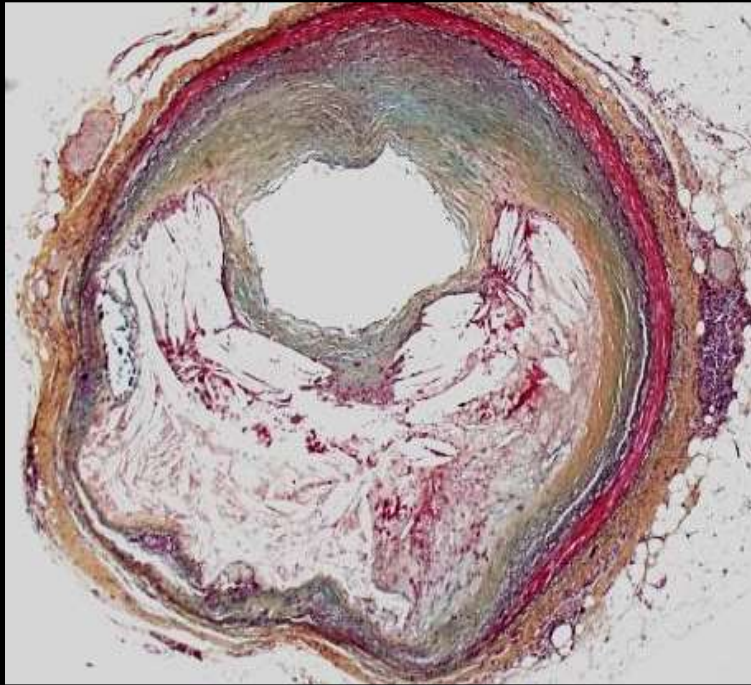
Independent Morphological Predictor of Rupture

50-75% cross-sectional stenosis



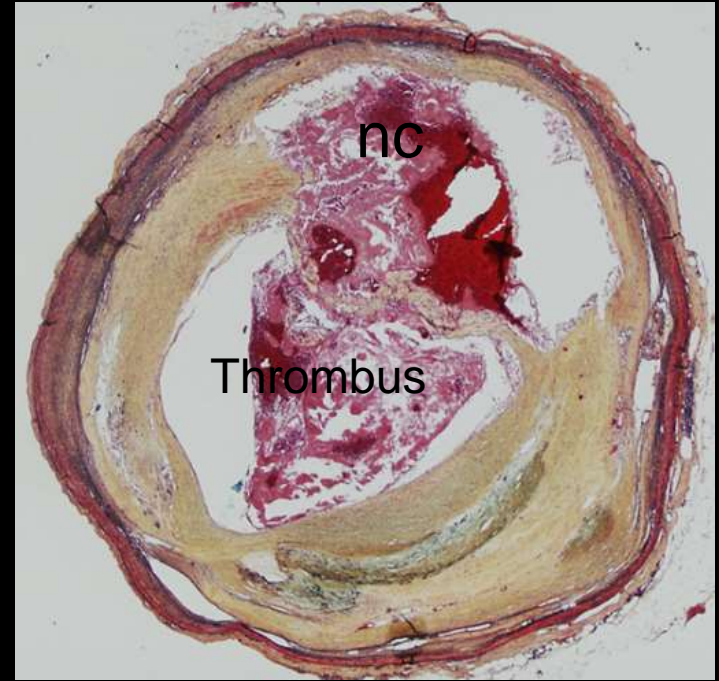
	P Value	Odds Ratio	95% CI
Cap thickness	0.005	0.35	0.16 – 0.69
%NC	0.02	2.0	1.1 – 3.7
%Macrophage	0.052	1.8	0.99 – 3.2

Do TCFA Continue to Progress and Rupture?



Thin cap fibroatheroma

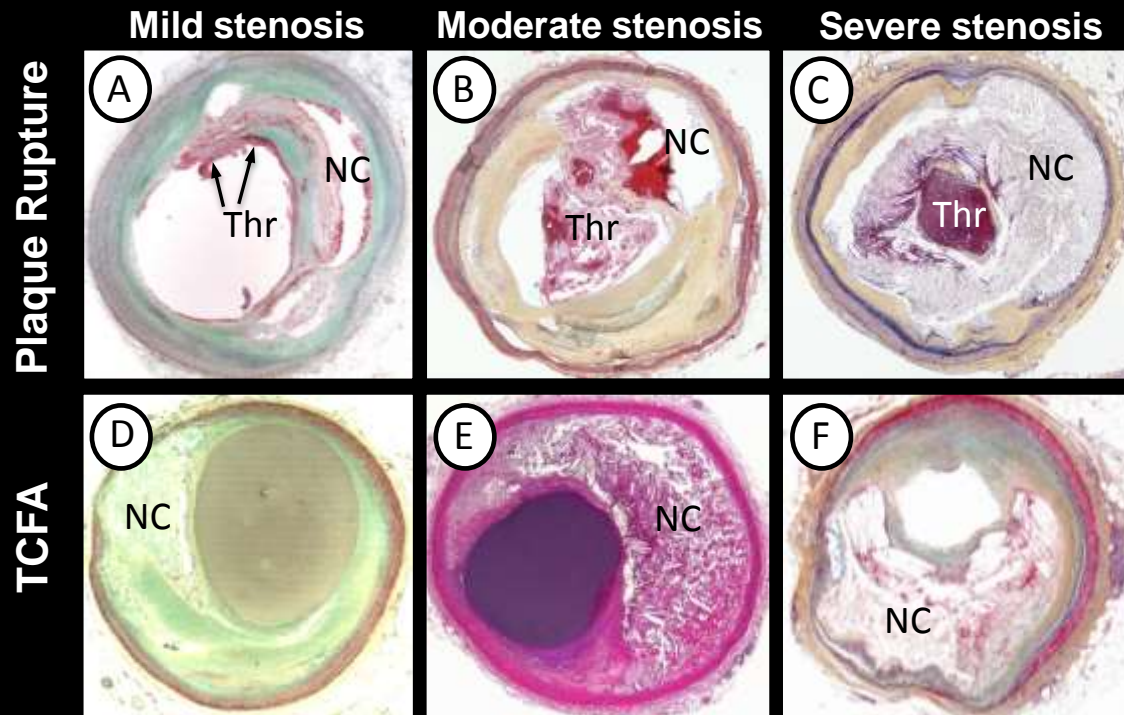
- Necrotic core ($21.6 \pm 23.7\%$)
- Thin fibrous cap ($< 65 \mu\text{m}$)
- Cap infiltrated by macrophages and lymphocytes
- Cap composition – type 1 collagen with few or absent smooth muscle cells



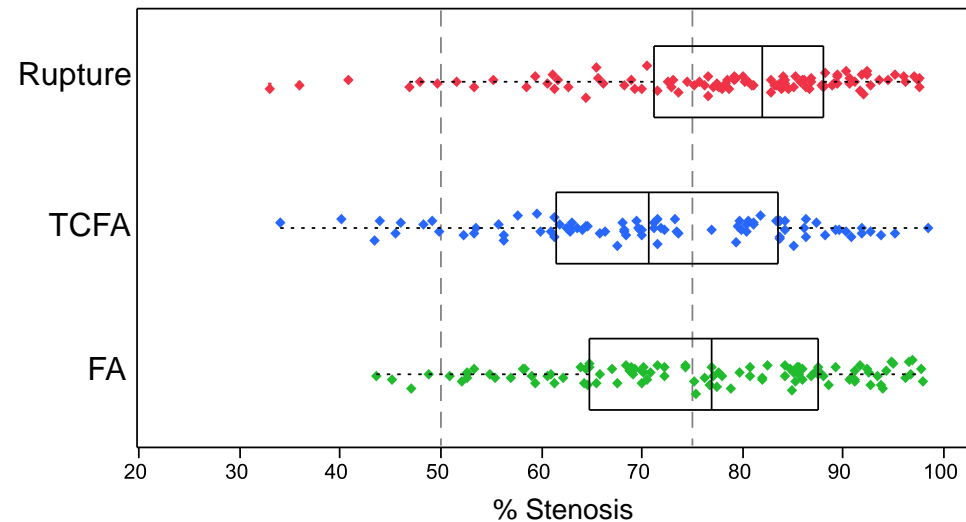
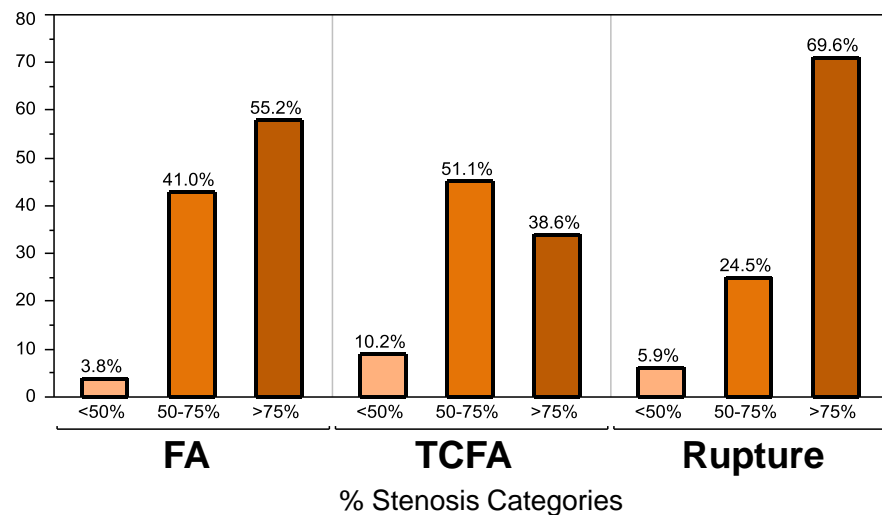
Plaque Rupture

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

Plaque Rupture and TCFA with Varying Luminal Stenosis

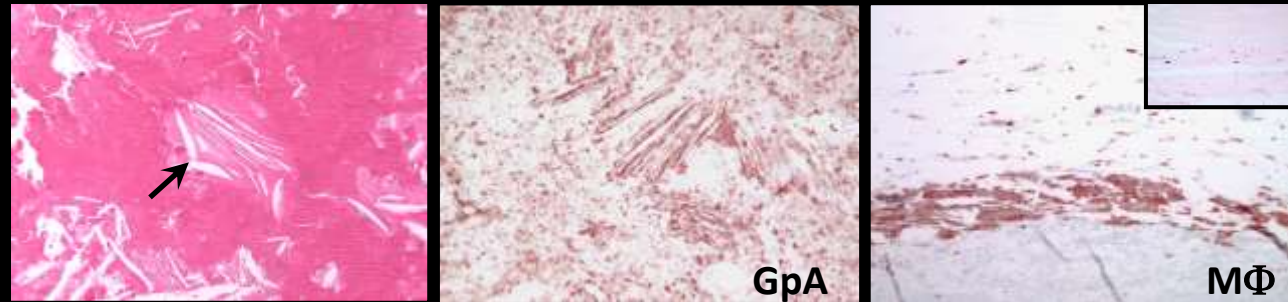


*Narula J, Nakano M, et al.
J Am Coll Cardiol 2013;61:1041-51.*

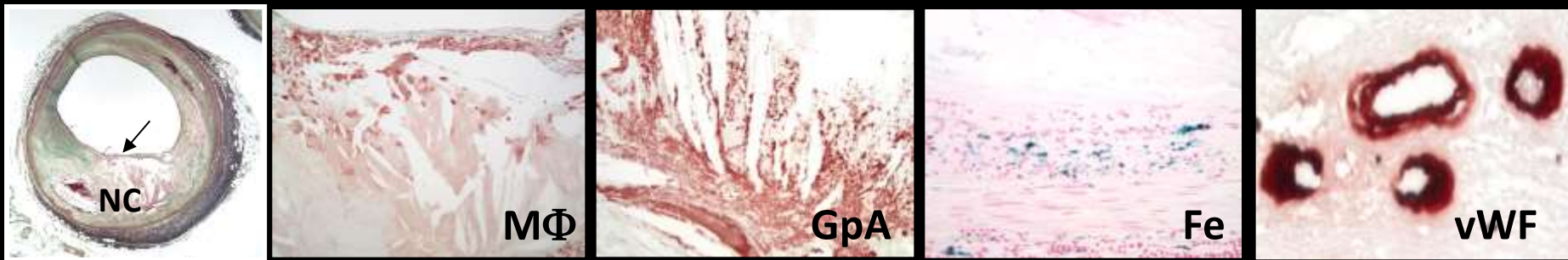


Morphometric Analysis of Hemorrhagic Events in Human

Hemorrhagic
Pericarditis



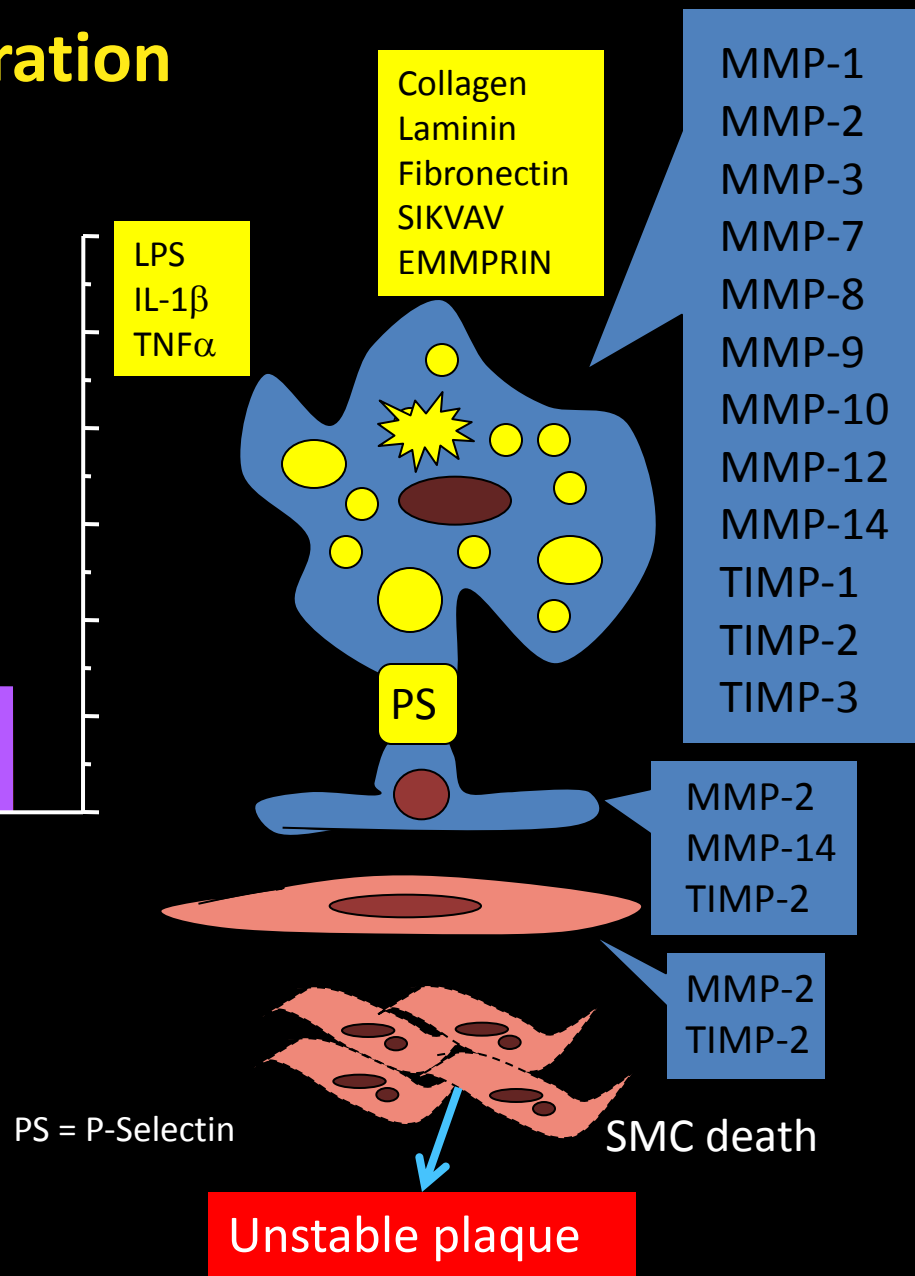
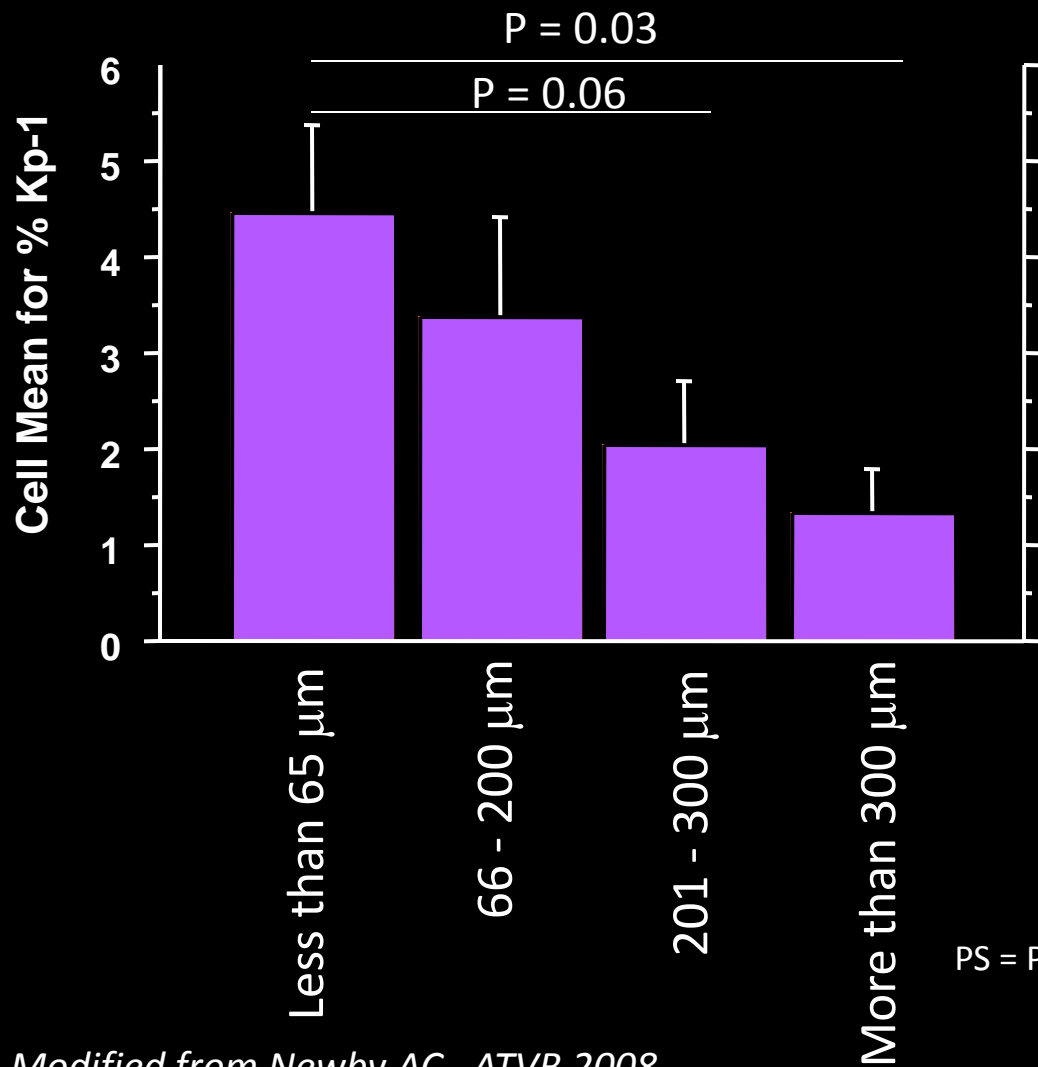
Vulnerable Plaque



Plaque Type	GpA Score	Iron	Necrotic Core (mm ²)	MΦ (mm ²)
PIT <i>no core</i> (n=129)	0.09 ± 0.04	0.07 ± 0.05	0.0	0.002 ± 0.001
FA <i>early core</i> (n=79)	0.23 ± 0.07	0.17 ± 0.08	0.06 ± 0.02	0.018 ± 0.004
FA <i>late core</i> (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

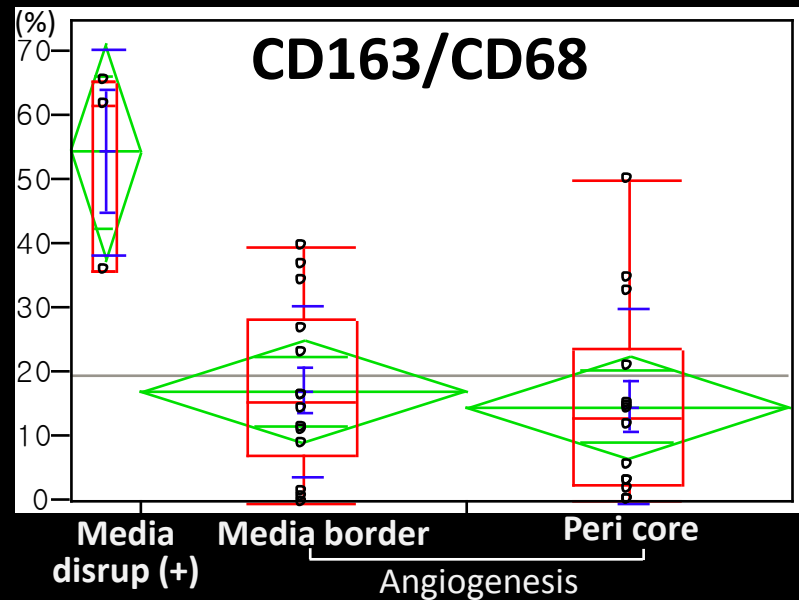
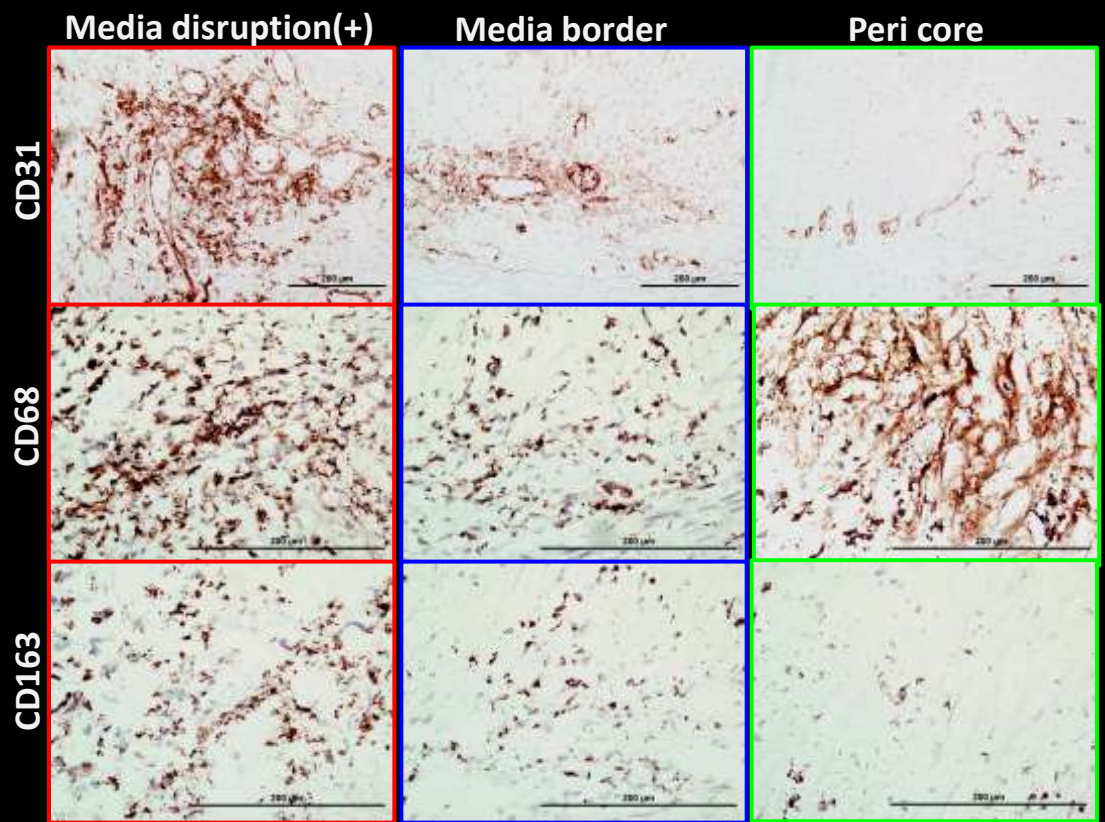
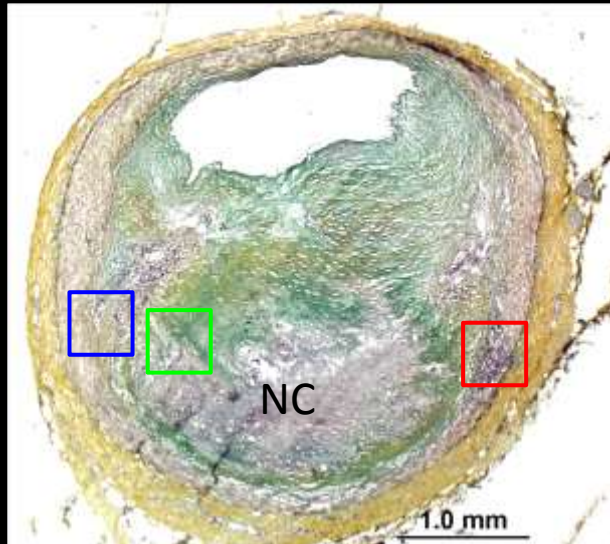
Values are reported as the means ± SE, *p < 0.001 versus early core. The number in parenthesis represent the number of lesions examined; the total number = 365. MΦ = macrophages

Relationship of Fibrous Cap Thickness to Macrophage Infiltration

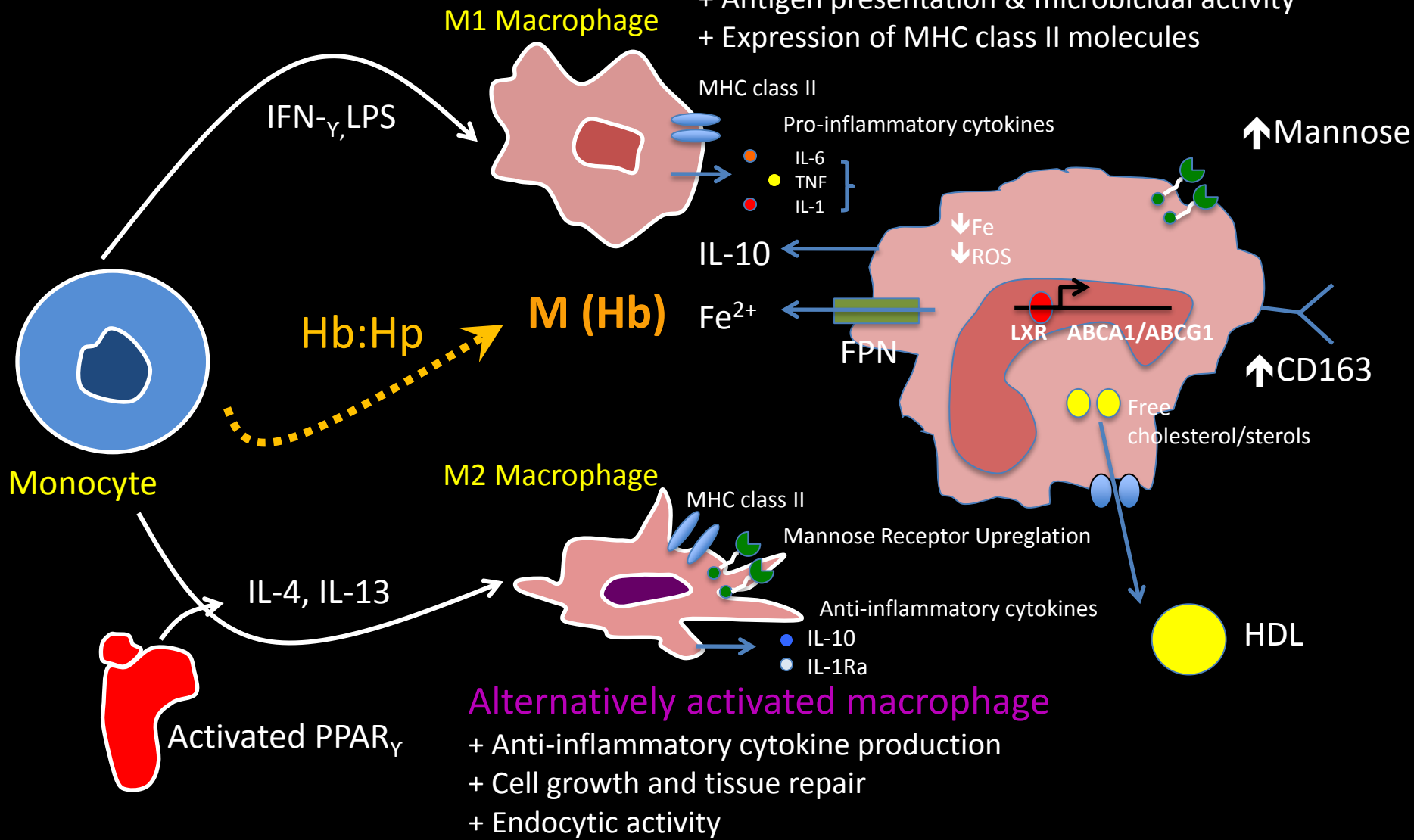


Distribution of Macrophage Sub-type

Human coronary plaque



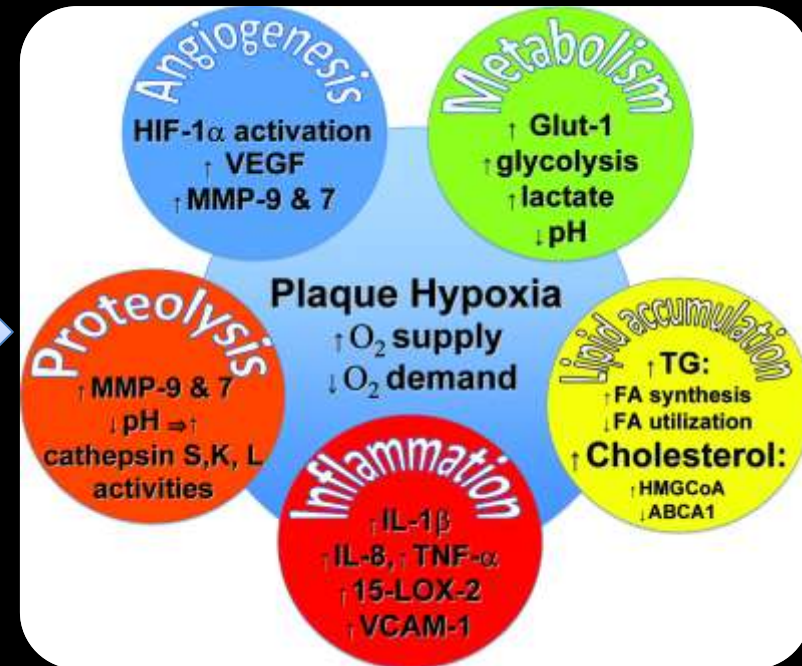
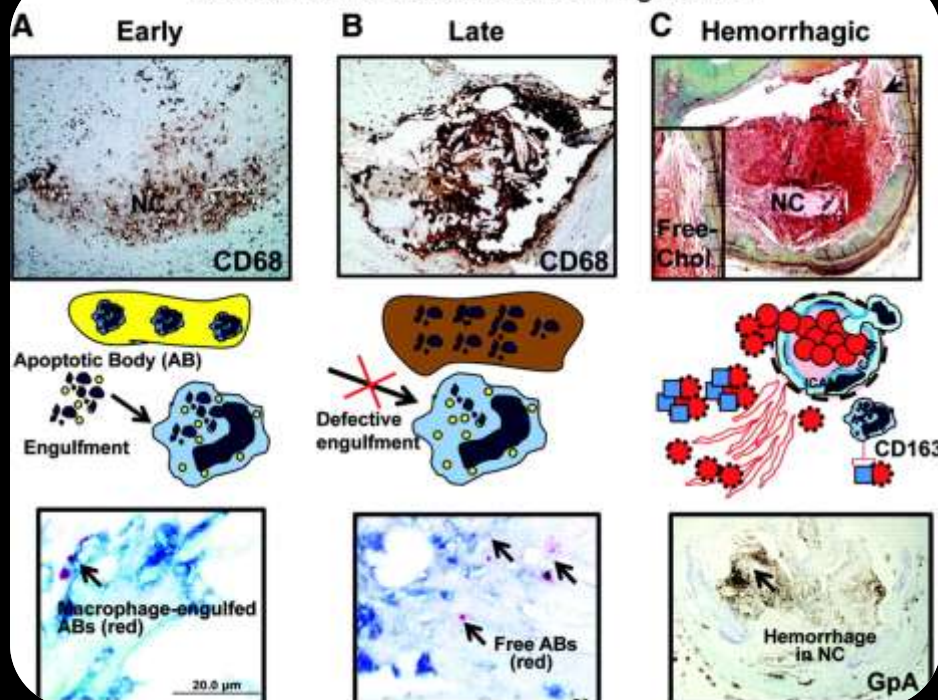
Macrophage Diversity



Putative Mechanisms of Necrotic Core Expansion

- Early NC is characterized by CD68-positive macrophages engulfing apoptotic bodies
- Late NC is characterized by defective engulfment with free apoptotic bodies
- Intraplaque hemorrhage further amplifies NC formation which is partly counteracted by CD163-positive macrophages
- Intra-plaque hypoxia is believed to be an important etiological factor stimulating neoangiogenesis, proteolysis, inflammation, lipid accumulation and change local metabolism

Mechanism of Necrotic Core Progression



Vulnerable Plaque: A Moving Target

Rupture of a thin fibrous cap is not the only mechanism resulting in arterial thrombosis....

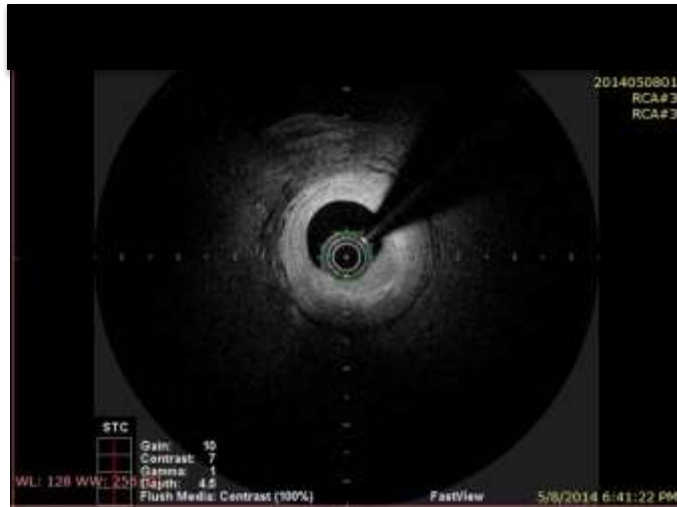
OFDI Imaging in Erosion at Autopsy

34-year old man with history of smoking and untreated hyperlipidemia, had epigastric pain and was found dead at home

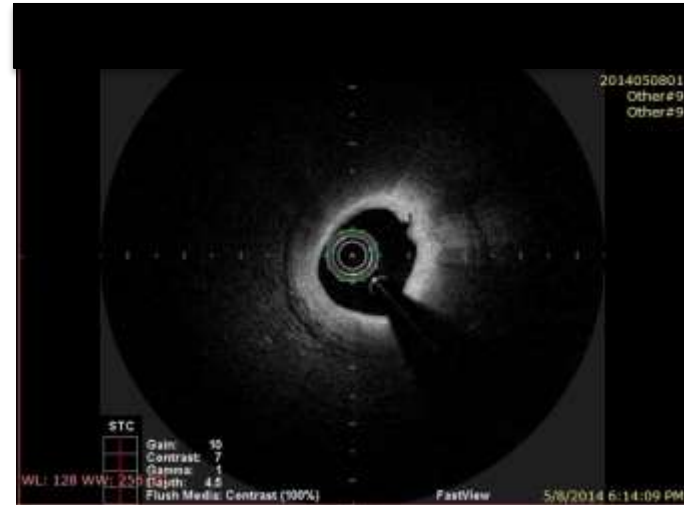
Definite Erosion by OCT: Thrombus with non-ruptured plaque or intact fibrous cap

Probable Erosion by OCT: Luminal surface irregularity or attenuation of underlying plaque by thrombus without superficial lipid or calcification in adjacent frame

RCA



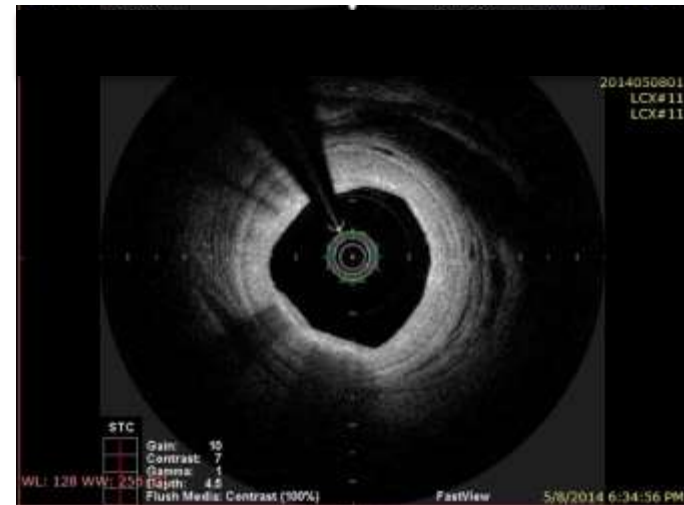
LD



LAD

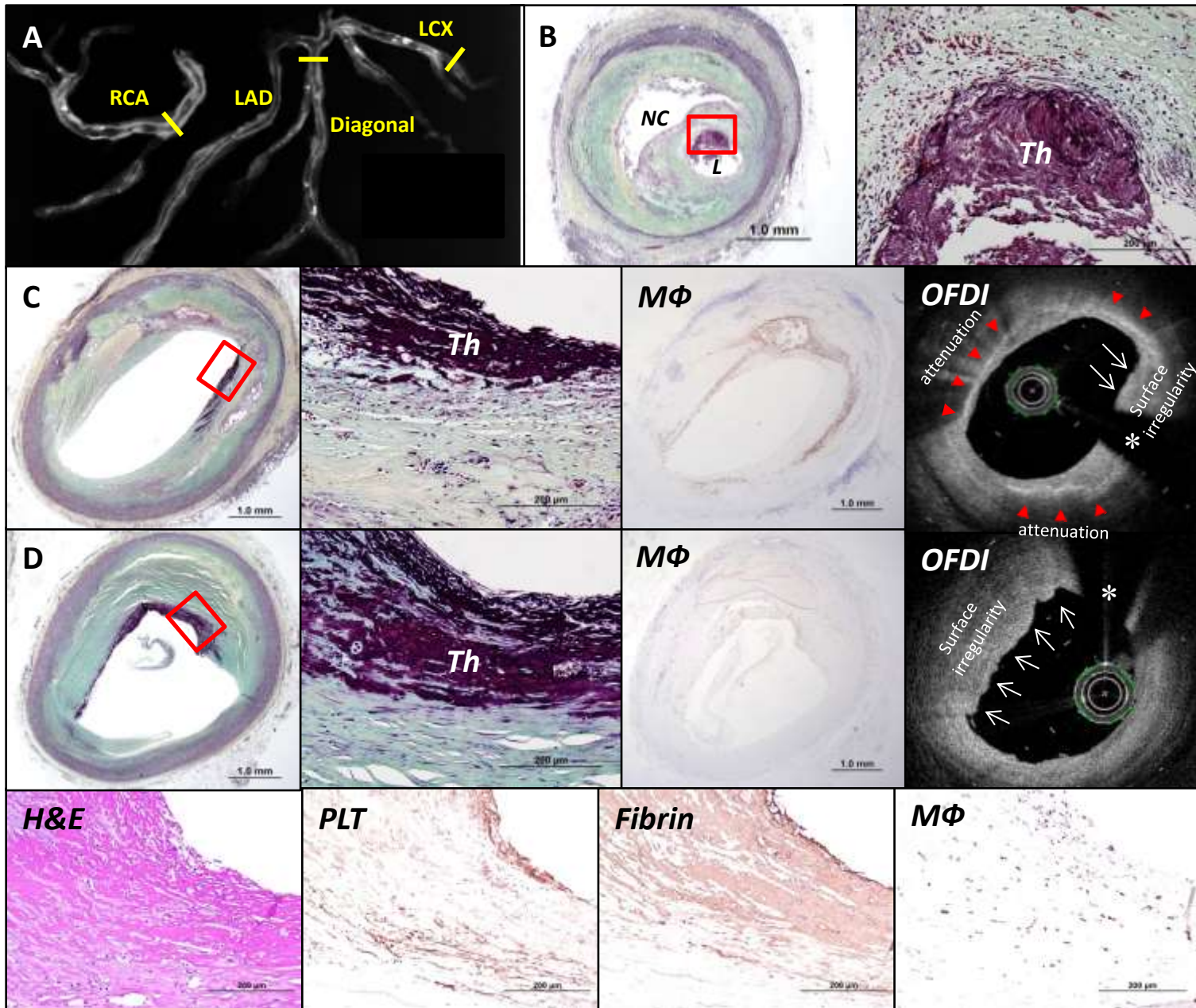


LCX



Erosion - Thrombus in the Absence of Rupture

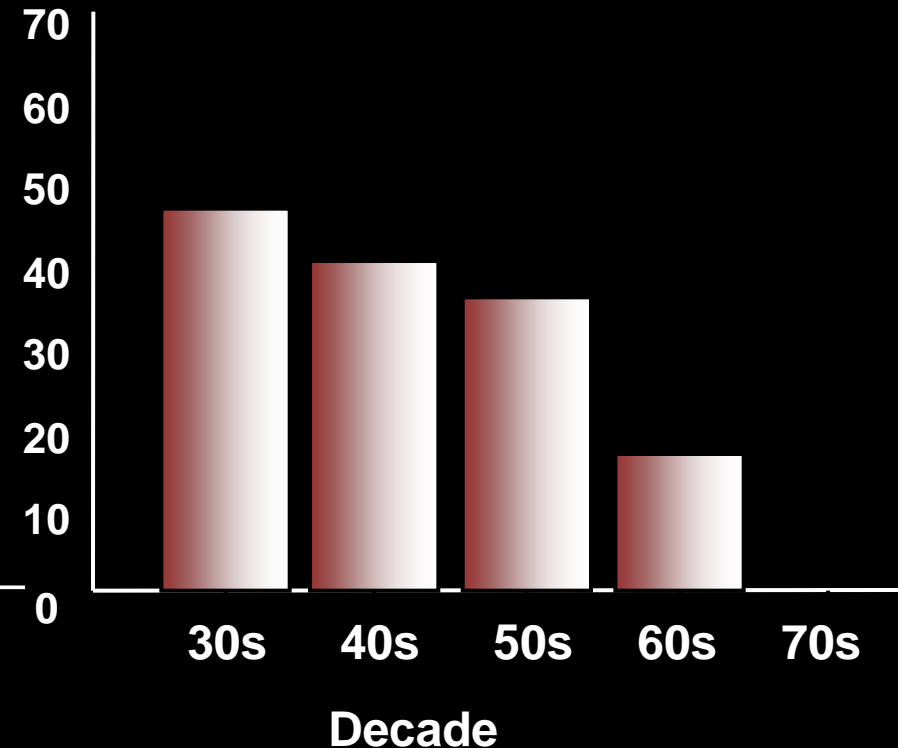
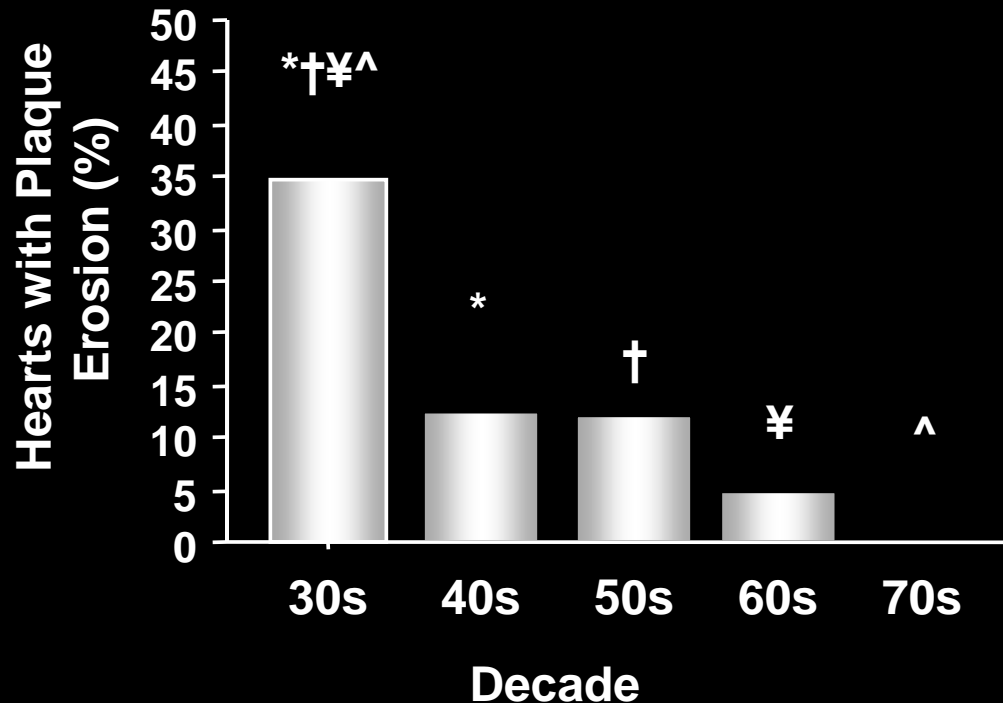
Presence of Necrotic Core



Plaque Erosions in Men and Women Stratified by Age

Men

Women

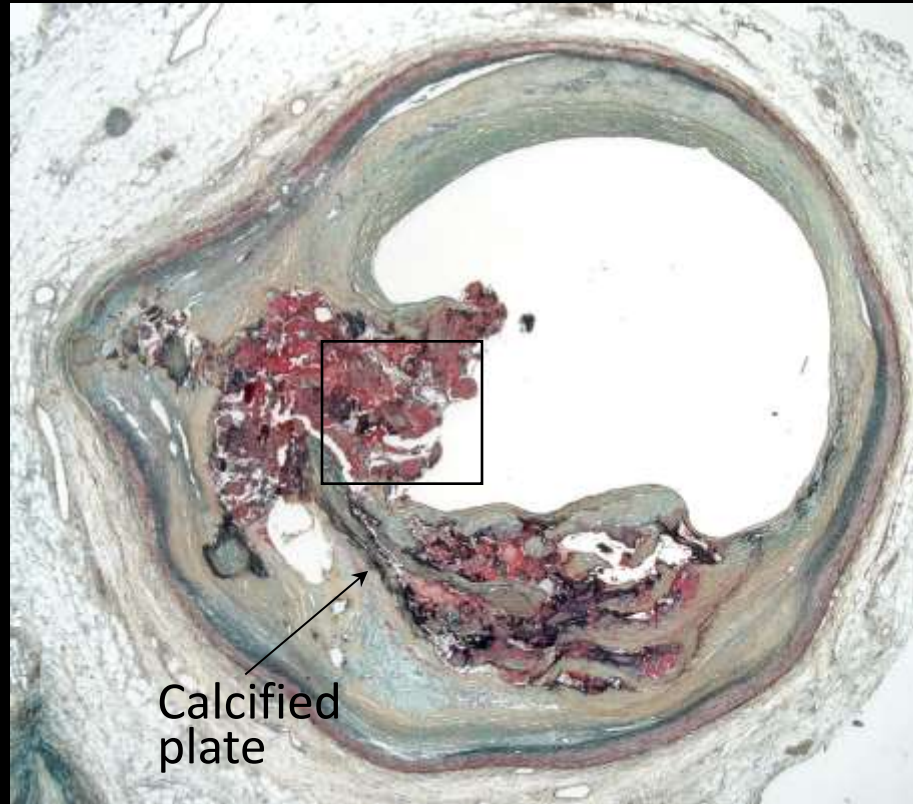


*P=0.01, †P=0.02, ¥p=0.01, ^P=0.03

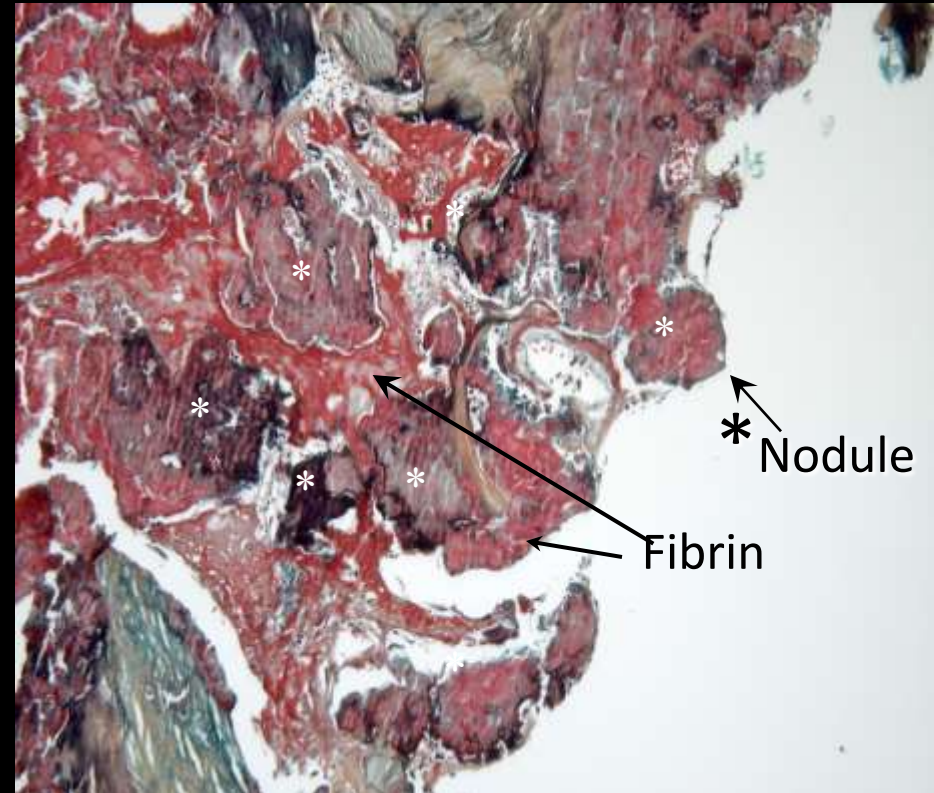
All P > 0.05

Calcified Nodule

A

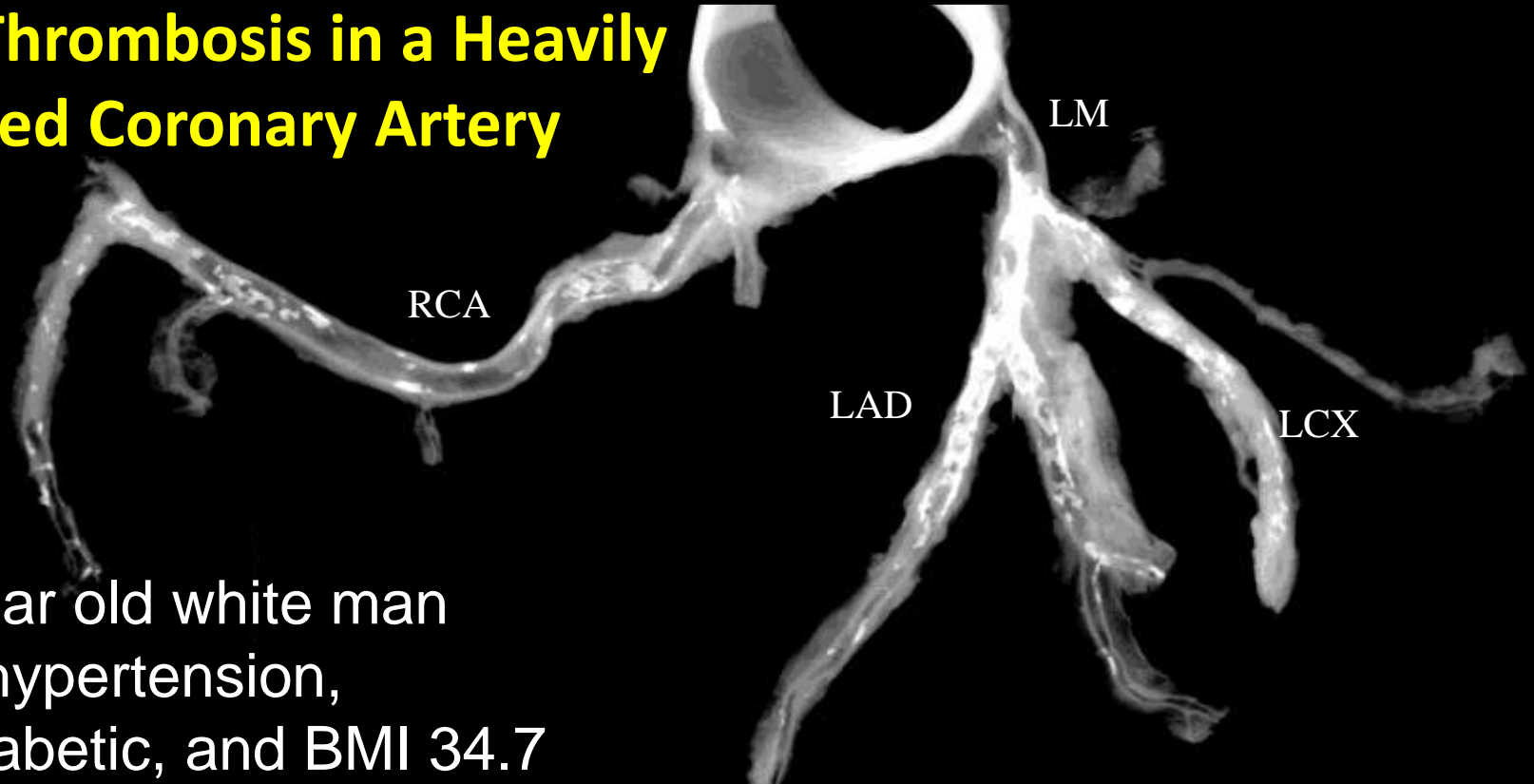


B

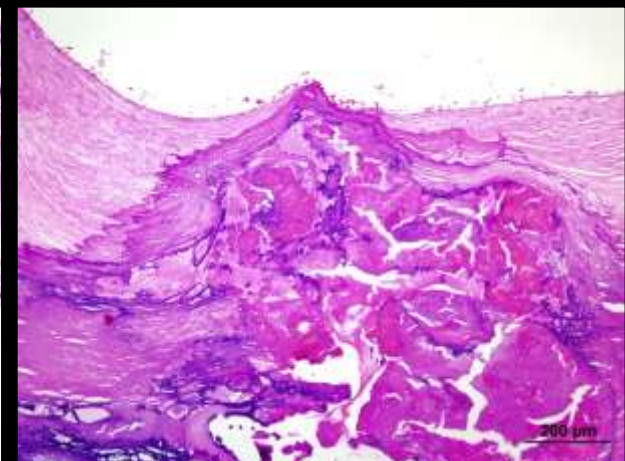
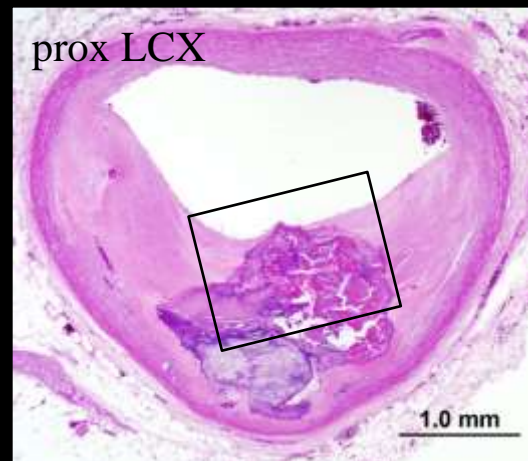
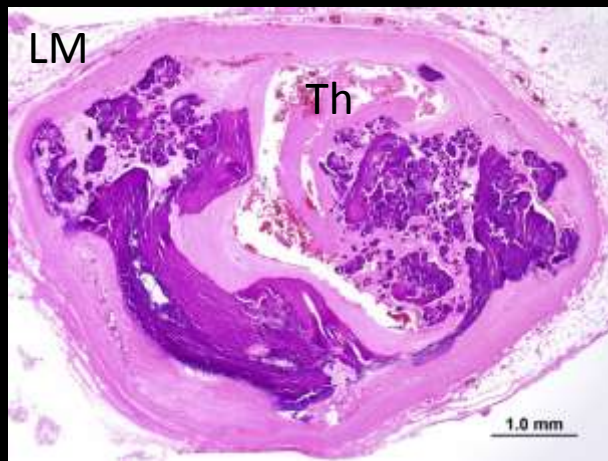


Frequency 2-7% of SCD, Older individuals, usually Men, equally common in tortuous right and left coronary arteries

Eruptive Calcified Nodule with Thrombosis in a Heavily Calcified Coronary Artery



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



Summary

➤ Hierarchical features of plaque vulnerability are.....

① 1. Necrotic core size

② 2. Macrophage infiltration

③ 3. Fibrous cap thickness

➤ Macrophage subtypes have been identified which possess differential plaque progressing potential and may play an important role for future VP imaging

➤ Defective efferocytosis (macrophages) and intra-plaque hypoxia are important putative etiological causes of necrotic core progression

➤ Erosion and Calcified Nodule also play an important role in arterial thrombosis

➤ Reliable upstream screening algorithms are important in the future to identify patients at risk for more detailed molecular imaging of high-risk lesions

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