Mechanisms of Plaque destabilization Pathologic Observations

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American College of Cardiology

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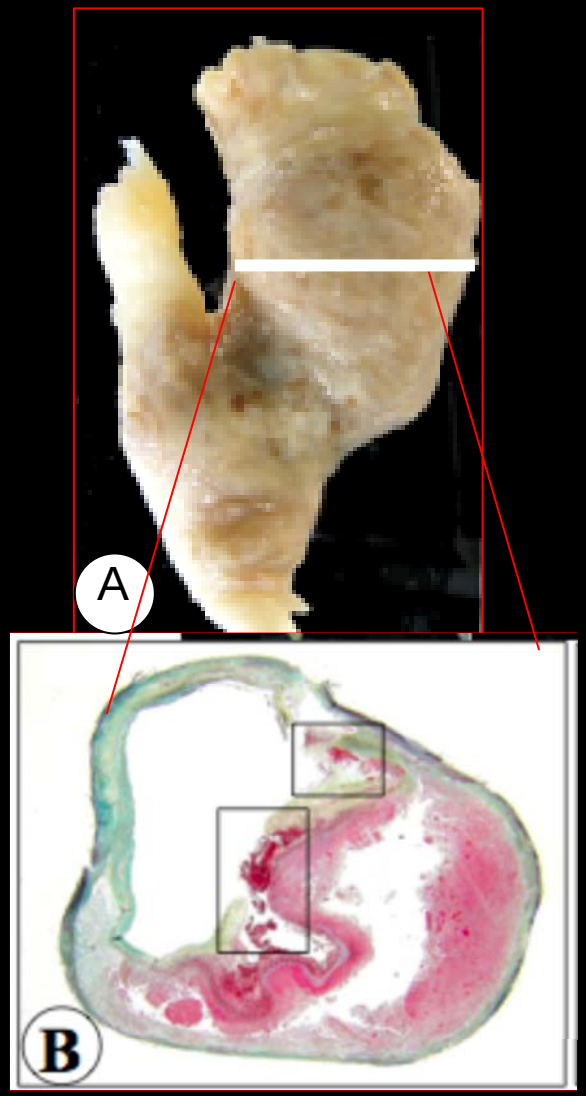
Conflict: Nothing to declare

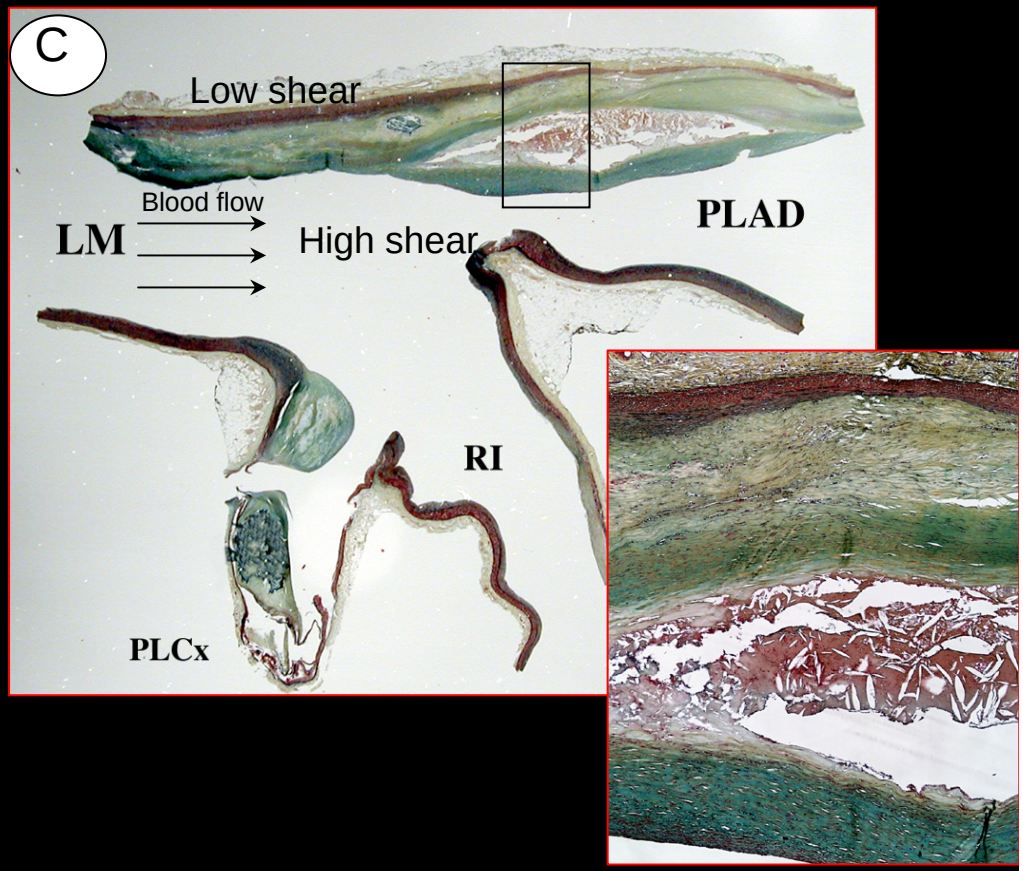
CVPath Institute, Inc.

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

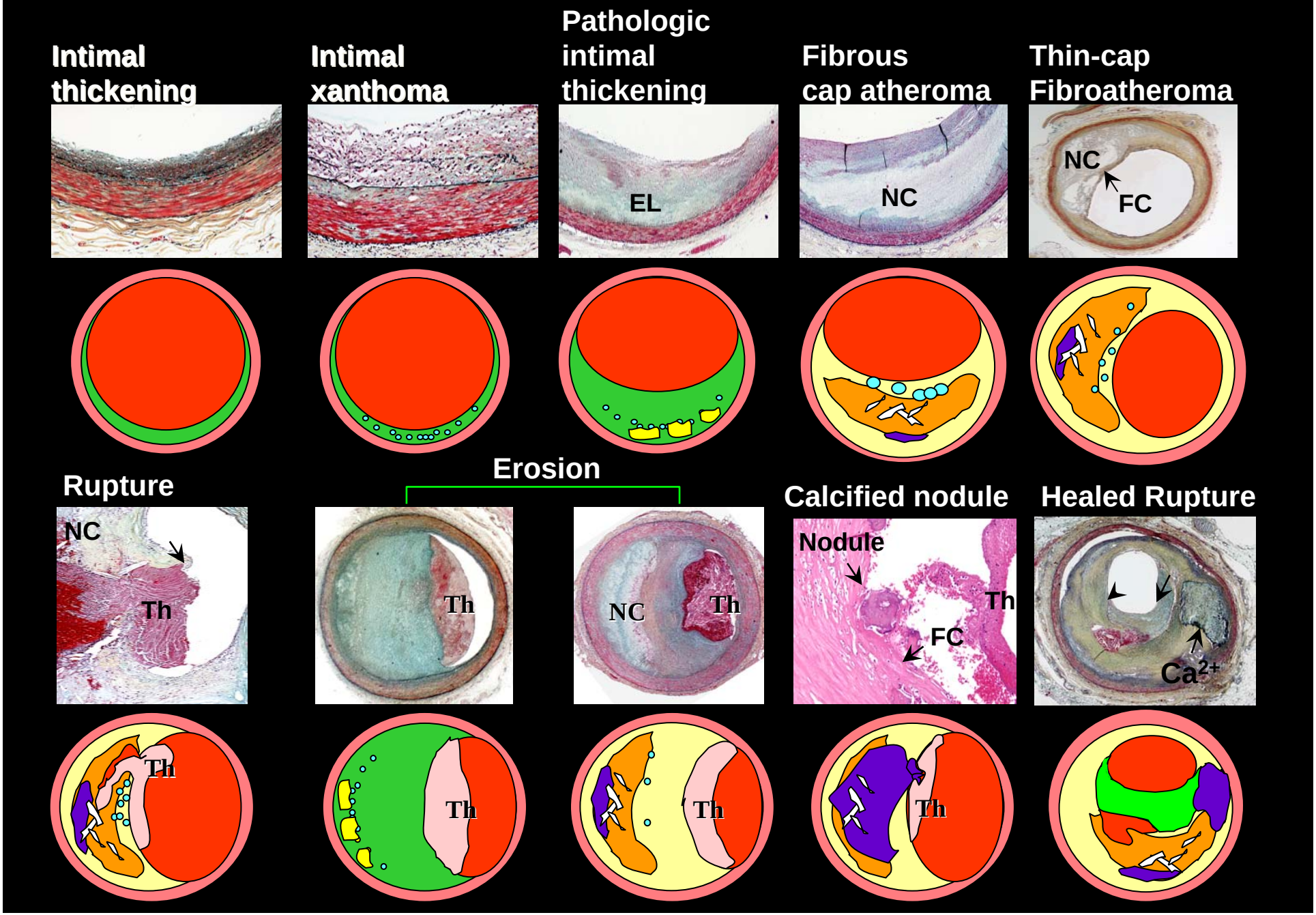
Carotid Artery



Left Coronary artery



Progression of Human Coronary Atherosclerosis

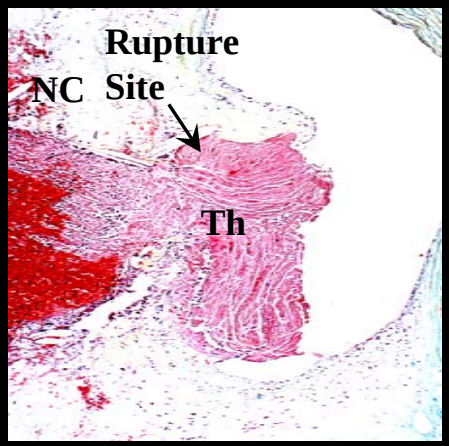


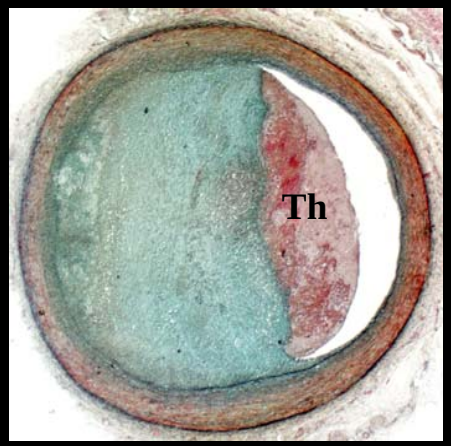
Causes of Coronary Thrombosis

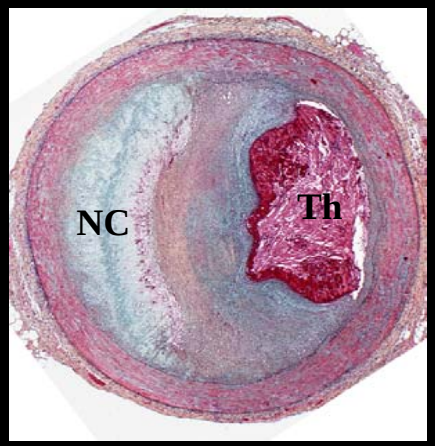
Rupture

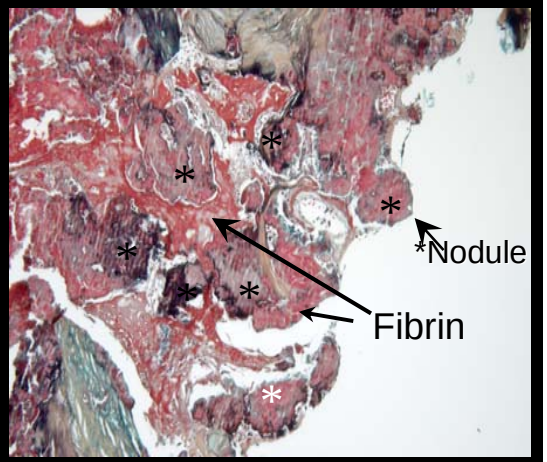
Erosion

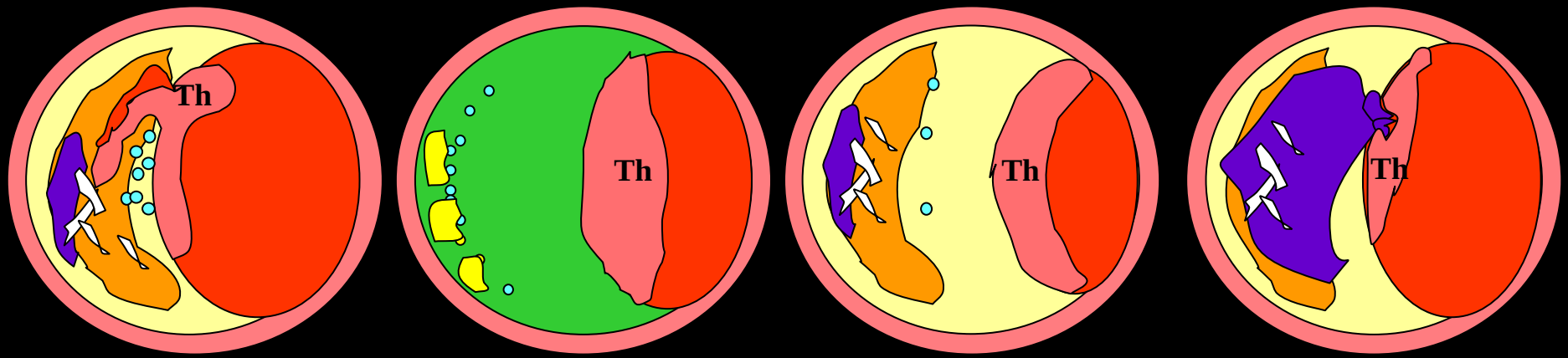
Calcified nodule





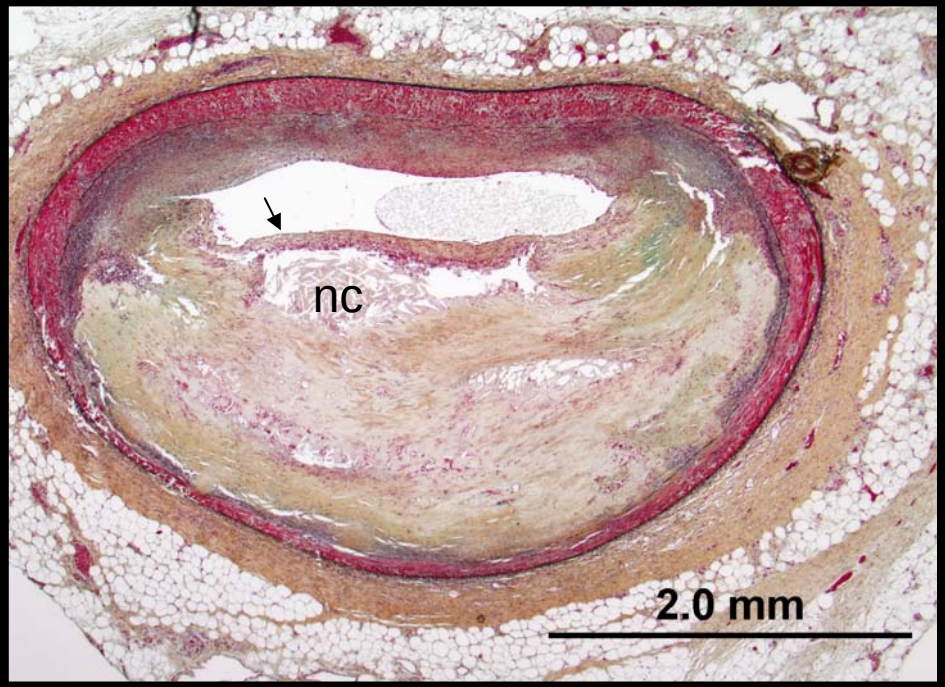






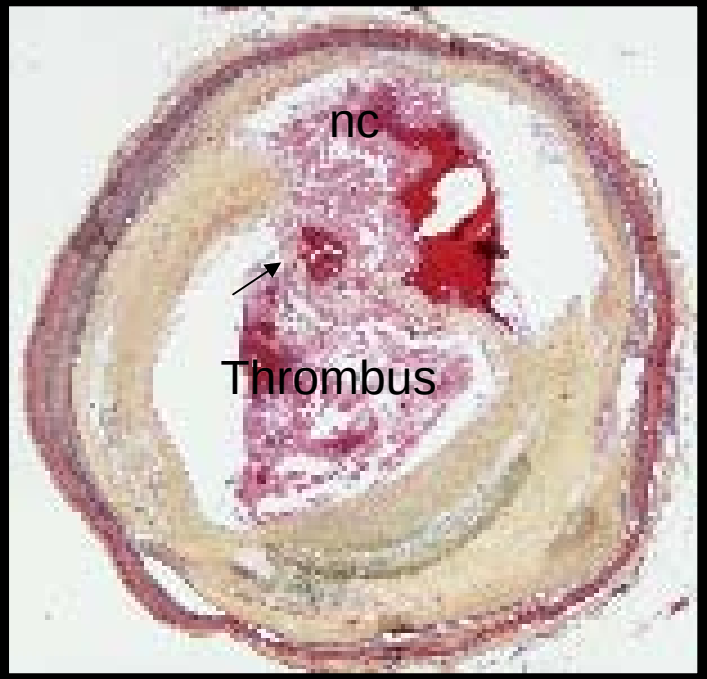
Virmani R, et al. Arterioscler Thromb Vasc Biol 2000;20:1262

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



Thin cap fibroatheroma

?

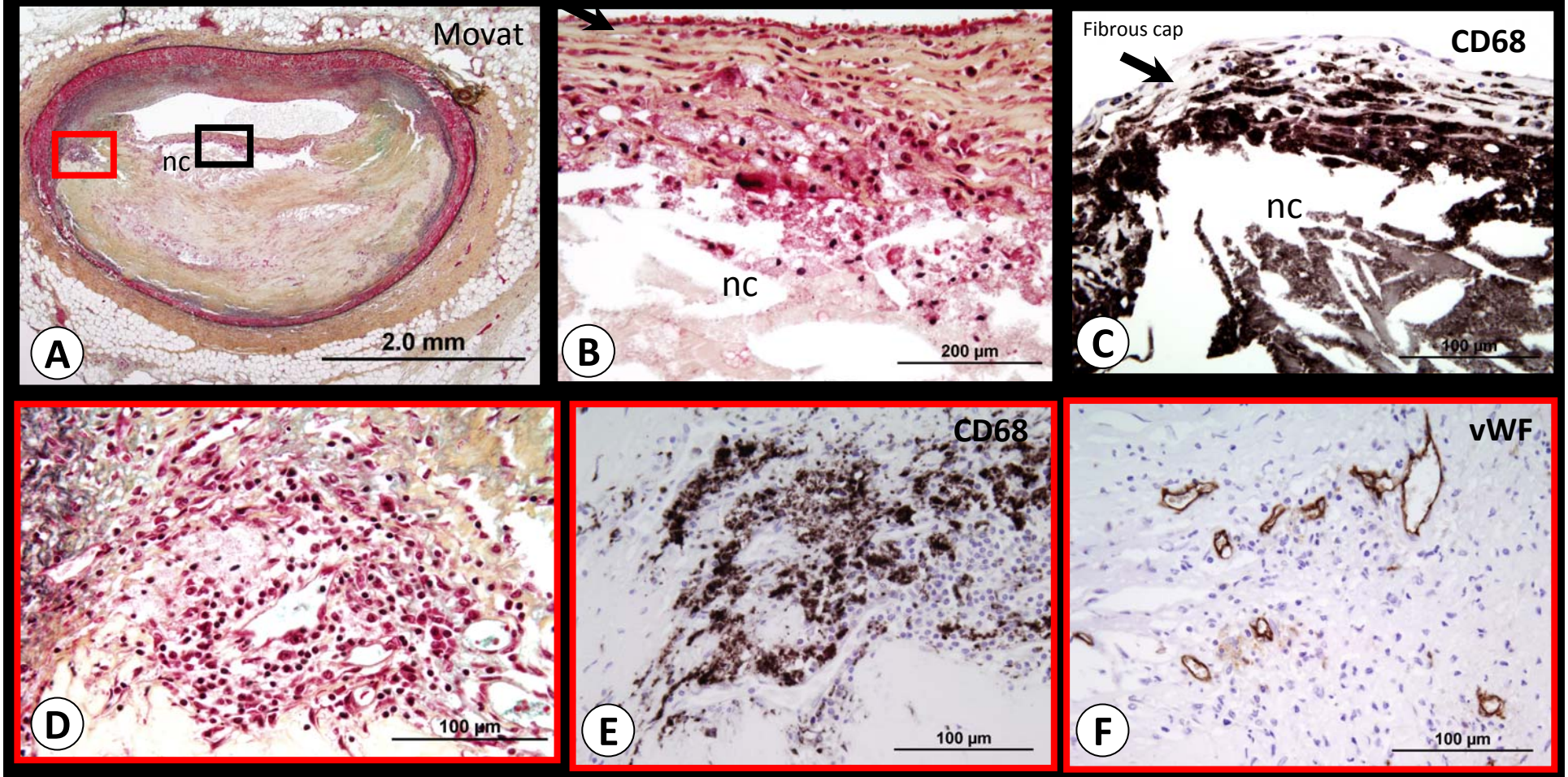


Plaque Rupture

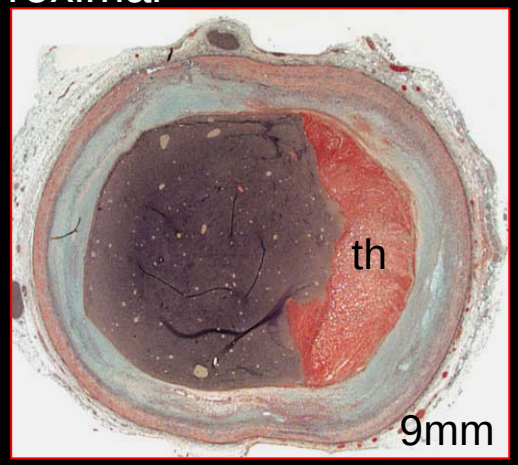
- **Necrotic core (21.6±23.7%)**
- **Thin fibrous cap (< 65 μm)**
- **Cap infiltrated by macrophages and lymphocytes**
- **Cap composition – type 1 collagen with few or absent smooth muscle cells**

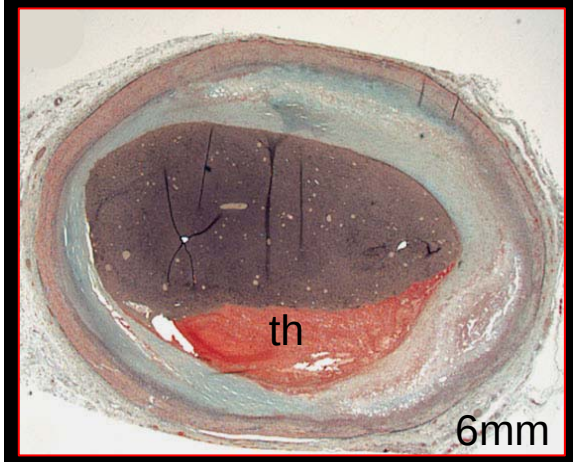
- **Discontinuous fibrous cap (23±19 μm)**
- **Underlying necrotic core (29.0±19.0%)**
- **Luminal thrombus**

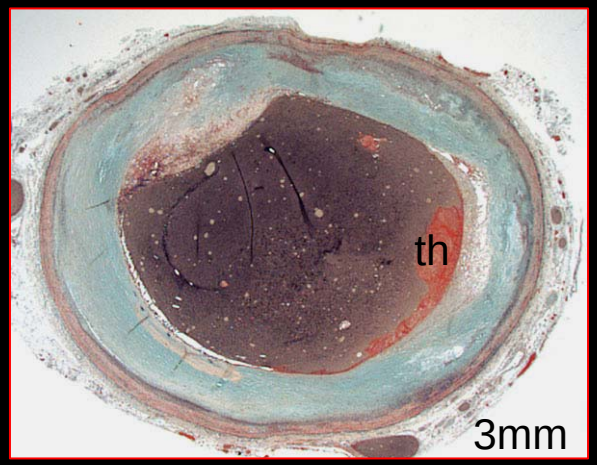
Thin cap Fibroatheroma (Vulnerable Plaque)
Coronary Artery

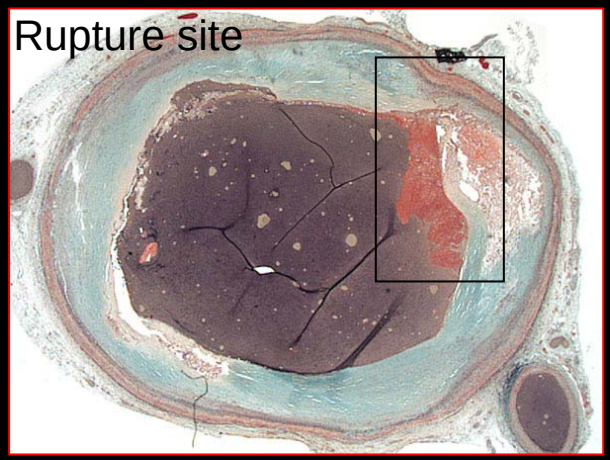


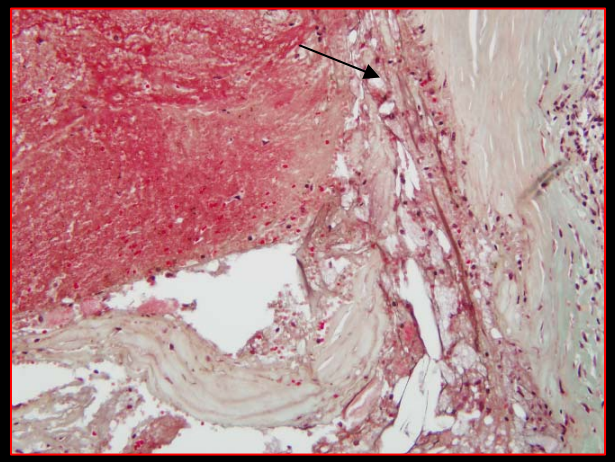
Plaque rupture with mild non occlusive thrombus: mechanism by which plaques progress (asymptomatic)

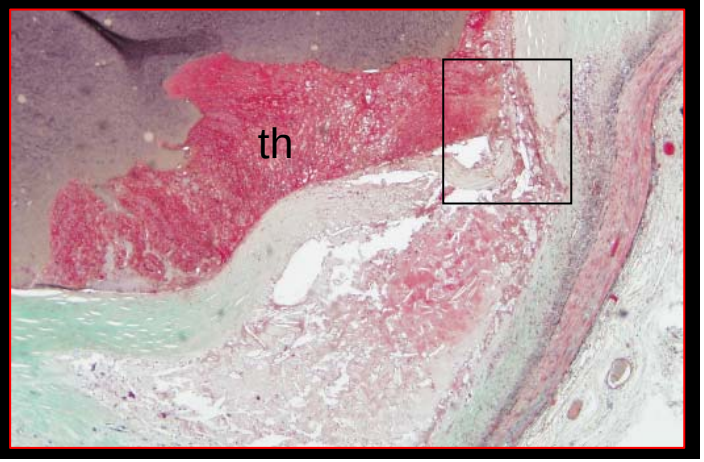




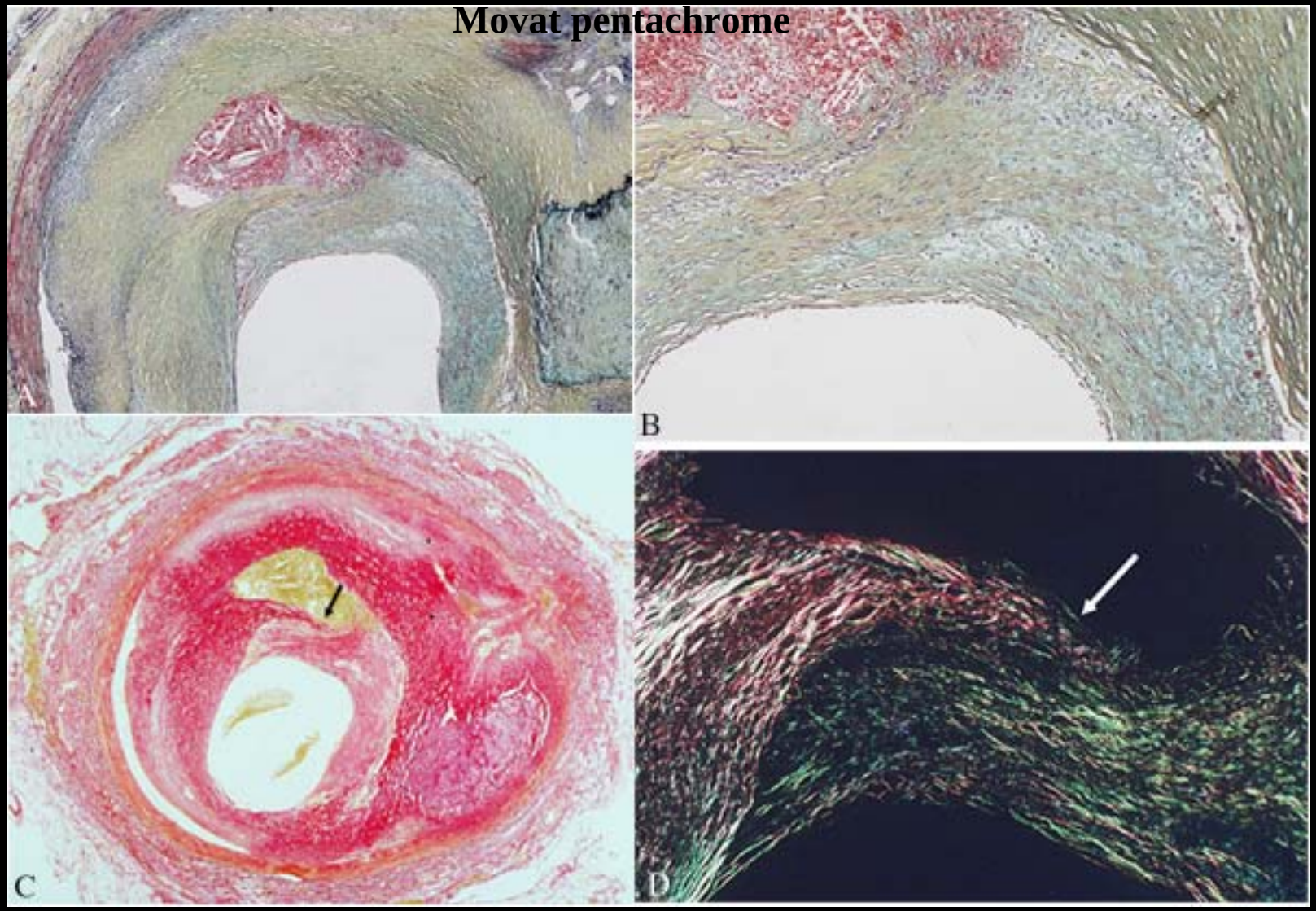








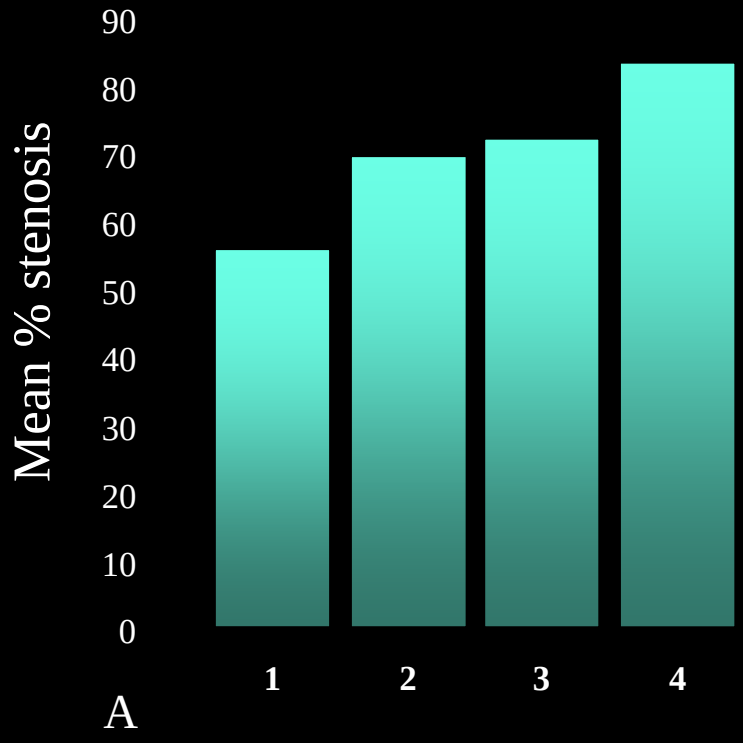
Silent Ruptures and Erosions lead to Plaque Progression



Sirius red

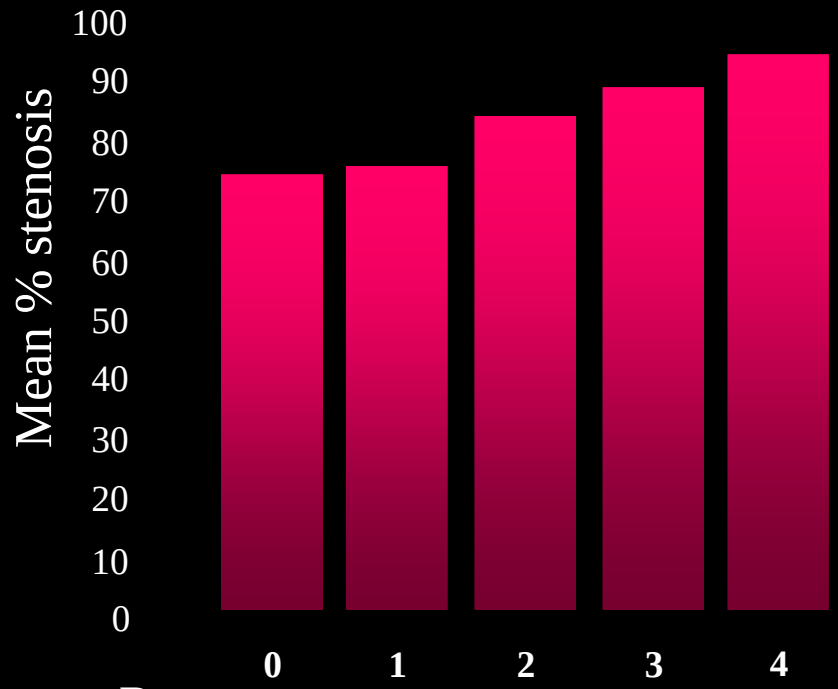
Sirius red with polarized light

Mean % stenosis increases with number of prior rupture sites



A

Number of prior ruptures, healed rupture sites



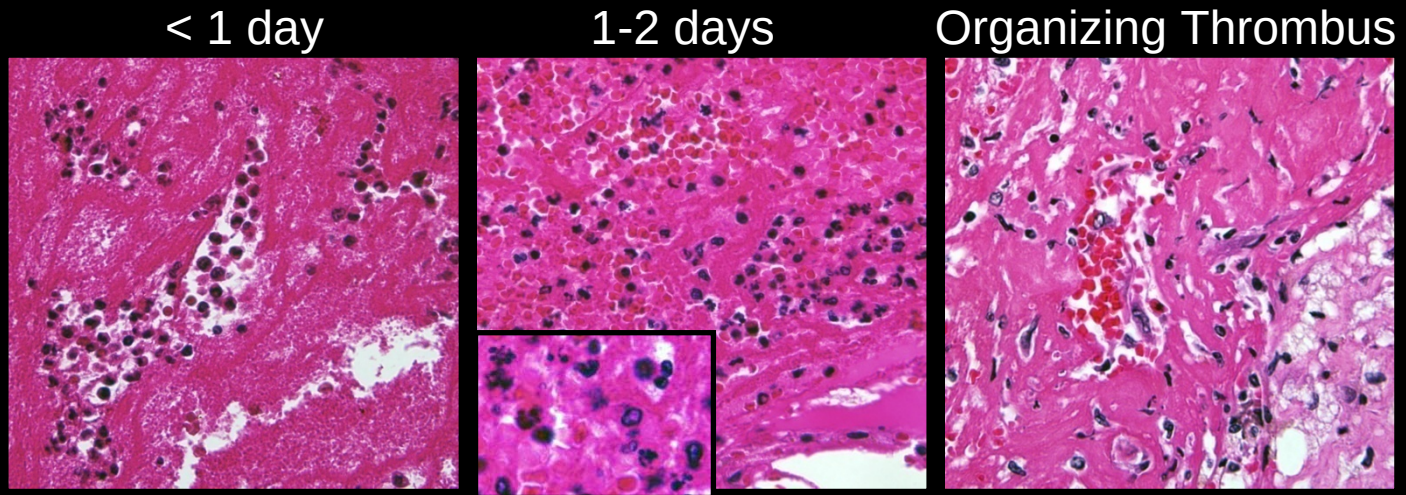
B

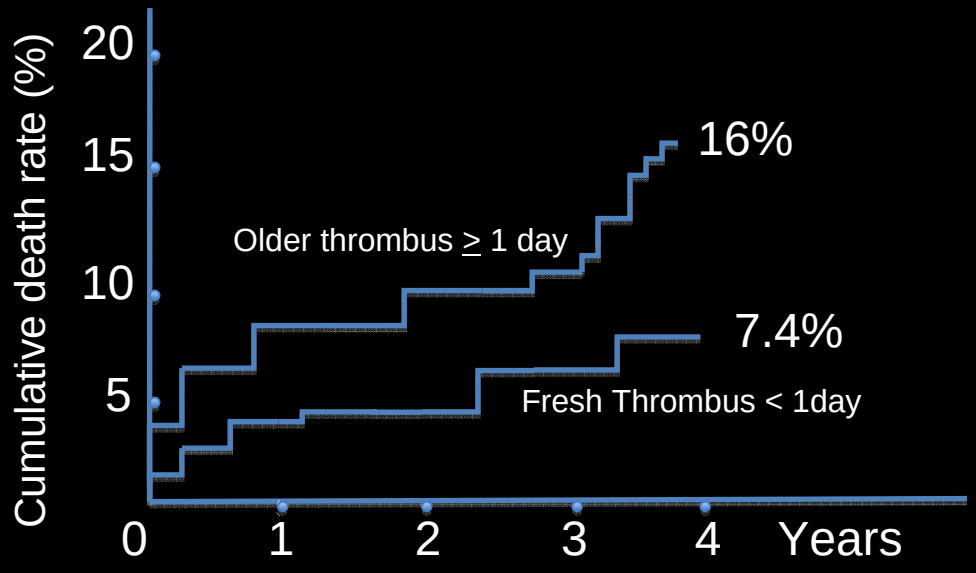
Number of prior ruptures, acute rupturesites

11% of plaque rupture are virgin

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

Prevalence of Older Thrombus is an Independent Predictor of Long-Term Mortality In Patients with STEMI



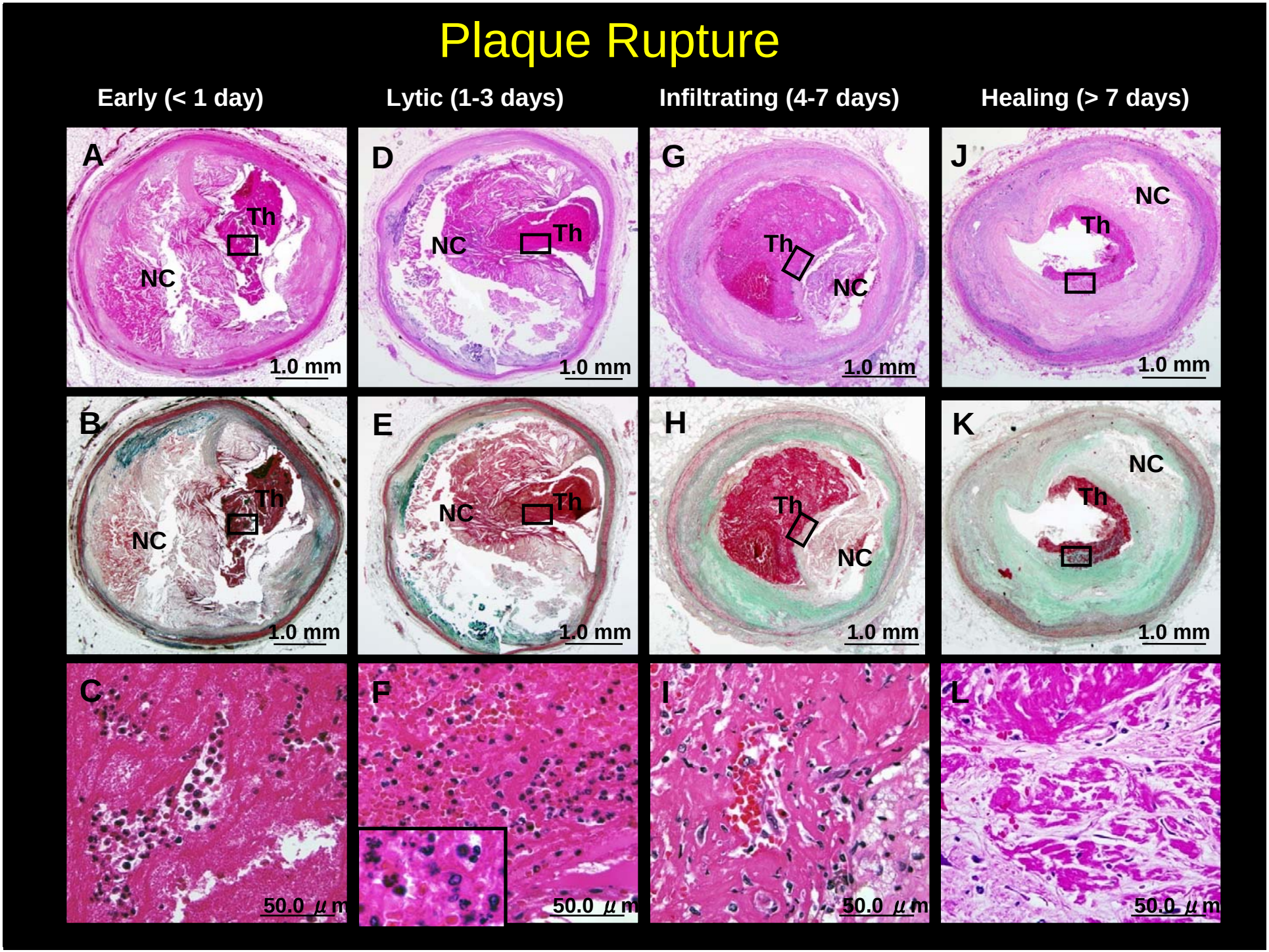


Kramer MCA, et al
Circulation 2008: 118;1810-1816

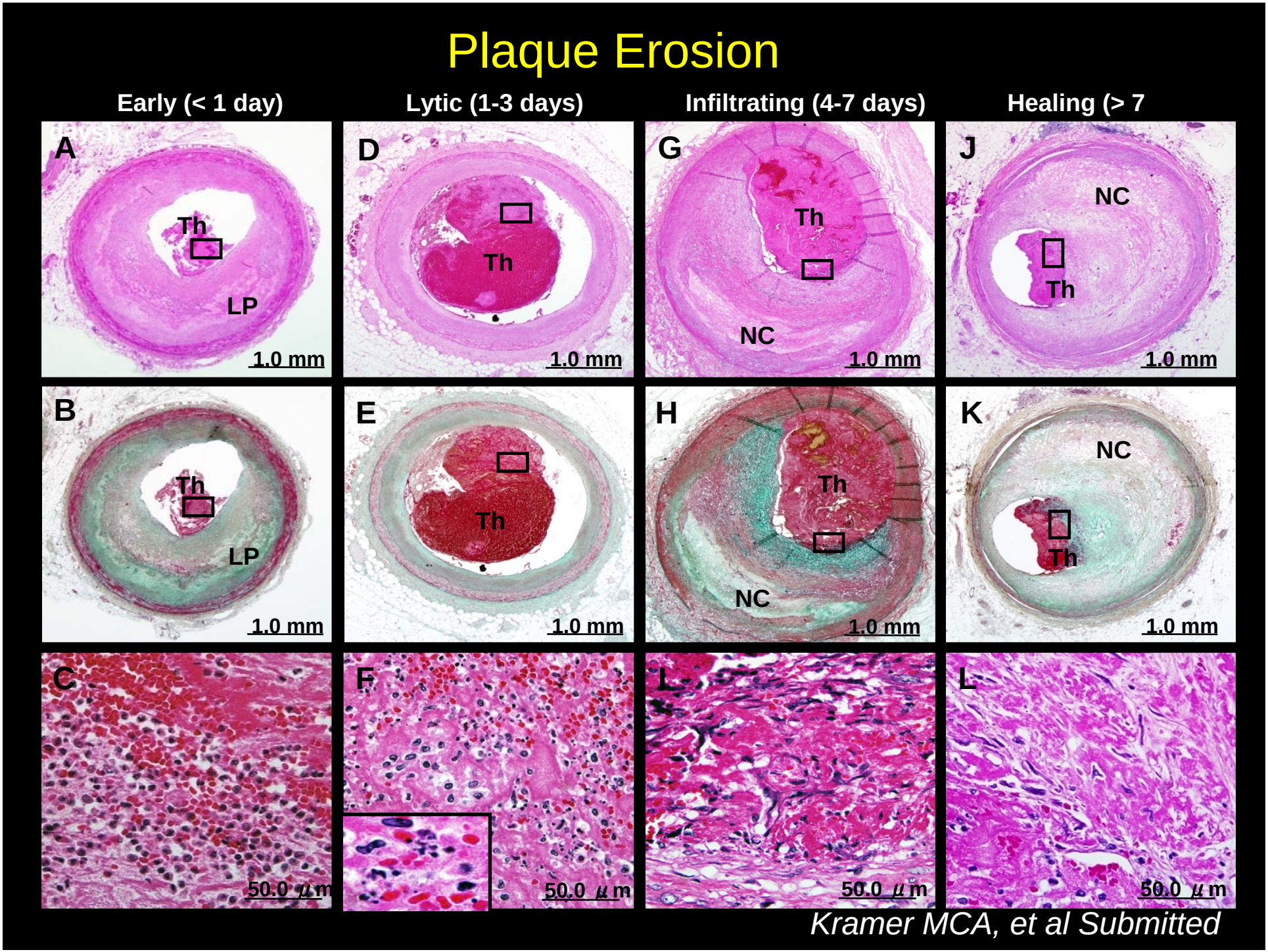
Patient Data, by Culprit Plaque

Culprit Lesion	Patient age (years)	Male Gender	Diabetes	Hyper-tension	Smoking
Rupture (n=65)	52±10	58 (89%)	7 (11)	15 (23)	11 (17)
Erosion (n=50)	43±9	37 (74%)	6 (12)	6 (12)	10 (20)
P value	<0.0001	0.03	0.67	0.84	0.13

Continuous variables are expressed as mean± SD


Plaque Rupture
Early (< 1 day)
Lytic (1-3 days)
Infiltrating (4-7 days)
Healing (> 7 days)
A
Th
NC
1.0 mm
D
NC
Th
1.0 mm
G
Th
NC
1.0 mm
J
NC
Th
1.0 mm
B
Th
NC
1.0 mm
E
NC
Th
1.0 mm
H
Th
NC
1.0 mm
K
NC
Th
1.0 mm
C
50.0 μm
F
50.0 μm
I
50.0 μm
L
50.0 μm

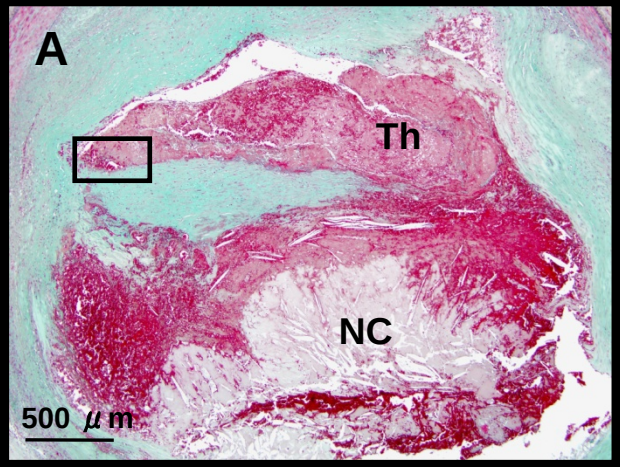
Plaque Erosion



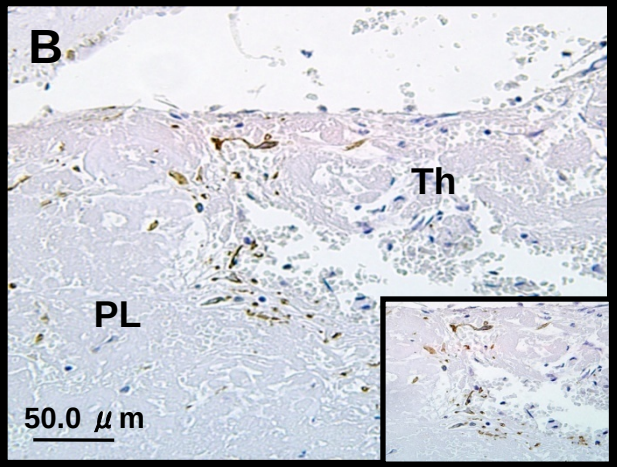
Kramer MCA, et al Submitted

Organizing Thrombus

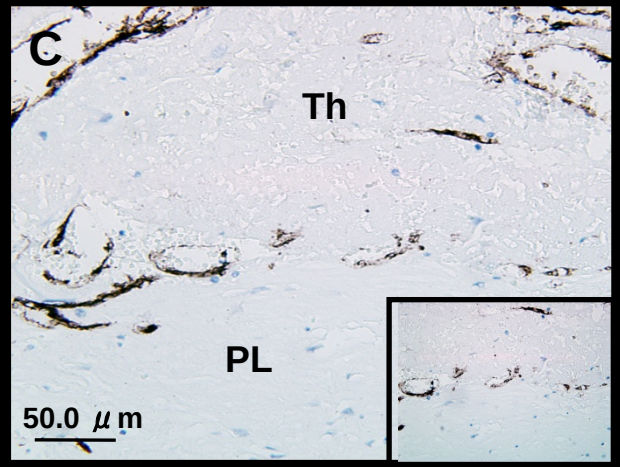
Rupture
Infiltrating thrombus (4-7 days)



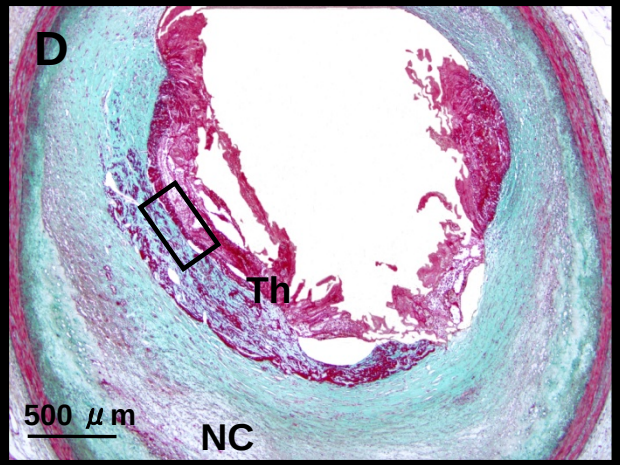
Smooth muscle cells



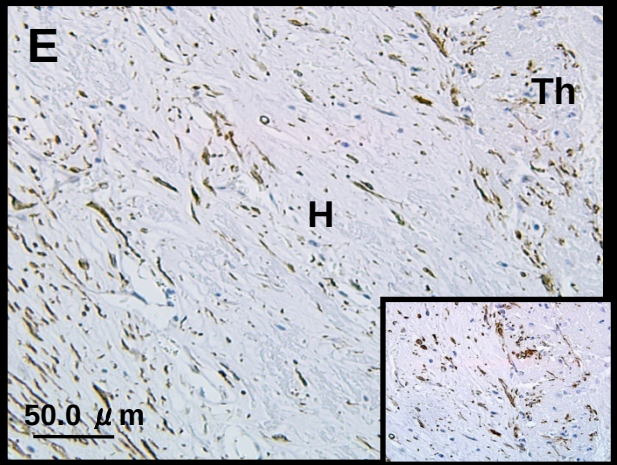
Endothelial cells



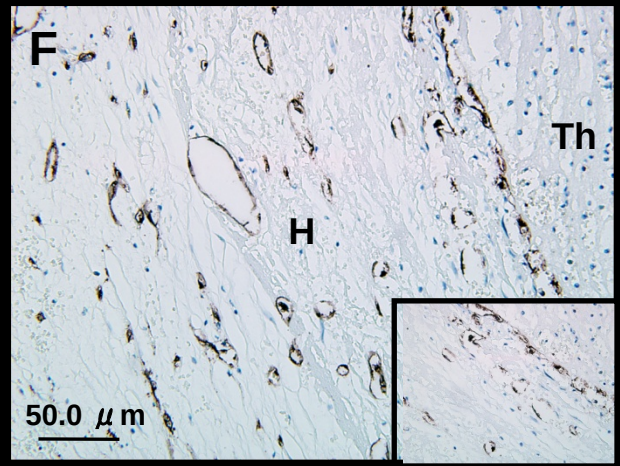
Erosion
Healing thrombus (> 7 days)



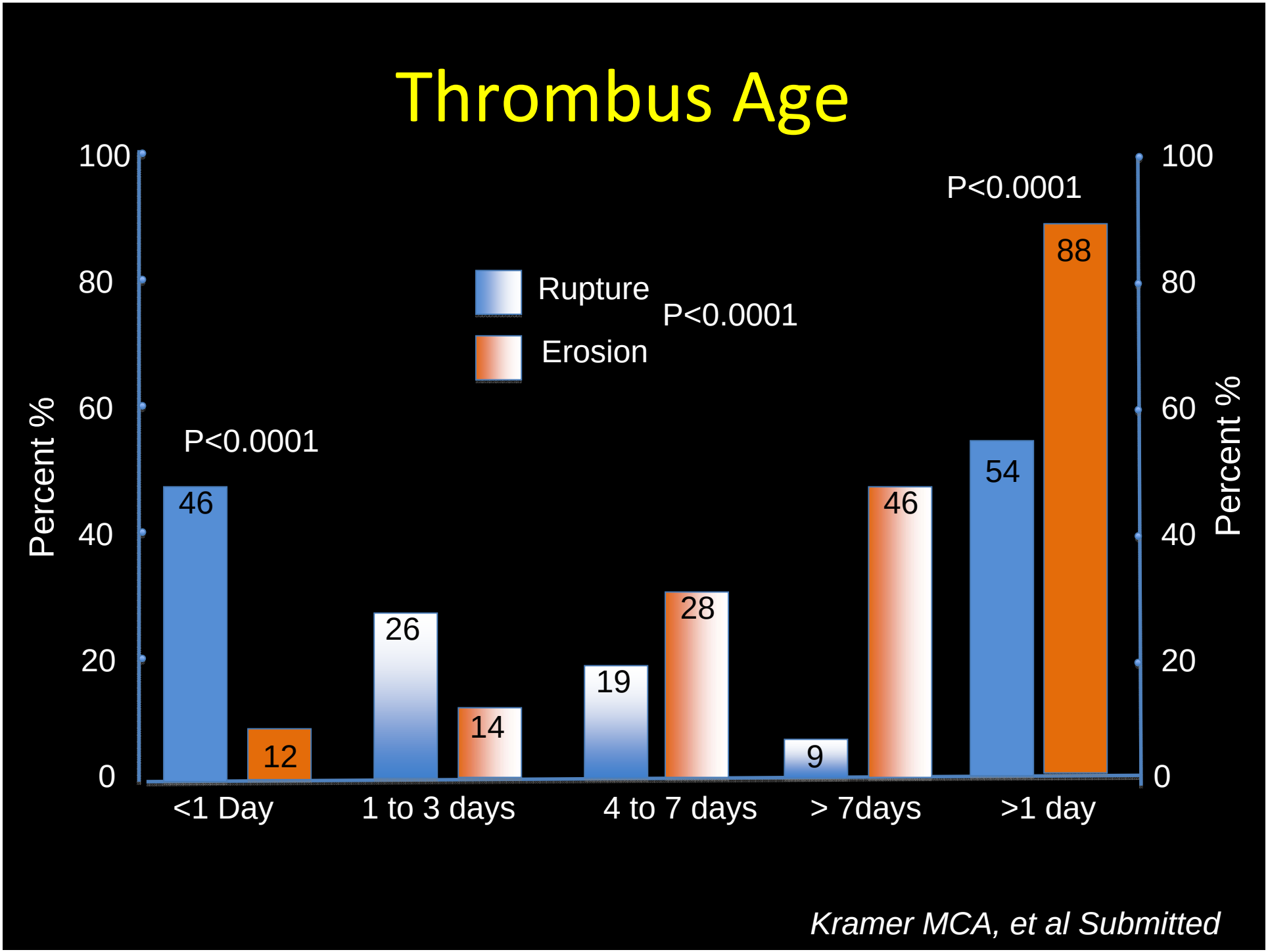
Smooth muscle cells



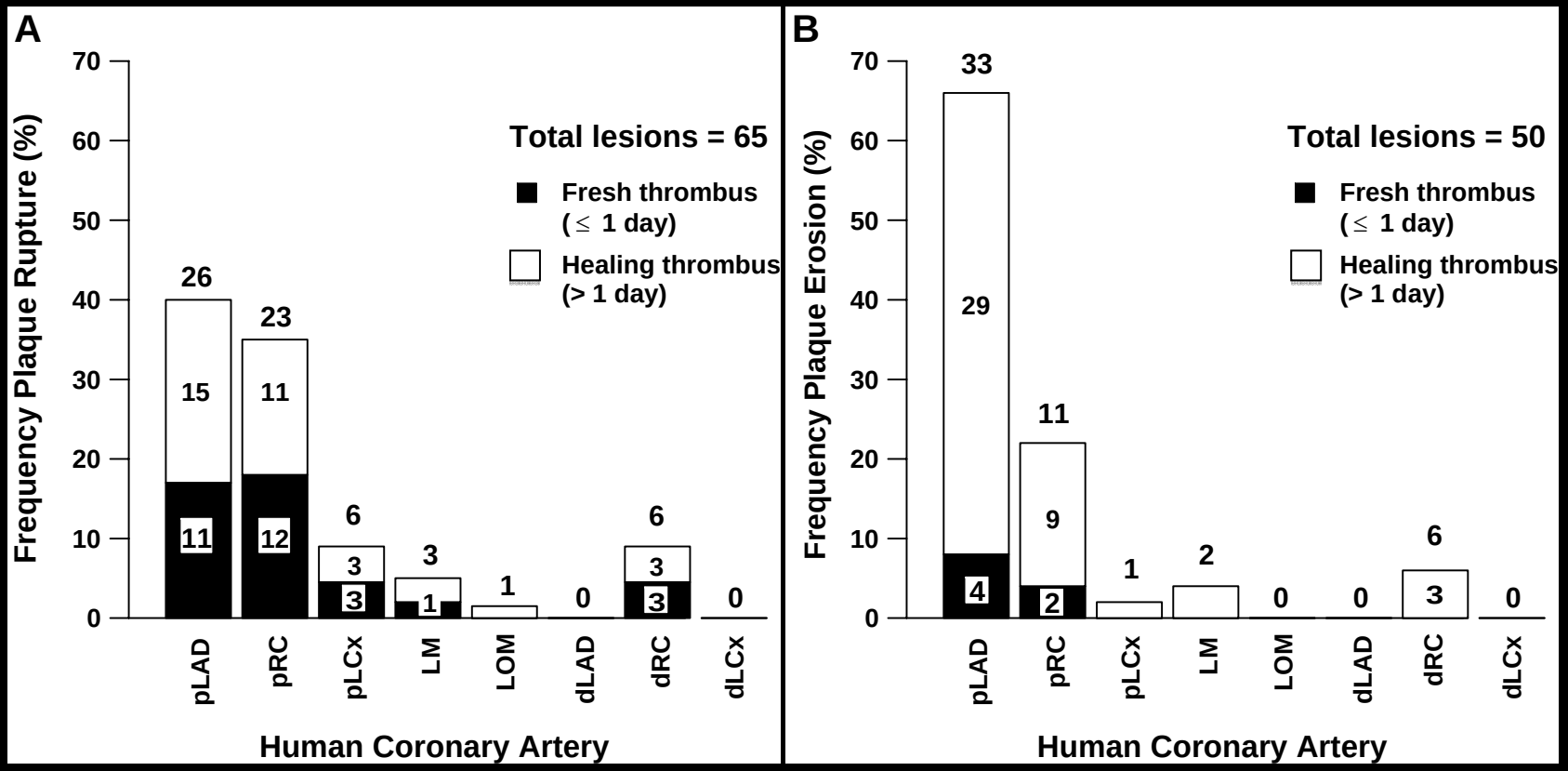
Endothelial cells



Kramer MCA, et al Submitted


Thrombus Age
100
80
60
40
20
0
Percent %
Rupture
Erosion
P<0.0001
P<0.0001
P<0.0001
46
12
26
14
19
28
9
46
54
88
<1 Day
1 to 3 days
4 to 7 days
> 7days
>1 day
Kramer MCA, et al Submitted

Location of Coronary Ruptures and Erosions and % Fresh and Healing Thrombi



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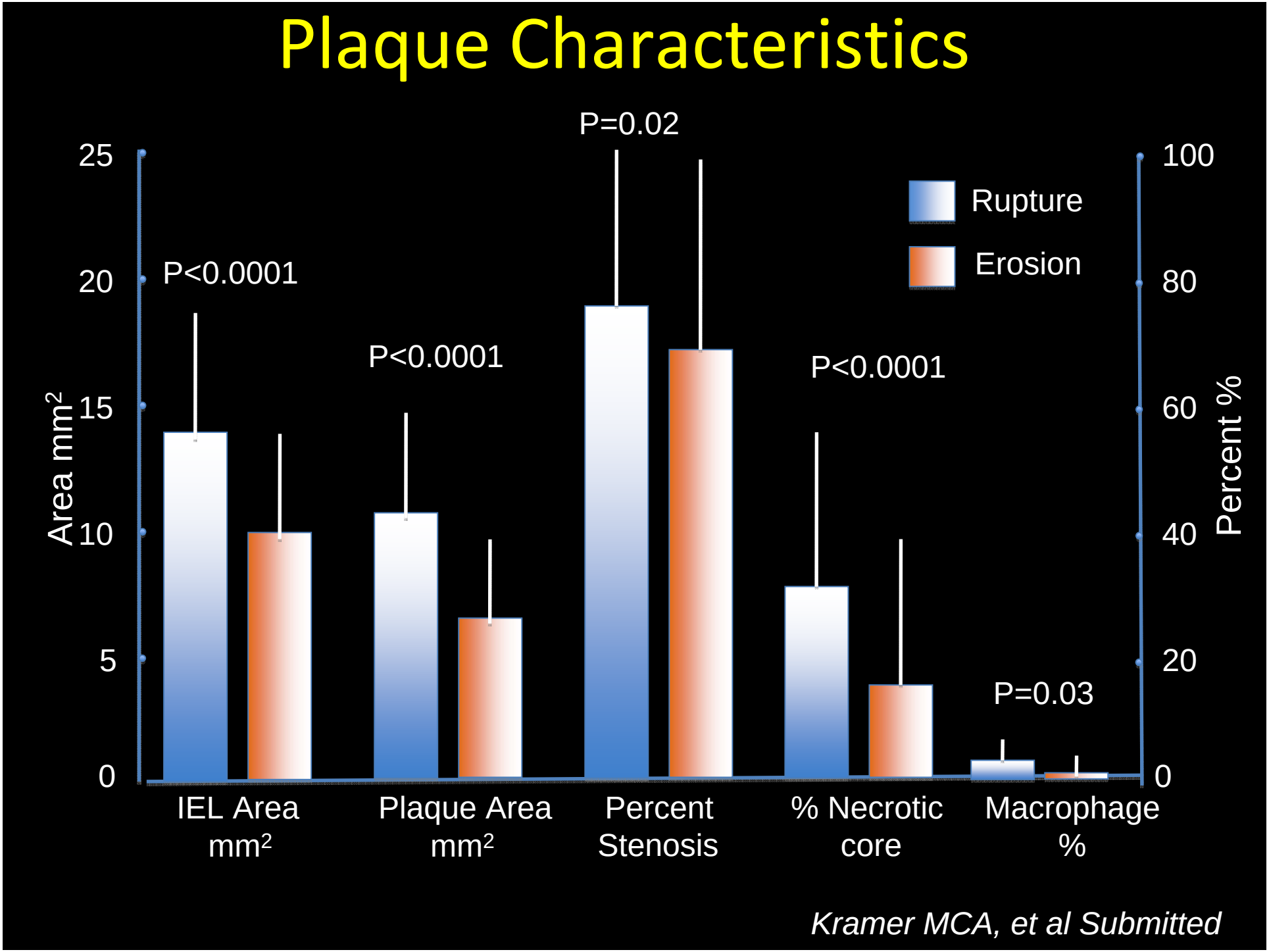
Plaque Characteristics

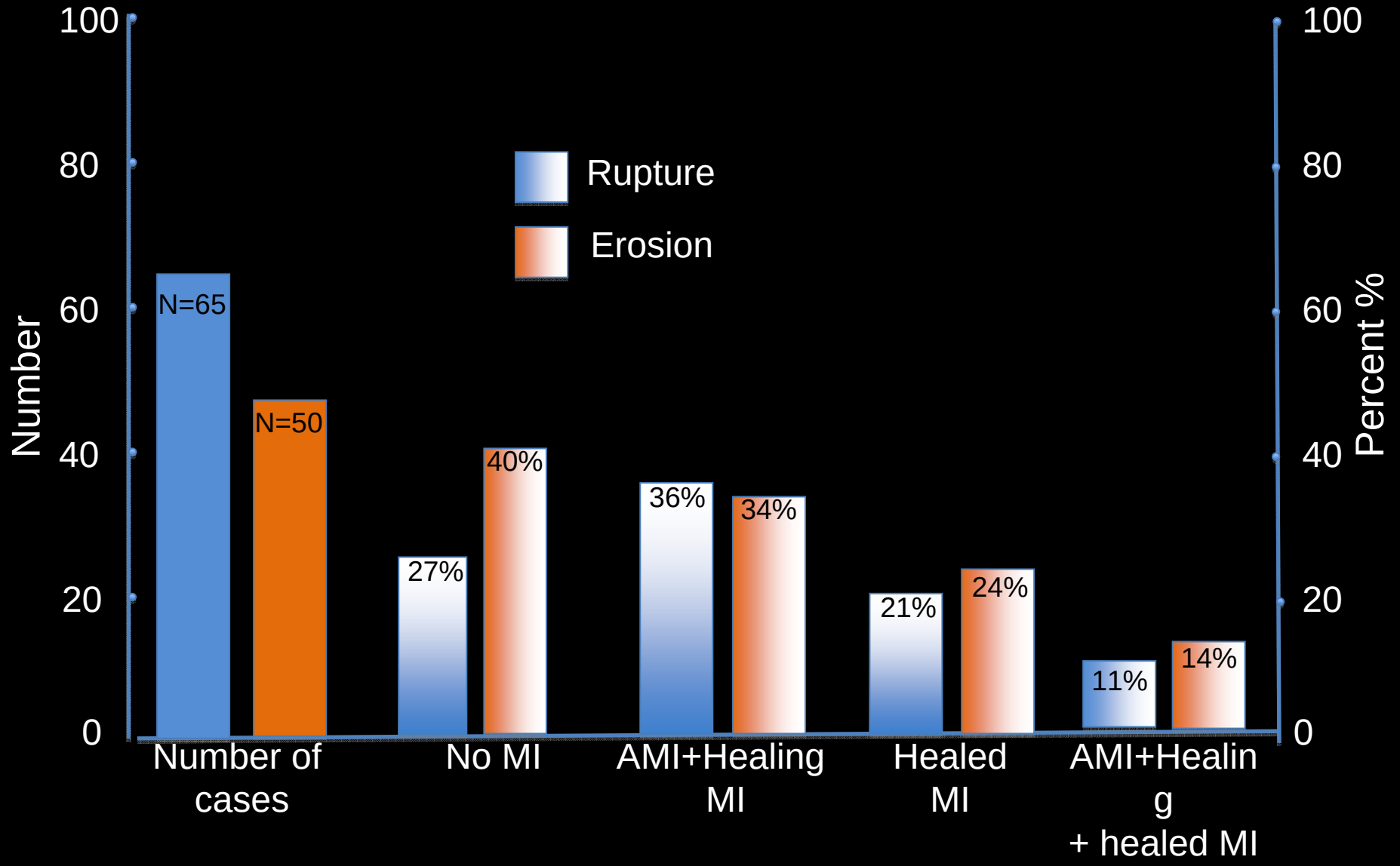


Kramer MCA, et al Submitted

Characteristics of Thrombi, and underlying x-sectional area narrowing

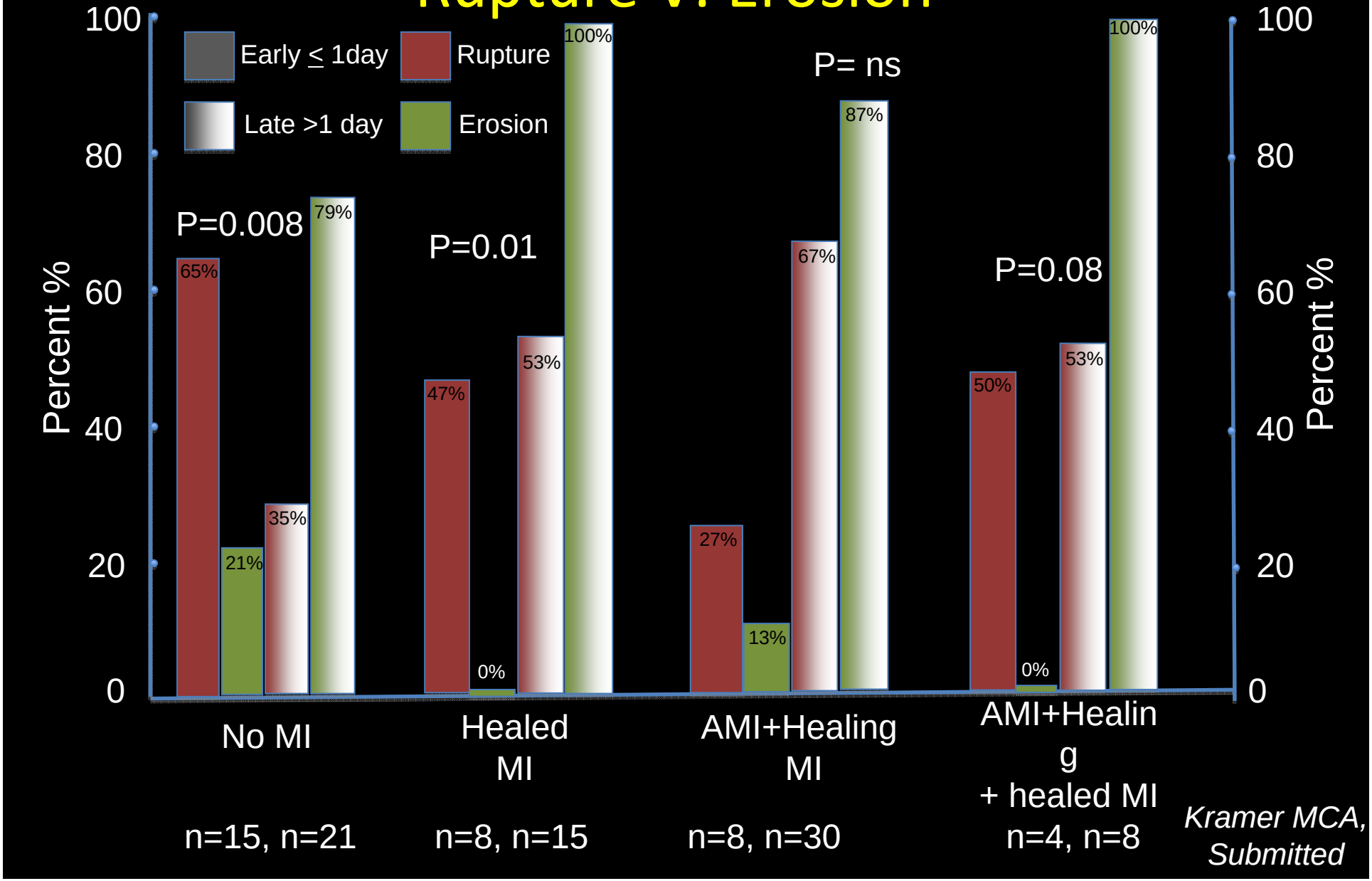
Patient /Plaque Characteristics	<75% Stenosis (n=53)			➢75% Stenosis (n=62)		
	Rupture (N=23)	Erosion (n=30)	P value	Rupture (n=42)	Erosion (n=20)	P value
Patient age	52±12	43±9	0.02	52.±9	44±8	0.003
Male Gender	22 (96)	22 (73)	0.02	36 (86)	15 (75)	0.30
Thrombus age			0.001			0.03
Early	12 (52)	3(10)		18(43)	3(15)	
Late	11(48)	27(90)		24(57)	17(85)	
IEL area (mm2)	13.6±5.2	9.2±3.9	0.001	13.7±6.5	10.0±6.7	0.002
Plaque Burden	217±72	179±69	0.08	237±65	207±73	0.18
Necrotic core	23(100)	14(47%)	<0.001	42 (100)	11(55)	<0.0001
Necrotic core area mm2	2.99±2.74	0.63±1.12	<0.0001	4.98±5.0	1.16±1.46	<0.0001
Necrotic core area %	33.6±23.5	10.4±17.9	<0.0001	36.8±23.4	15.5±18.1	0.001
Macrophage area mm2	4.3±2.7	2.2±2.2	0.003	3.0±2.7	3.1±3.2	0.86

Myocardial Infarction: Rupture vs. Erosion

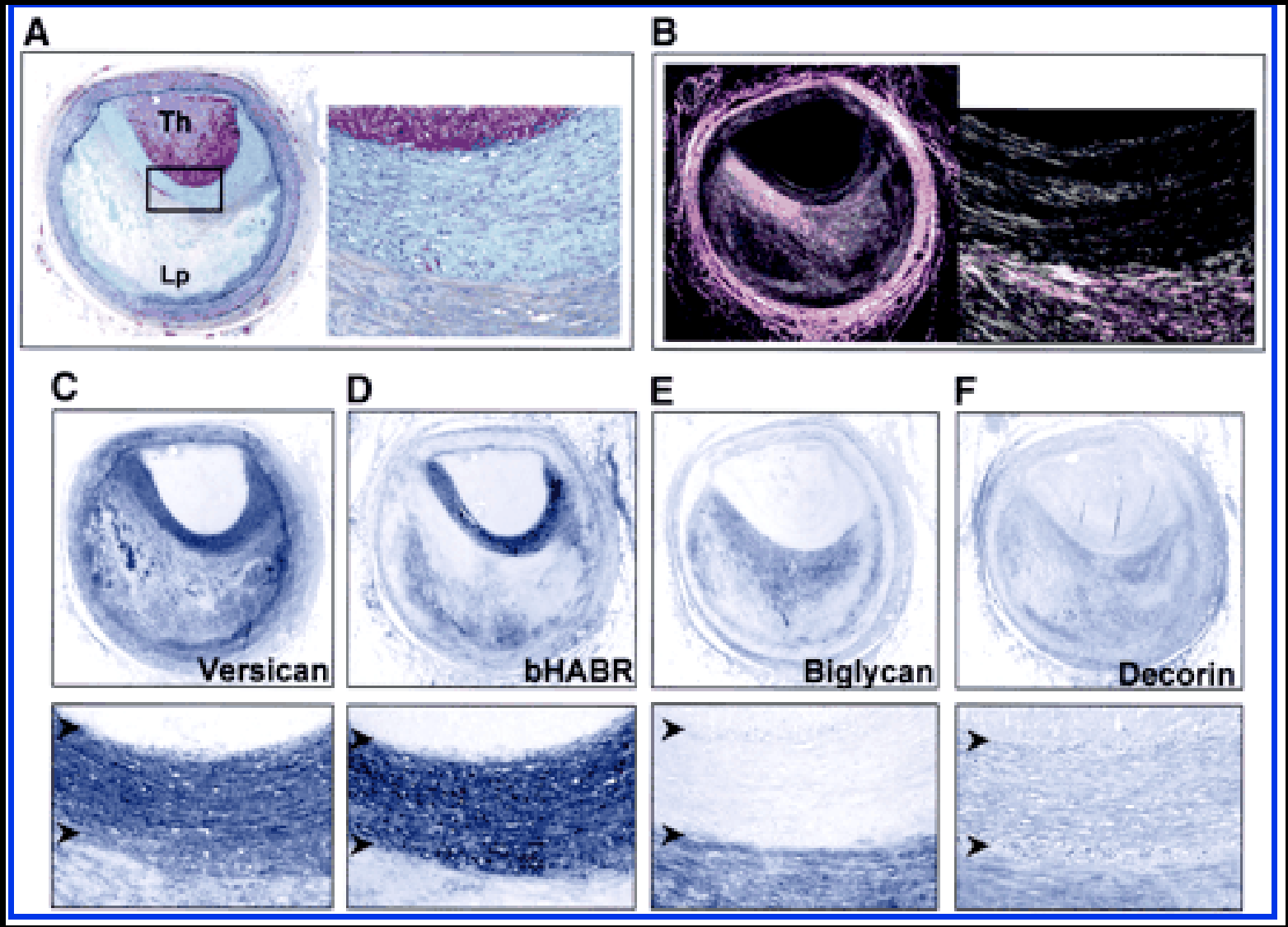


Kramer MCA, et al Submitted

Myocardial Infarction: Early vs. Late and Rupture V. Erosion

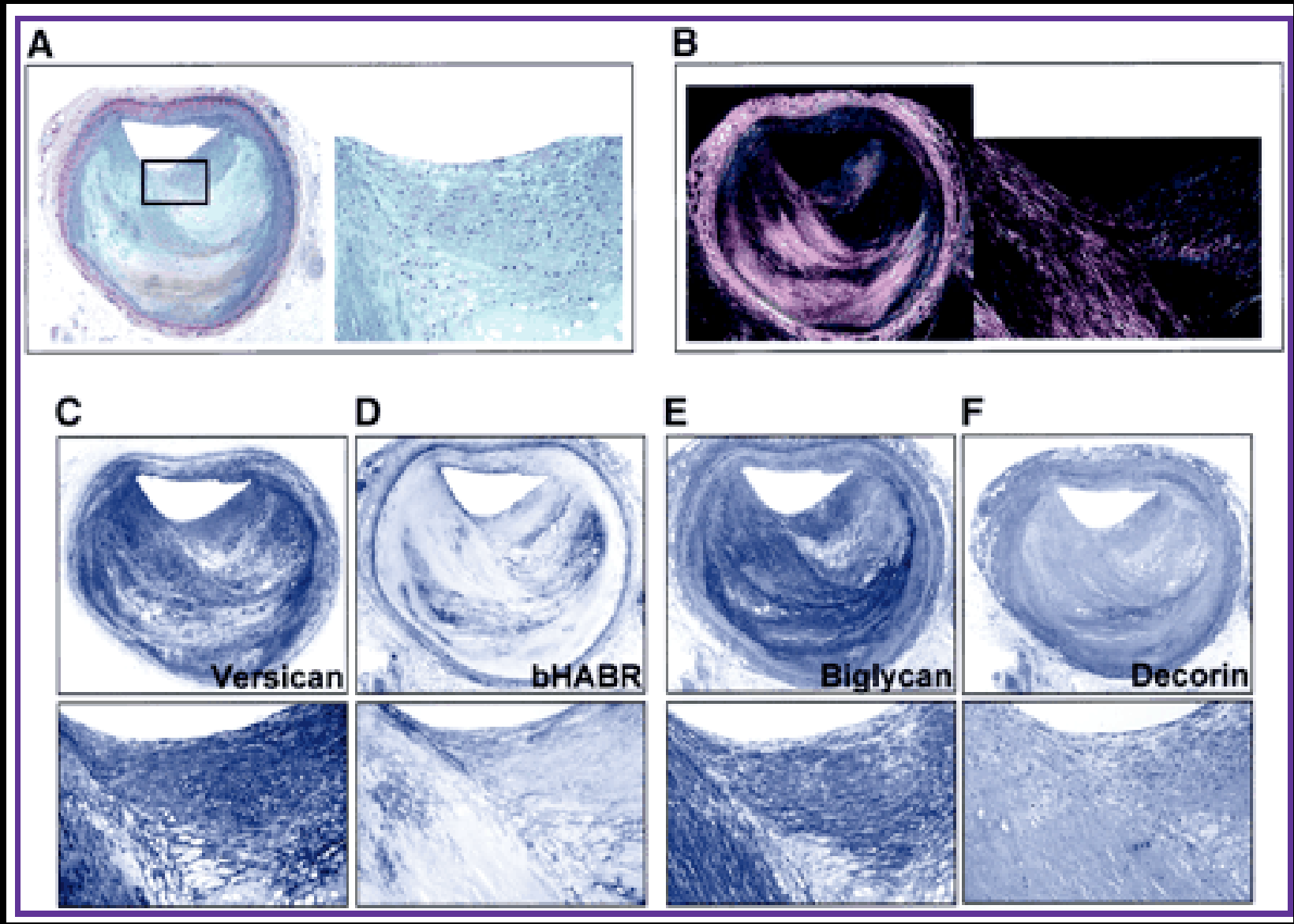


Plaque Erosion



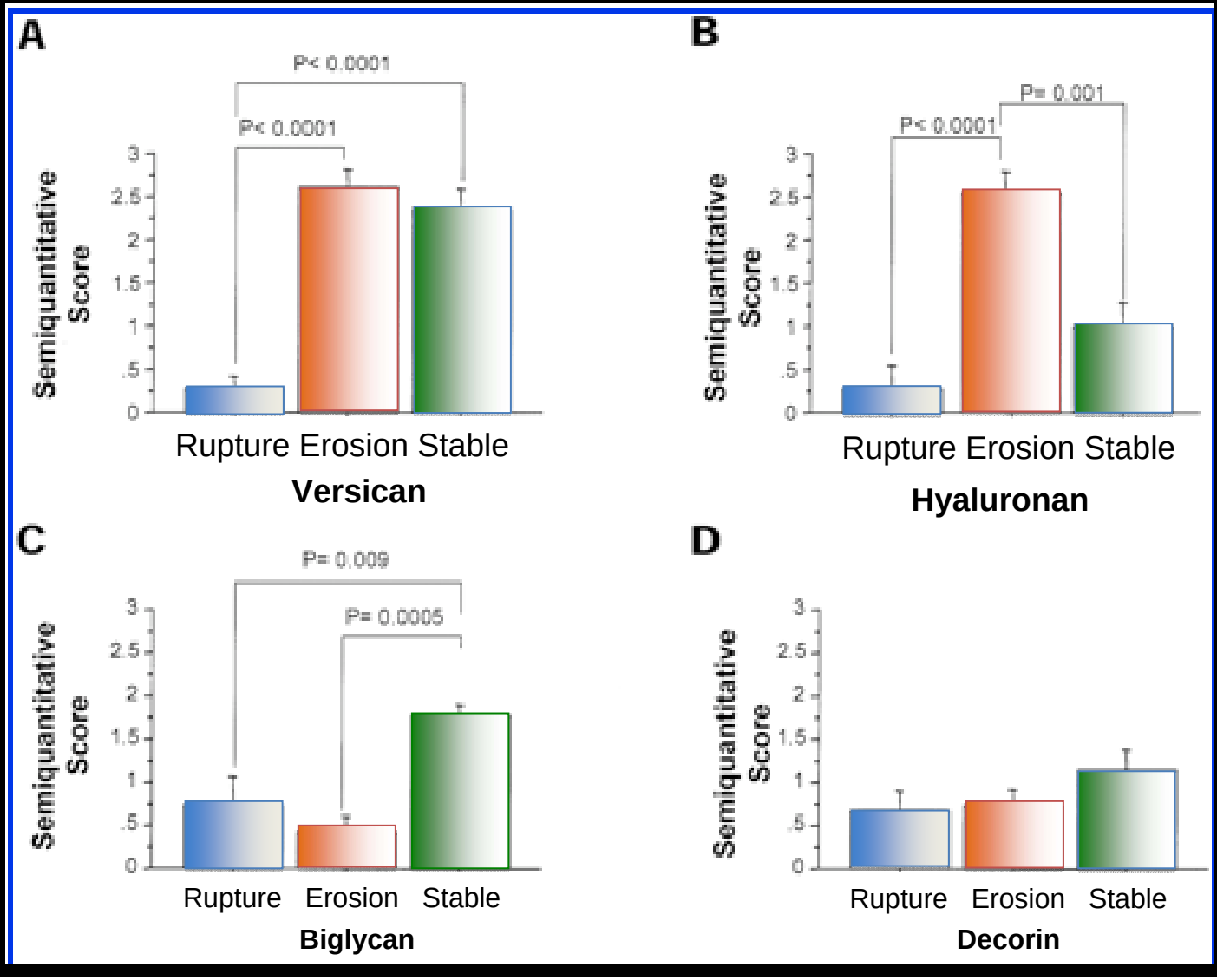
Kolodgie FD, et al. ATVB 2002;22:1642

Stable Erosion



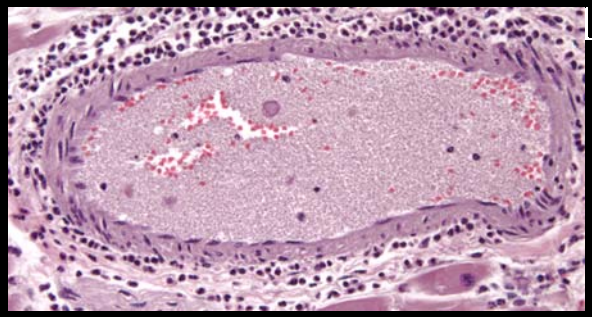
Kolodgie FD, et al. ATVB 2002;22:1642

Different Accumulation of Proteoglycan and Hyaluronan in Different Culprit lesions

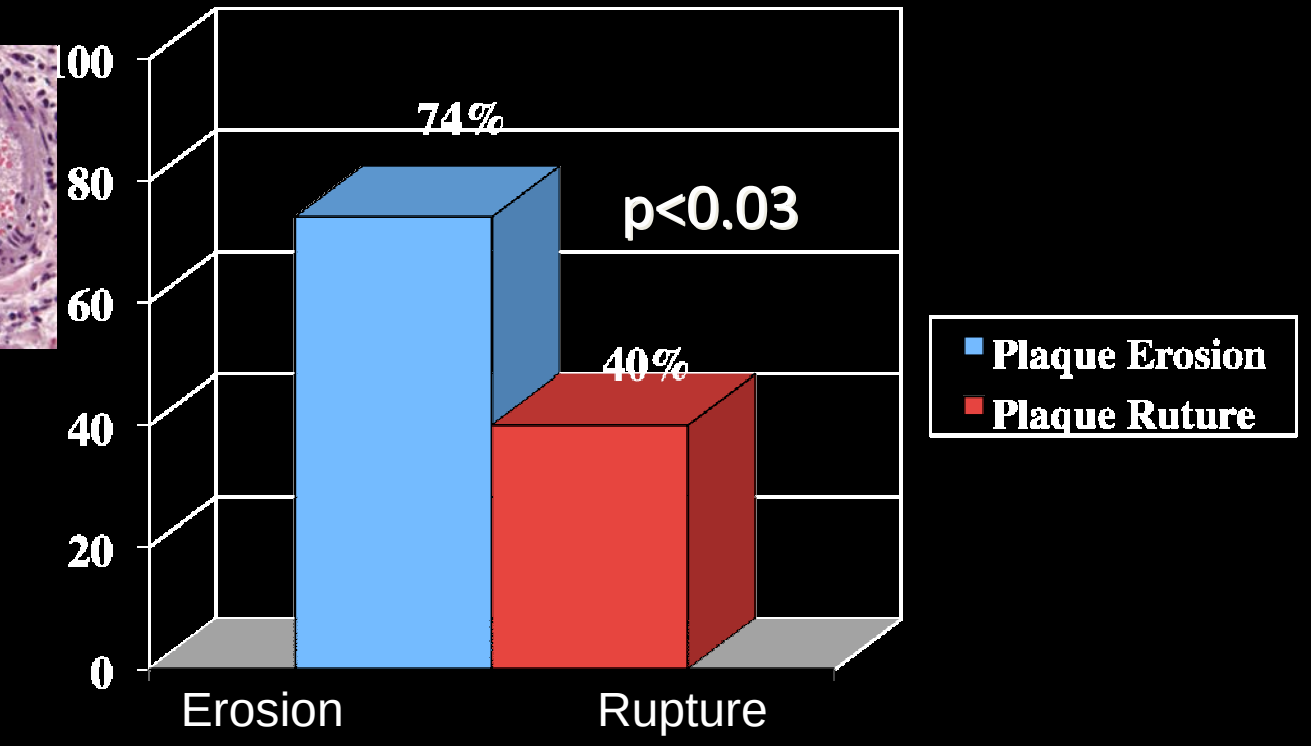


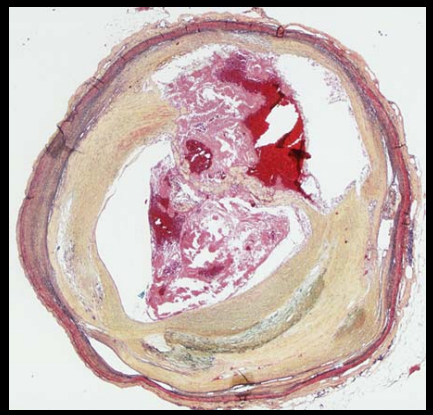
Kolodgie FD, ATVB 2002

Intramyocardial Emboli more Common in Plaque Erosion vs. Plaque Rupture



%Hearts with Intramyocardial Emboli

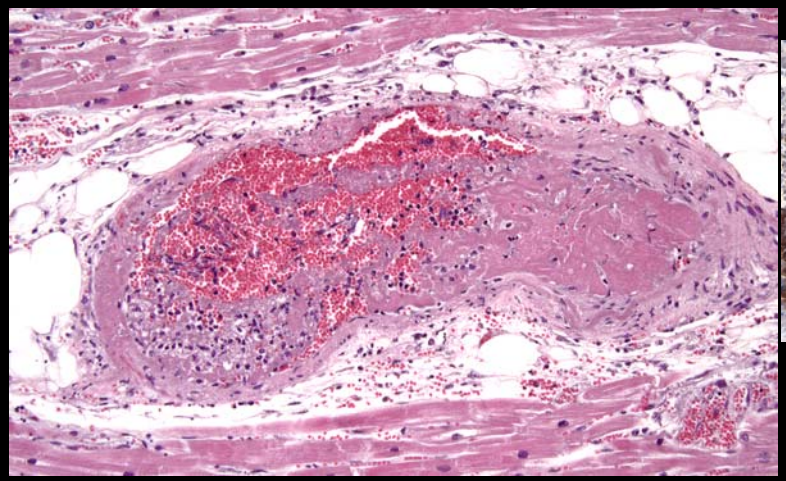


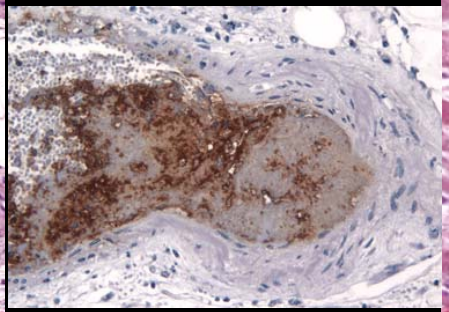


Intramyocardial Emboli and Myocardial Necrosis

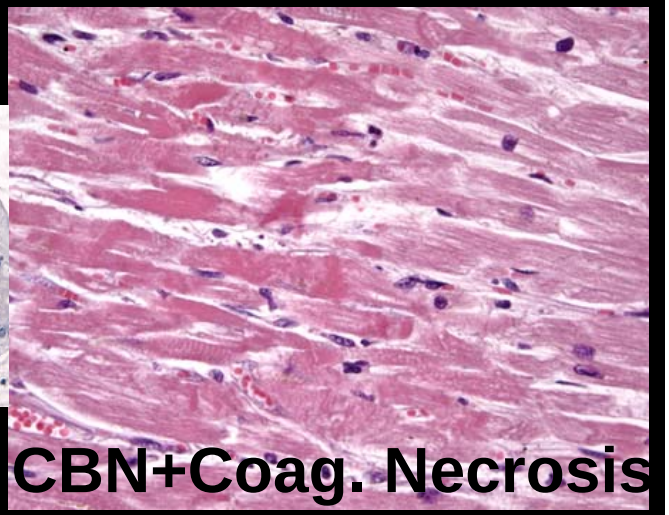
In hearts with intramyocardial emboli:

- 57% associated with focal myocardial necrosis
  - Of these, 83% with multiple emboli (86% in vessels <120 μm in diameter)
- 24% associated with acute MI, 5% with myocardial scars (healed MI), 14% with normal myocardium





CD61

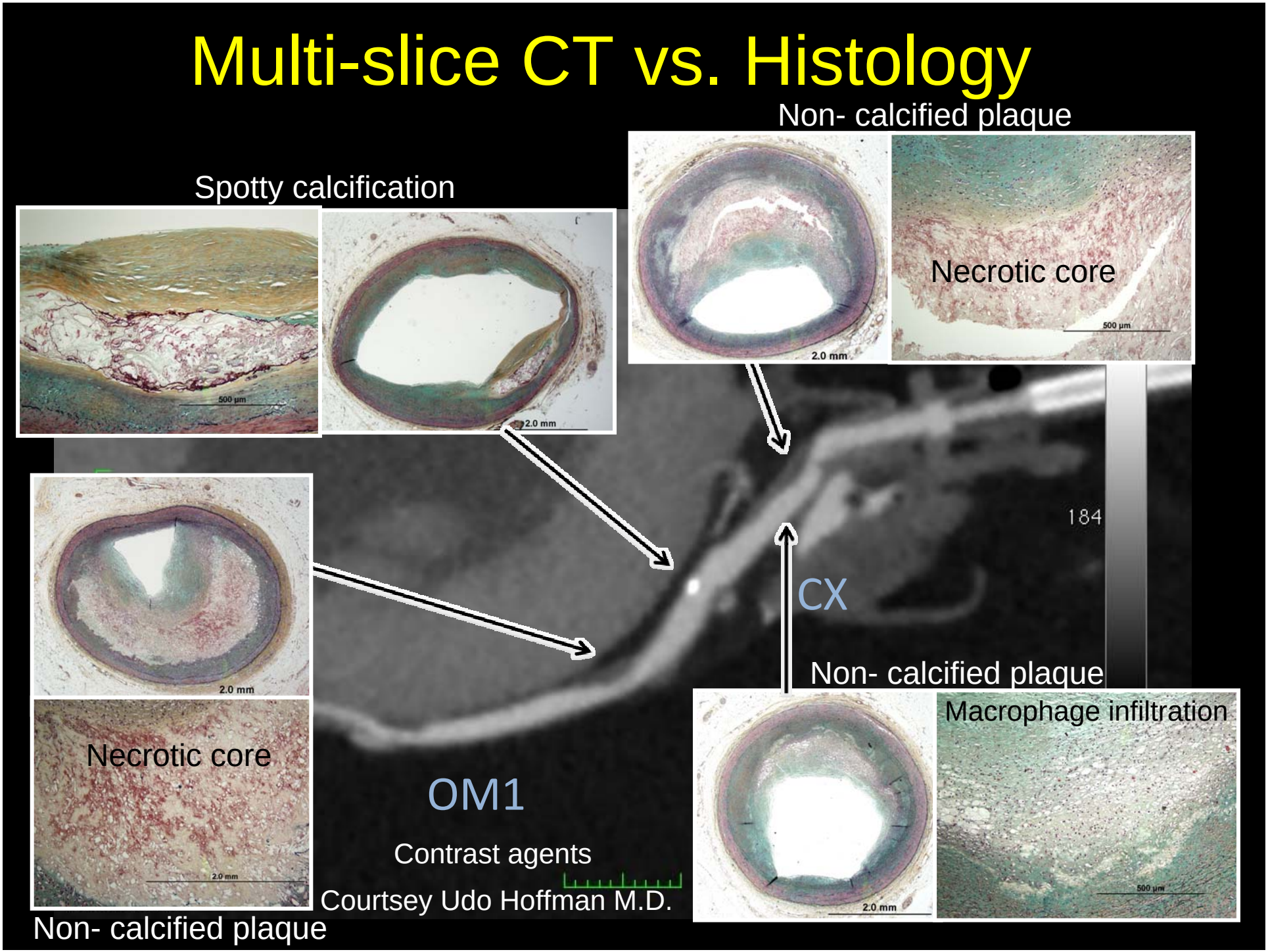


CBN+Coag. Necrosis

Conclusions: Healing of Ruptures vs. Erosions

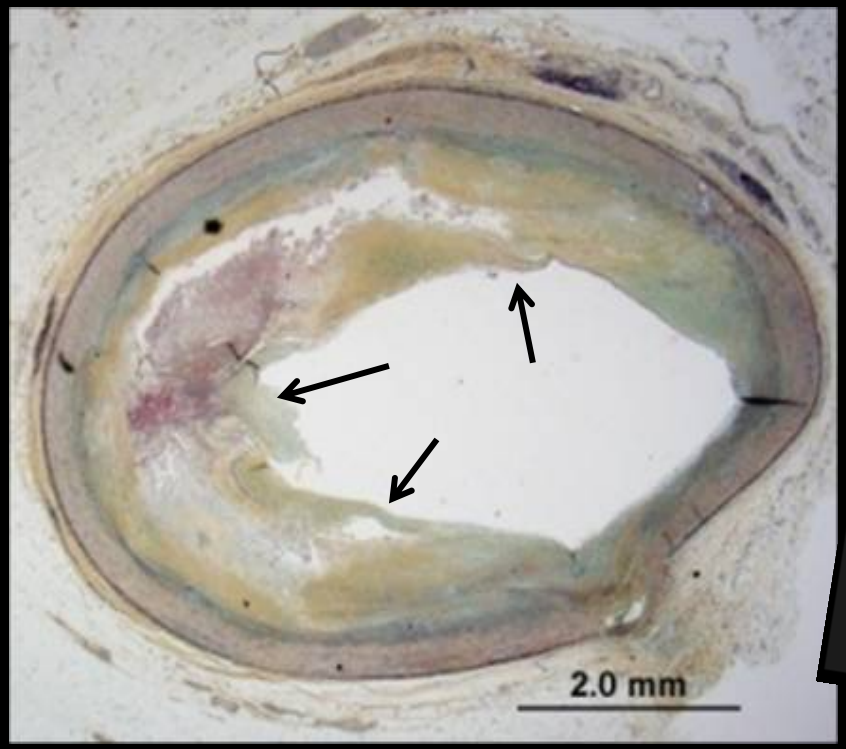
- The etiology and pathologenesis of Ruptures and Erosions is significantly different regarding inflammation, remodeling, growth rate, and healing of thrombus.
- Plaque erosions are associated with late stage maturation of thrombus as compared to ruptures
- Healing thrombi are seen in 85% of erosions versus 55% of ruptures and clinical studies have suggested that healing thrombi clinically have worse prognosis in patients presenting with STEMI (*Kramer MCA, Circulation 2008*.)
- Plaque erosions have been associated with greater distal embolization as compared to rupture (74% vs. 38%)
- Therefore understanding erosions which are more common in women <50 years may need different modality of artery interrogation as well as treatment strategies than men.

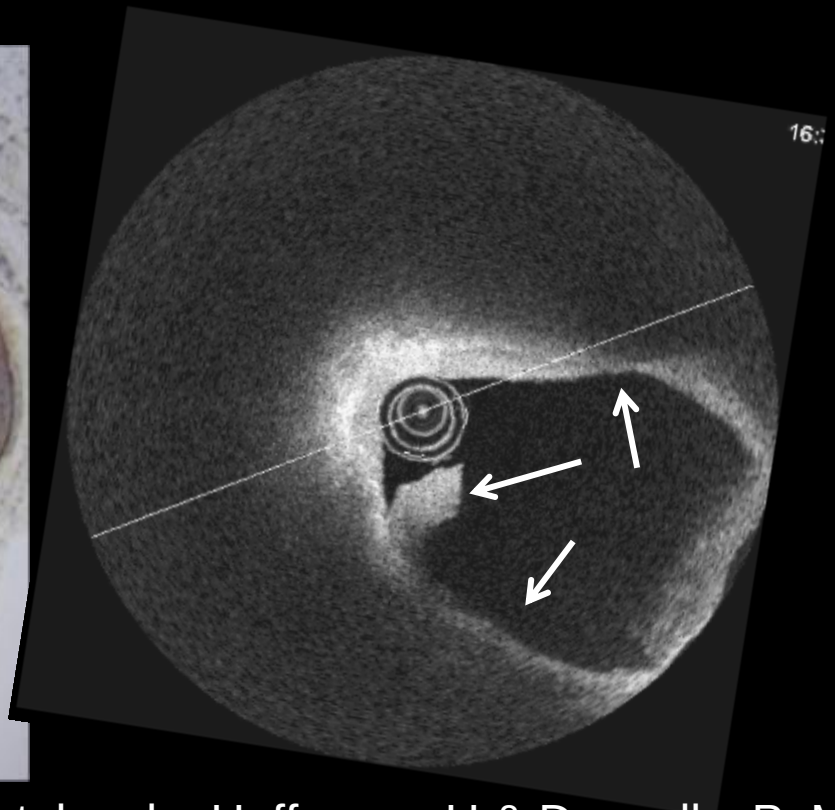
Multi-slice CT vs. Histology



Possibility of OCT imaging
Findings from Ex-Vivo Imaging

Thin-cap fibroatheroma

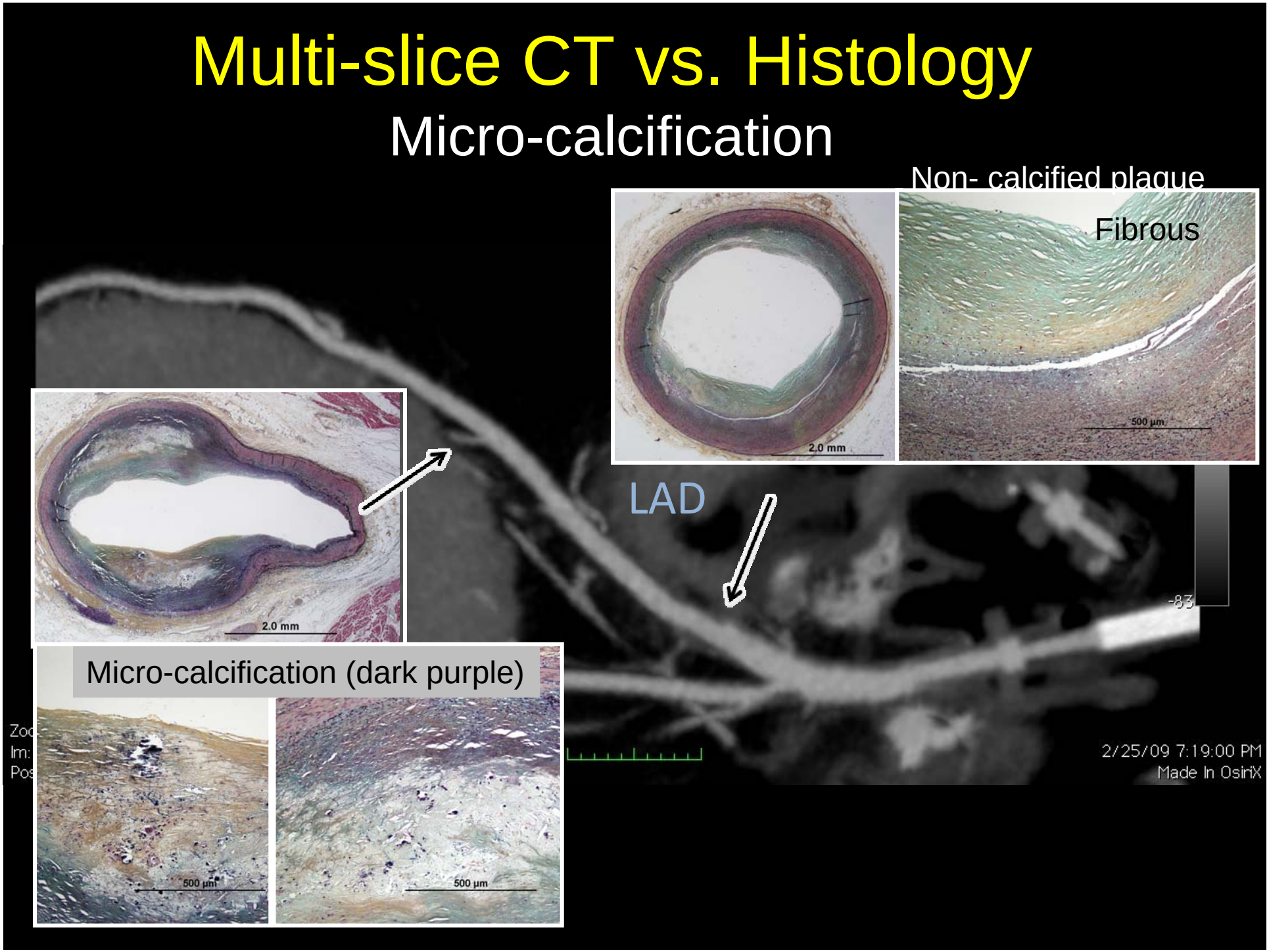




OCT images taken by Hoffmann, U & Donnelly, P. MGH

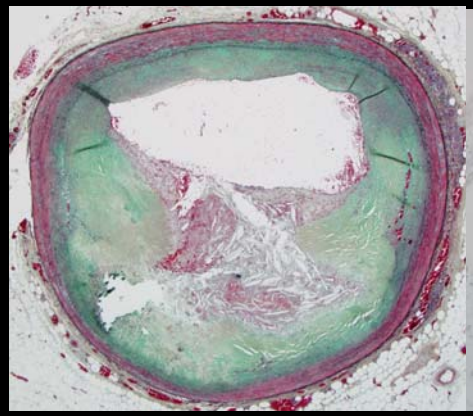
Multi-slice CT vs. Histology

Micro-calcification

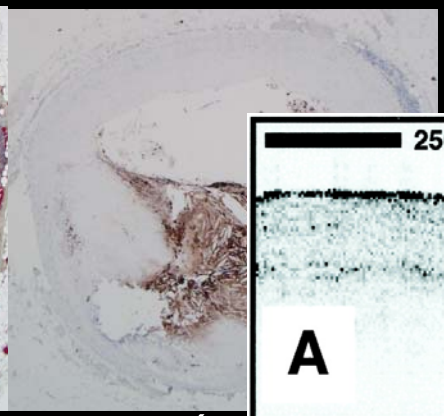


Detecting Macrophages in Vulnerable Plaque

Thin-cap fibroatheroma

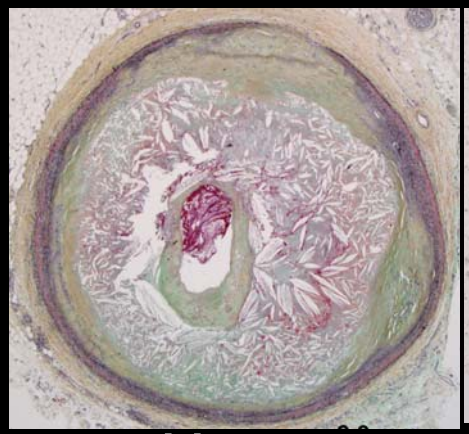


Movat



Kp-1 (M

Thin-cap fibroatheroma



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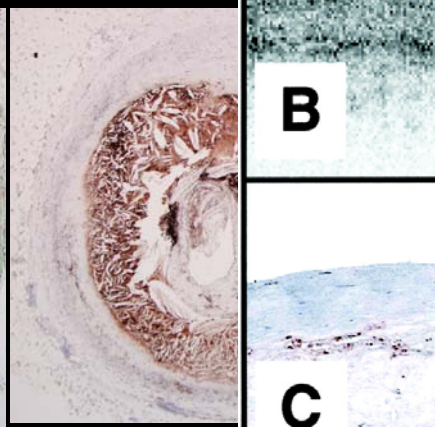
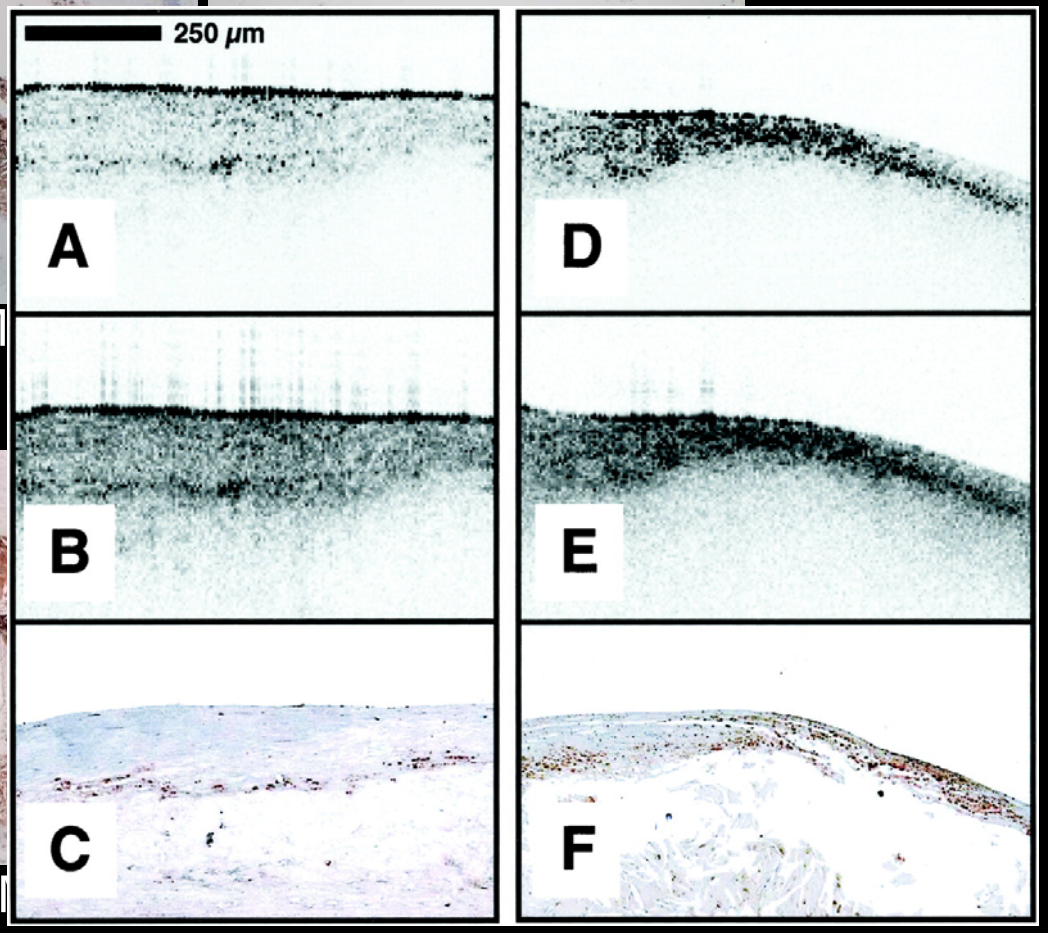


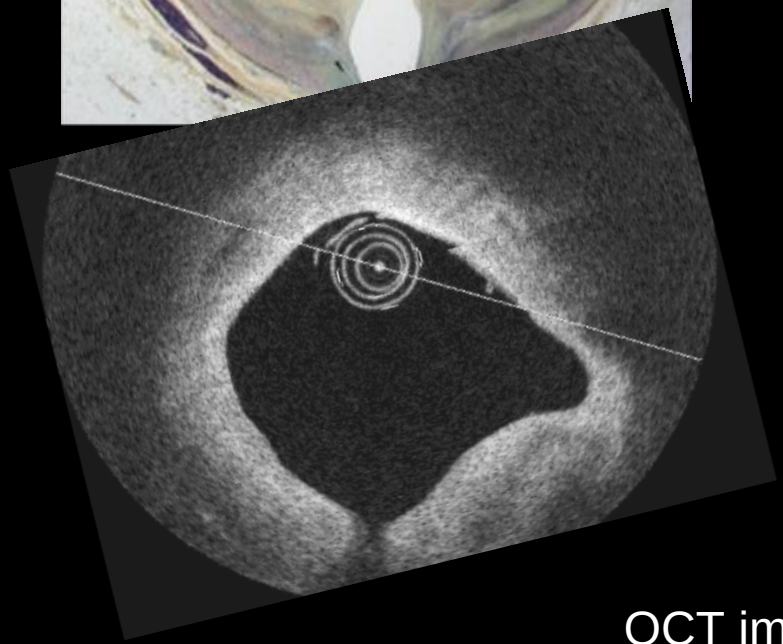
Kp-1 (



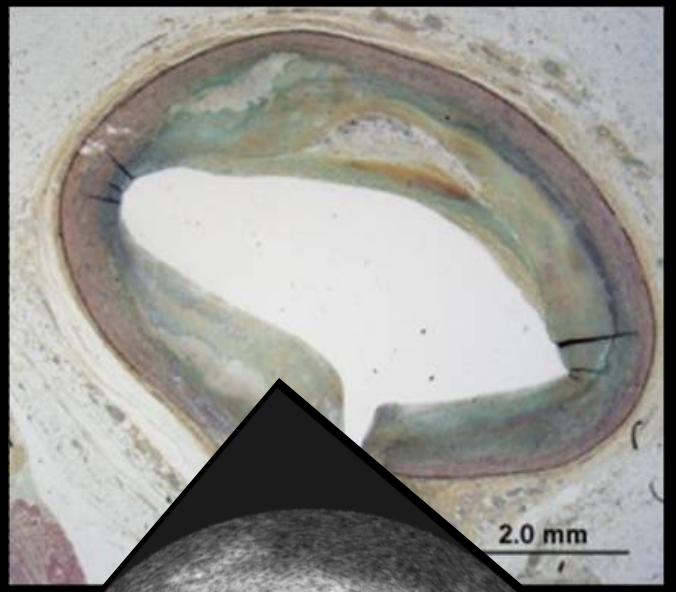
Tearney, G. J. et al. Circulation 2003;107:113-119

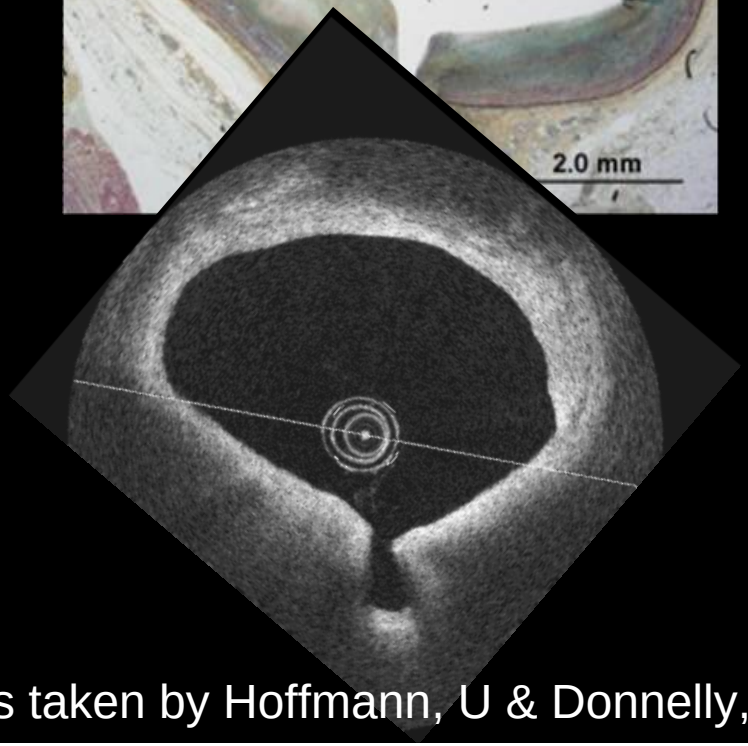
Possibility of OCT imaging
Findings from Ex-Vivo Imaging

Fibrous plaque with calcification



Fibroatheroma





OCT images taken by Hoffmann, U & Donnelly, P. MGH