

Define Vulnerable Plaque Opinion from Expert

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Consultant: 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore.

Employment in industry: No

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Owner of a healthcare company: No

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What is the vulnerable plaque? Does it exist?

From the pathological perspective

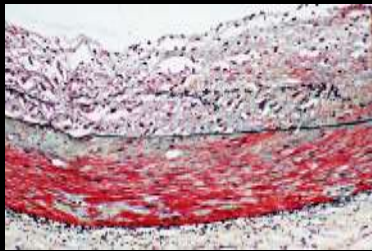
- What is a vulnerable plaque and plaque rupture (PR)
- Healed plaque ruptures responsible for plaque progression
- Location - all occur in the proximal portions of the coronary arteries
- Necrotic cores (NC) are larger in PR than in vulnerable plaques, contribution from hemorrhage.
- Inflamed plaques are more likely to rupture than non-inflamed thin-cap fibroatheromas (vulnerable plaque).

Non-Progressive and Progressive Coronary Plaques

non-progressive

progressive

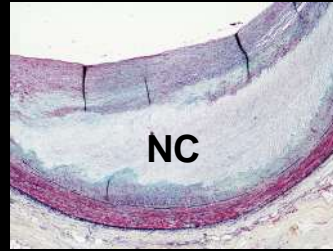
Intimal
xanthoma



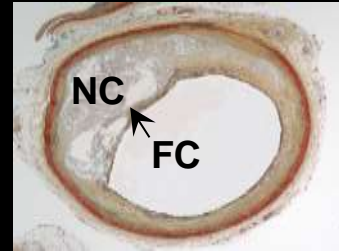
pathologic
intimal
thickening



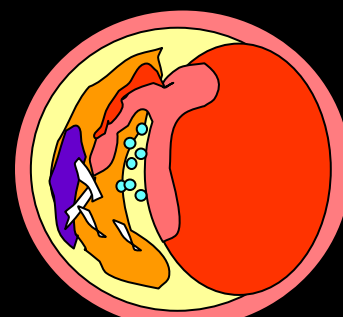
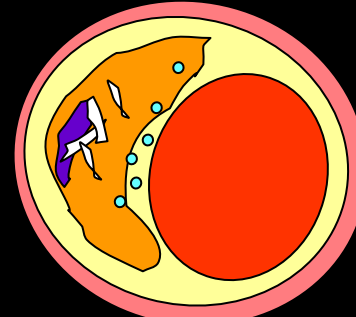
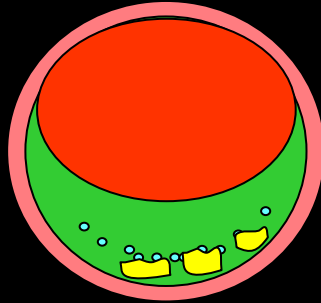
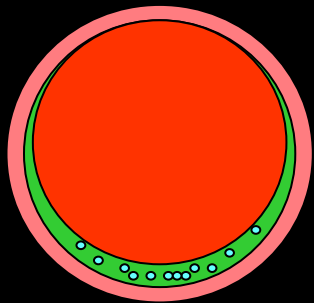
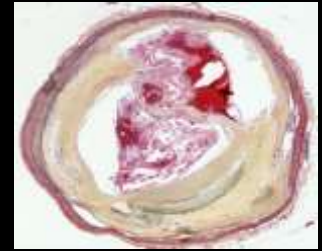
fibroatheroma



thin-cap
fibroatheroma



rupture



lipid pool

necrotic core

Early → late necrosis

Adaptive Intimal Thickening

Pathologic Intimal Thickening

Smooth muscle cell

- proliferation
- death (apoptosis)
- microcalcification

Extracellular lipid (lipid pool) ± luminal macrophages

Macrophages

Macrophage
Infiltration into LP,
apoptosis

Inflammation – T-cells

Fibroatheroma (± calcification)

(early and late)

Macrophage infiltration
(proteolytic enzymes)

Hemorrhage (red cell membrane)

Thin cap fibroatheroma

Microcalcification
of macrophages + iron

Flow disturbances +
inflammation at I/M
border

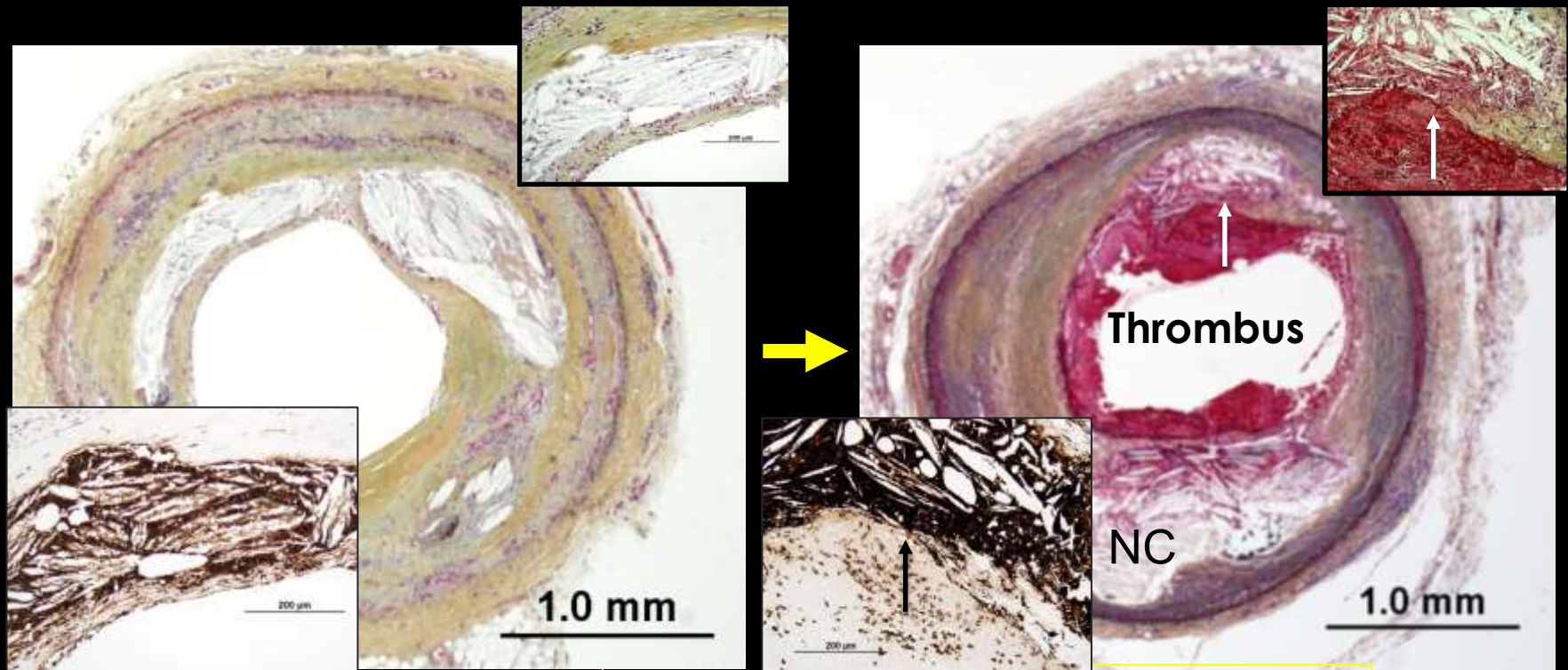
Plaque rupture

“Fatty streak”

Associated with
lesion regression

Lesion enlargement – asymptomatic or symptomatic

Similarity of Plaque Rupture and Thin cap fibroatheromas (vulnerable plaques)



Thin cap fibroatheroma

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

Plaque Rupture

- Discontinuous thin fibrous cap
- Macrophage, T-cell infiltration of cap
- Underlying large necrotic core
- Neovascularization
- Expansive remodeling
- Luminal thrombus

Features of ruptured plaques

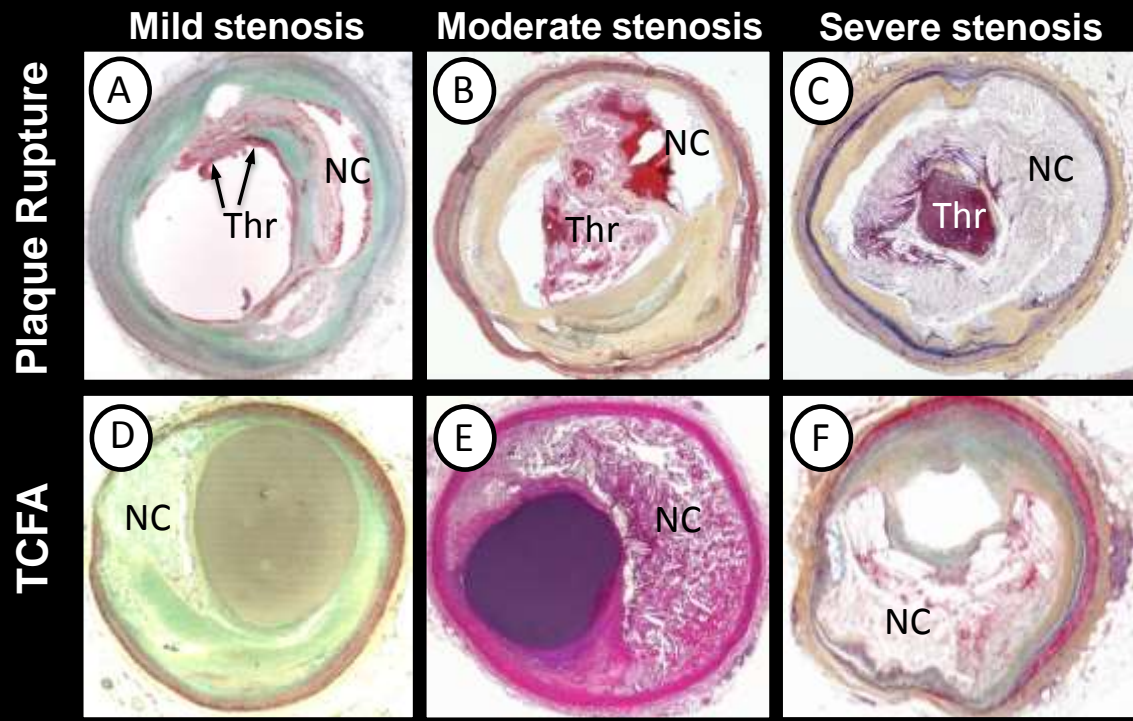
- Thrombus
- Large necrotic core (>30% of plaque)
- Fibrous cap covering the necrotic core
 - thin (thickness usually <65 μm)
 - many macrophages (inflammation, M1, M2)
 - few smooth muscle cells (apoptosis)
- Expansive remodeling preserving the lumen
- Neovascularization from vasa vasorum
 - Plaque hemorrhage
- Adventitial/perivascular/intimal medial inflammation
- “Spotty” calcification

Morphologic Characteristics of Plaque Rupture and Thin-cap Fibroatheromas

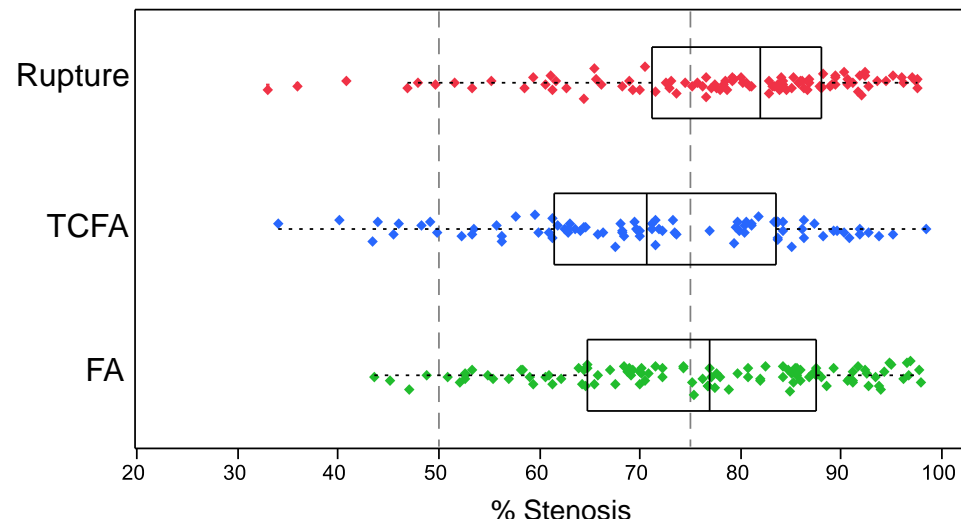
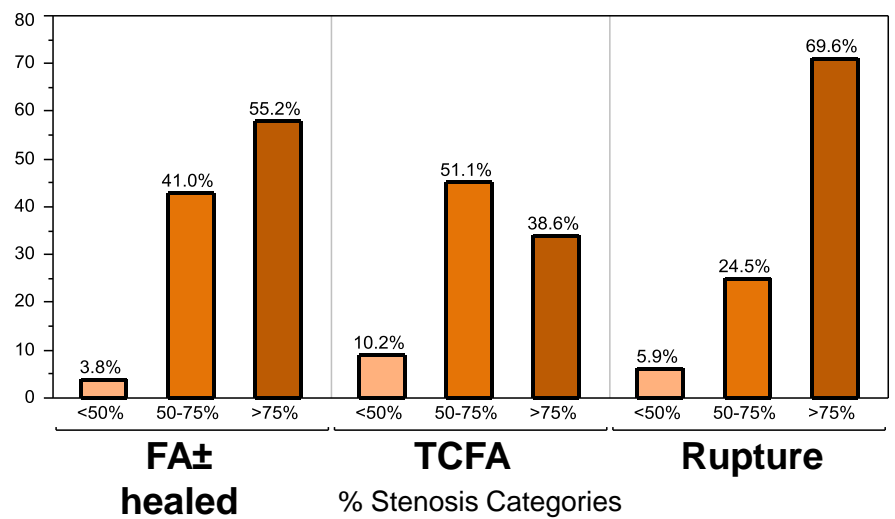
Plaque type	Necrotic Core (%)	Fibrous cap Thickness (μm)	M σ (%)	SMCs (%)	T-lymph	Calcification Score
Rupture	34 \pm 17	23 \pm 19	26 \pm 20	0.002 \pm 0.004	4.9 \pm 4.3	1.53 \pm 1.03
Thin-cap Fibroatheroma	23 \pm 17	<65 μm	14 \pm 10	6.6 \pm 10.4	6.6 \pm 10.4	0.97 \pm 1.1
P value	0.01		0.005	ns	ns	0.014

Mean values are represented \pm standard deviation. Abbreviations: M Φ s= macrophages, SMCs= smooth muscle cells, T-lymph= T-lymphocytes

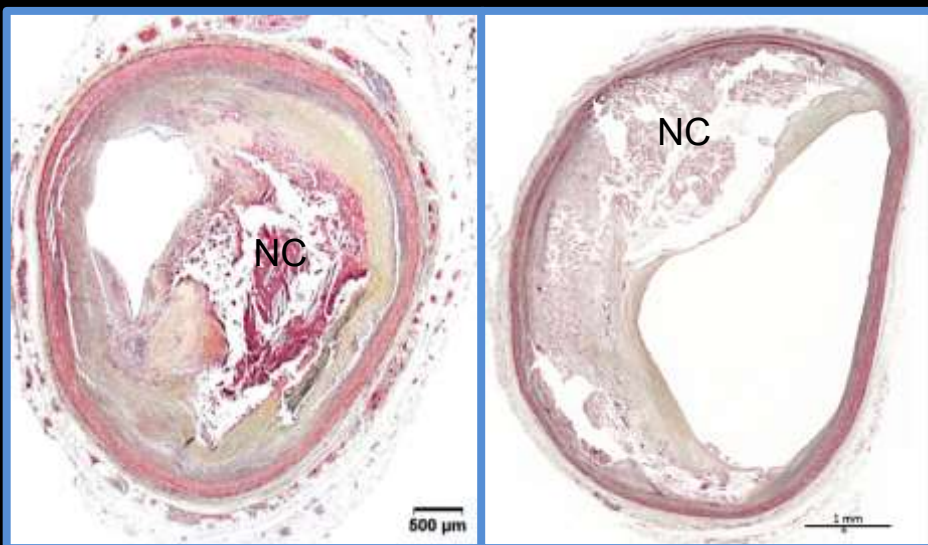
Plaque Rupture and TCFA with Varying Luminal Stenosis



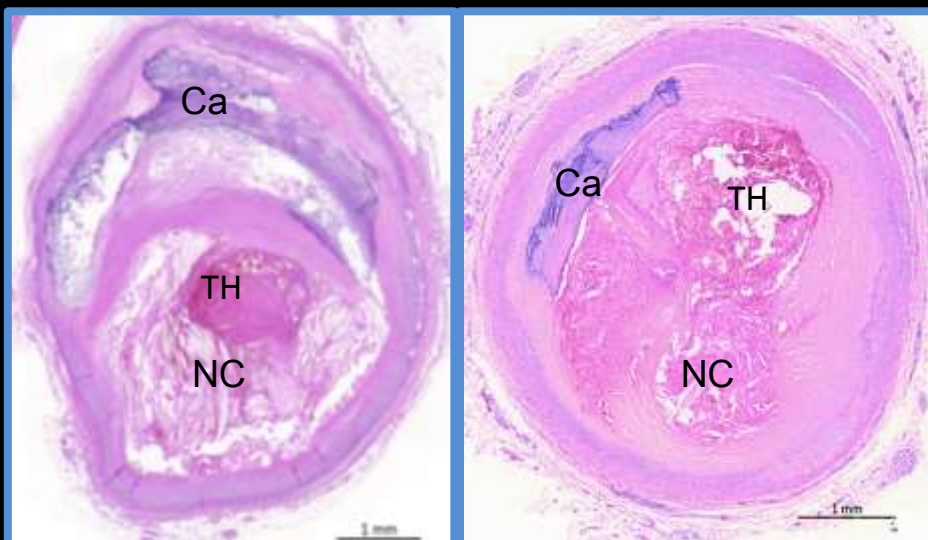
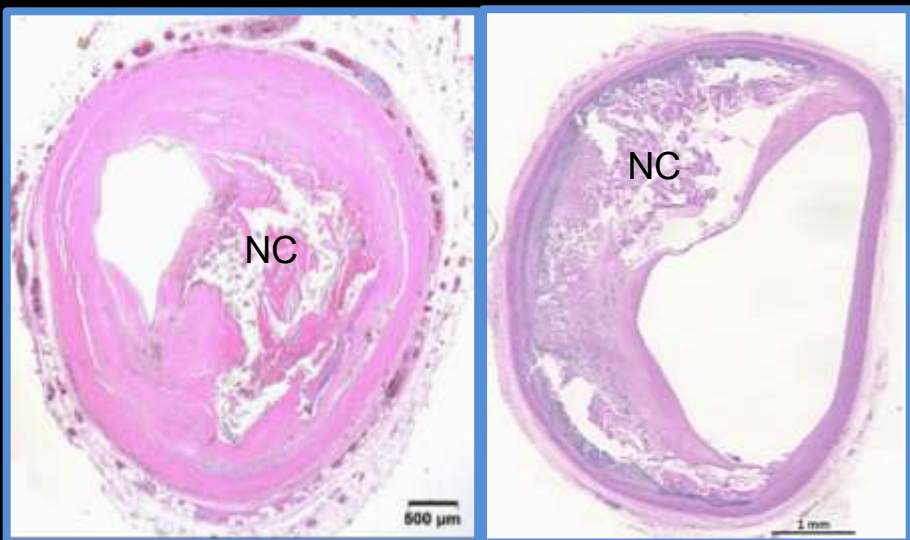
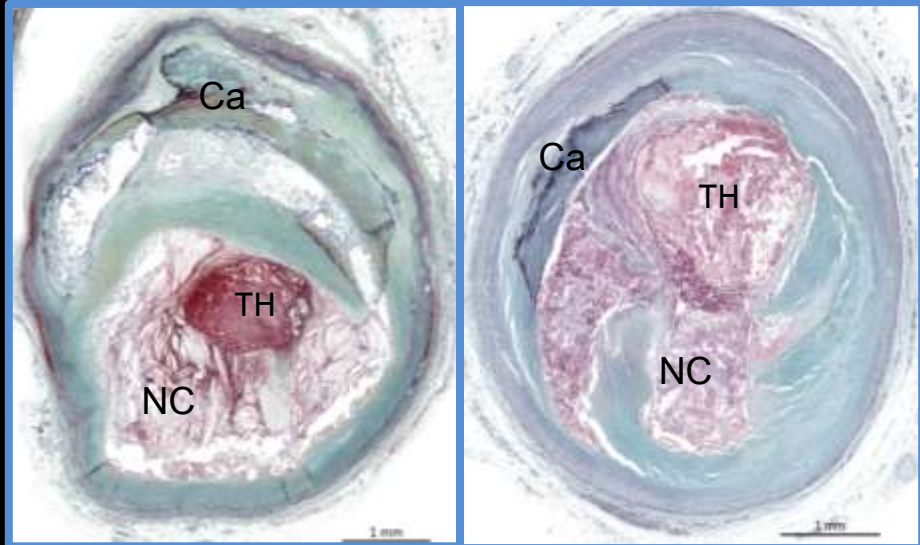
Narula, et al. J Am Coll Cardiol. 2013 March 12; 61(10): 1041-1051



Thin cap Fibroatheroma



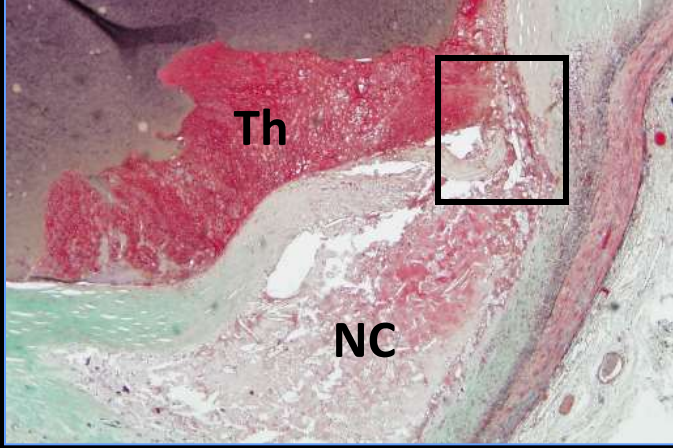
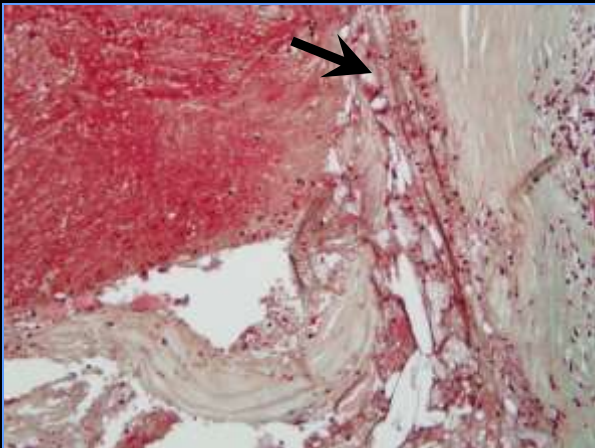
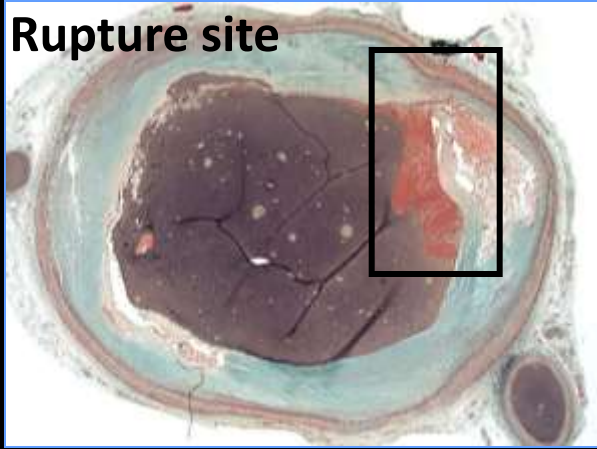
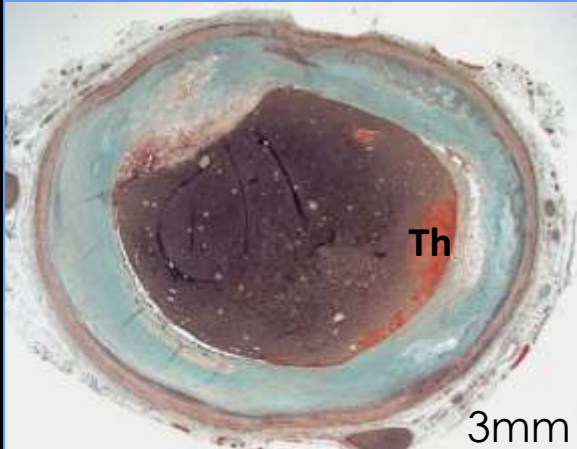
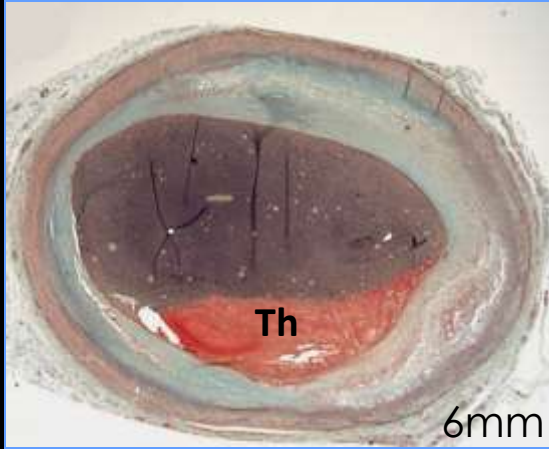
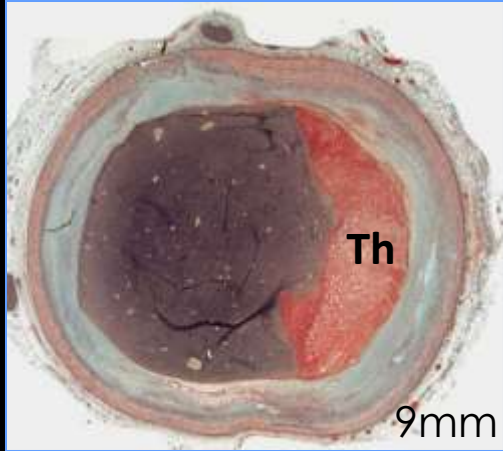
Plaque Rupture



Implications of the Findings for the Invasive and Noninvasive Detection of Vulnerable Plaques

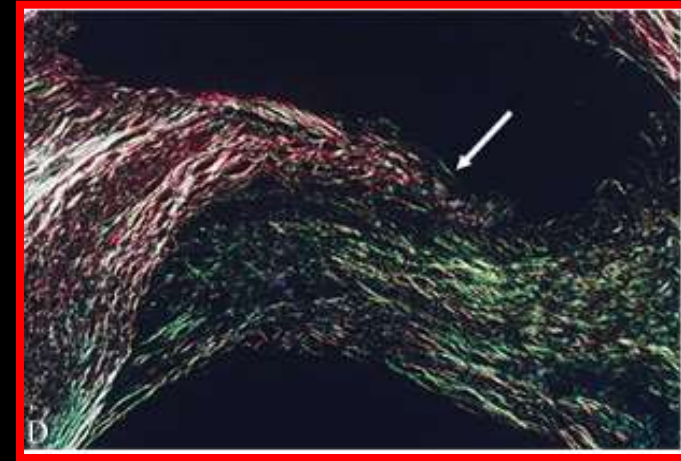
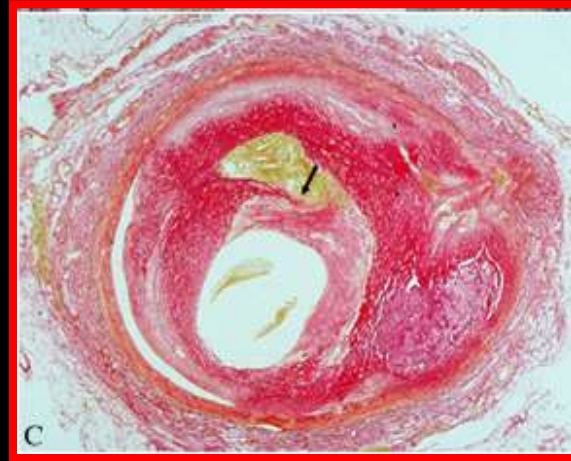
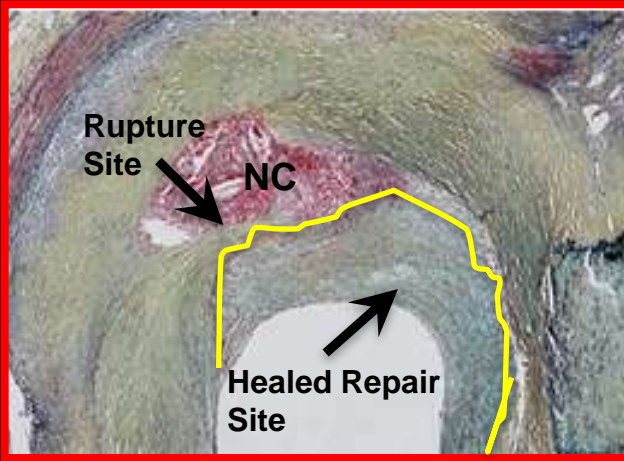
- Thickness of the fibrous cap emerged as the best predictor of plaque type: PR $<55\mu\text{m}$; FA $>84\mu\text{m}$; TCFA 54 to $84\mu\text{m}$, those with thickness $<54\mu\text{m}$ were more likely to show $>74\%$ luminal narrowing.
- After exclusion of cap thickness, the analysis revealed macrophage infiltration and necrotic core to be the 2 best discriminators of plaque type

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

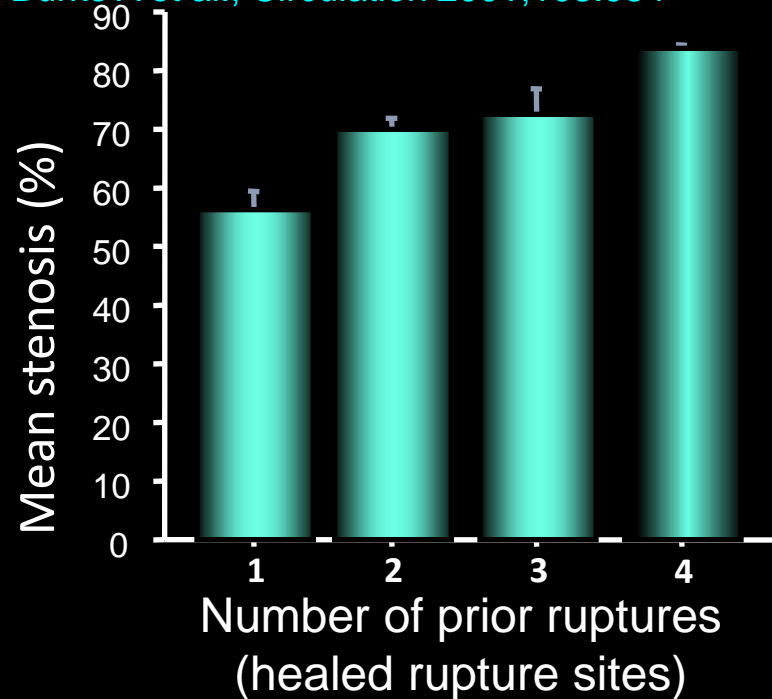


Healed Ruptures are responsible for Plaque Progression

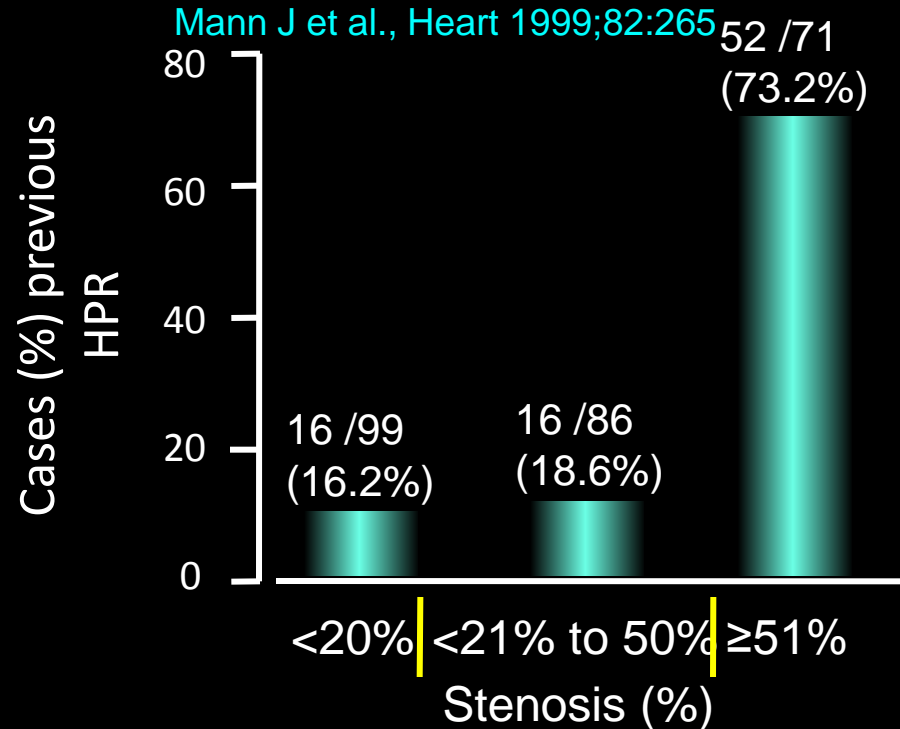
Movat **Picrosirius Red** **Picrosirius Red (Polarized)**



Burke A et al., *Circulation* 2001;103:934

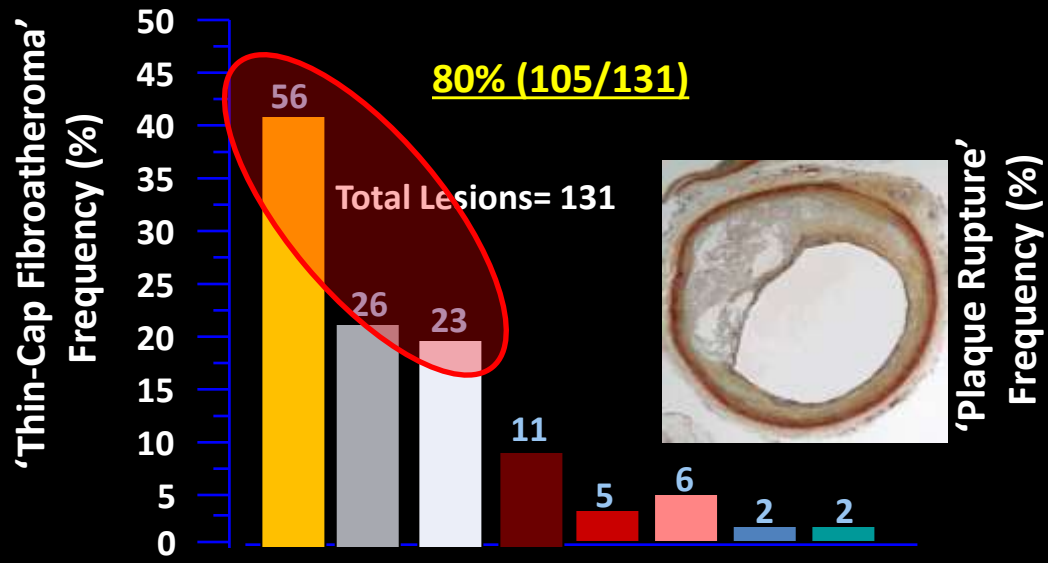


Mann J et al., *Heart* 1999;82:265

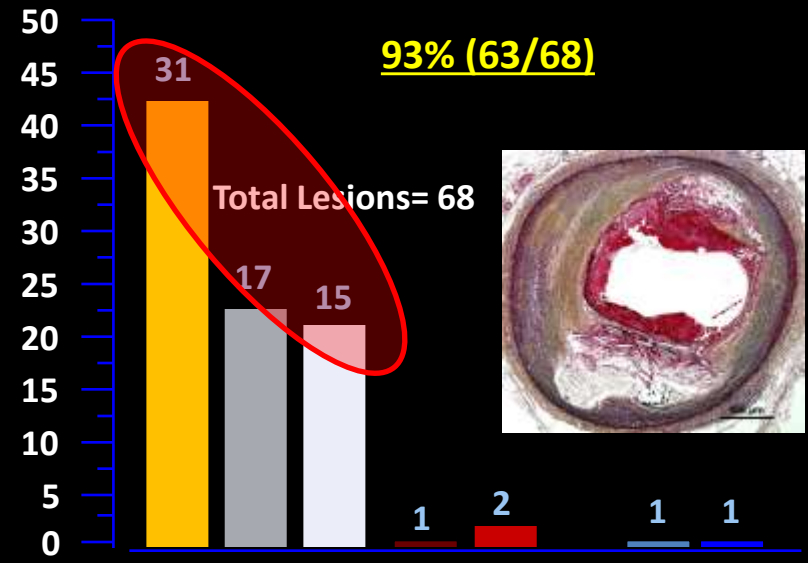


Frequency and Location of Unstable Lesions: Thin-cap Atheromas, Acute and Healed Ruptures in the Coronary Circulation

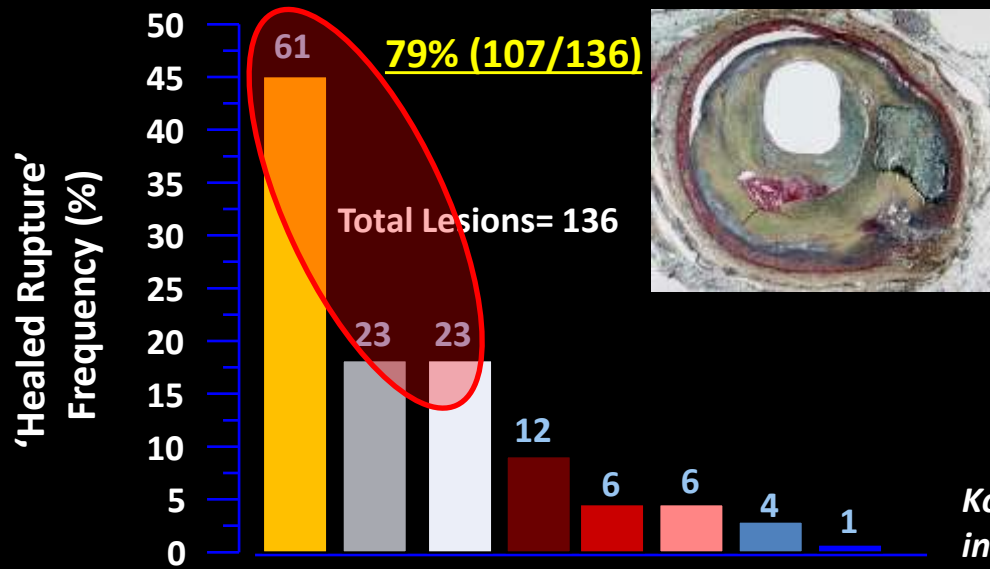
Thin-cap Fibroatheroma



Acute Plaque Rupture



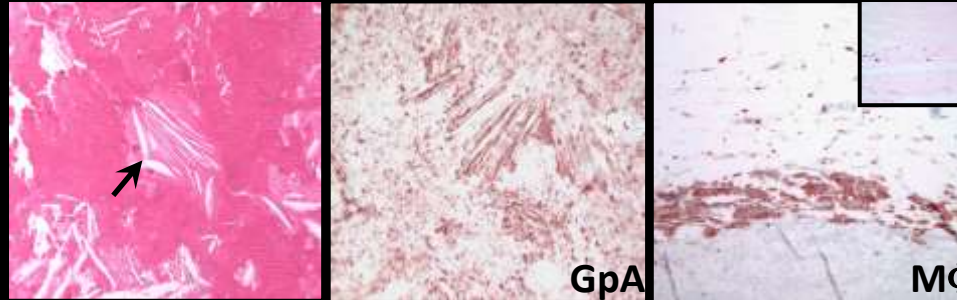
Healed Plaque Rupture



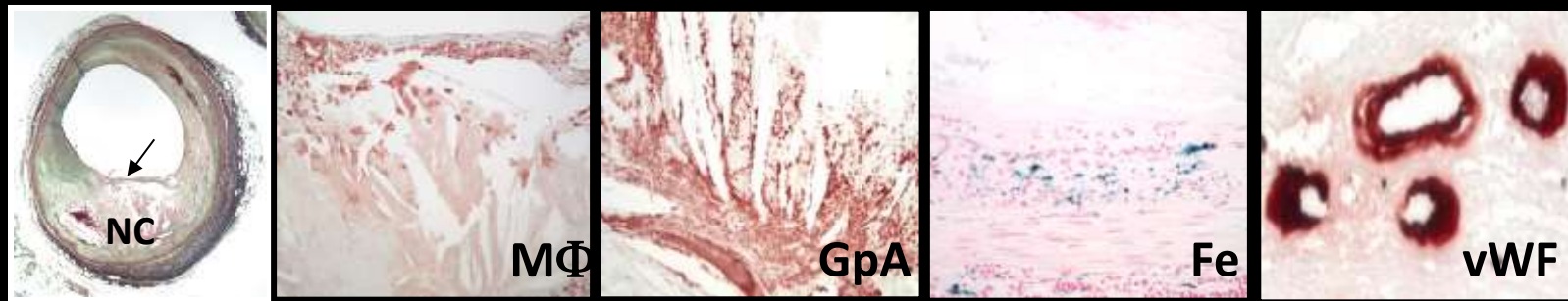
- pLAD
- mRC
- pLCx
- LM
- LOM
- dRC
- dLAD
- dLCx

Morphometric Analysis of Hemorrhagic Events in Human

Hemorrhagic
Pericarditis



Vulnerable Plaque

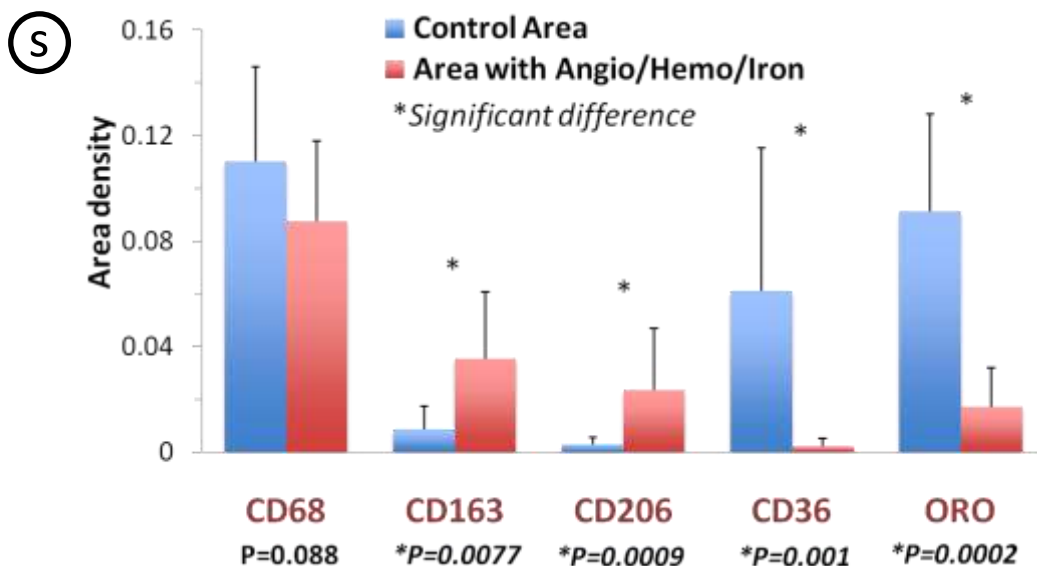
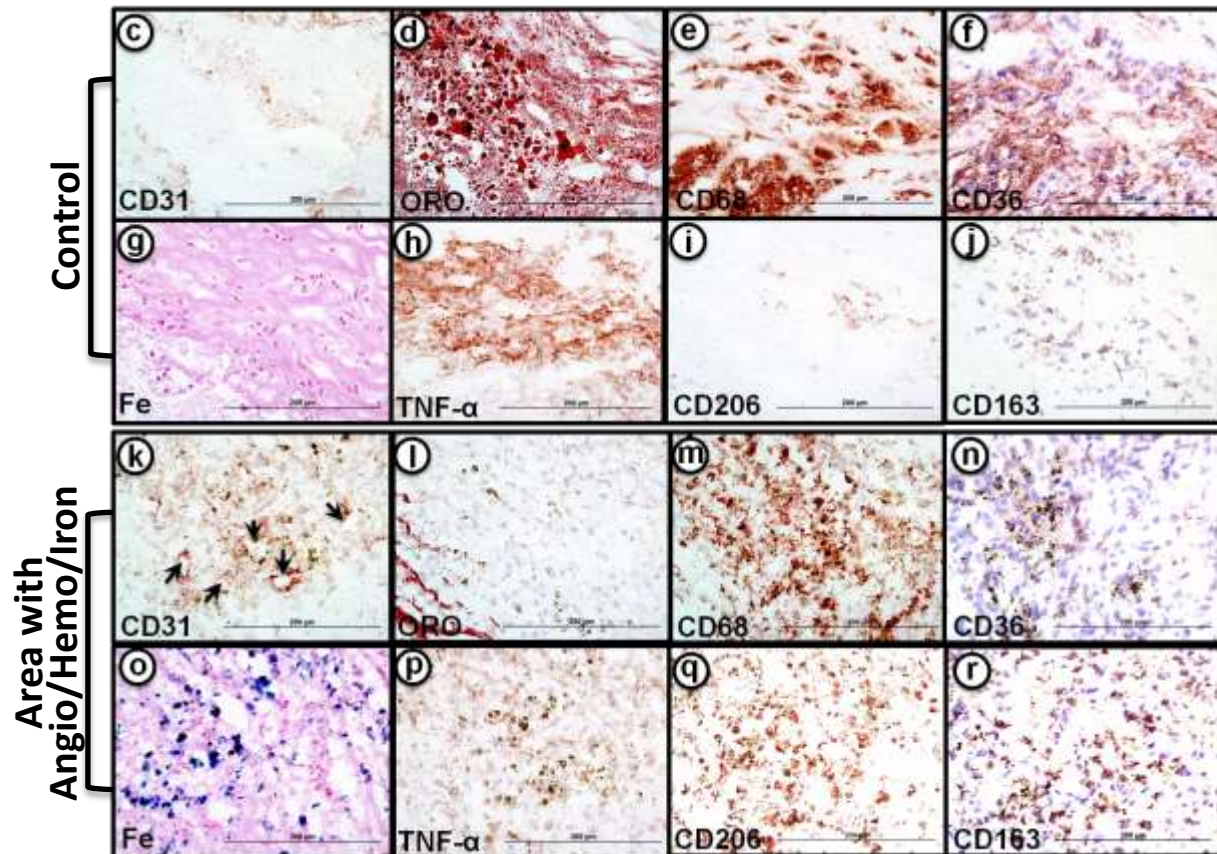
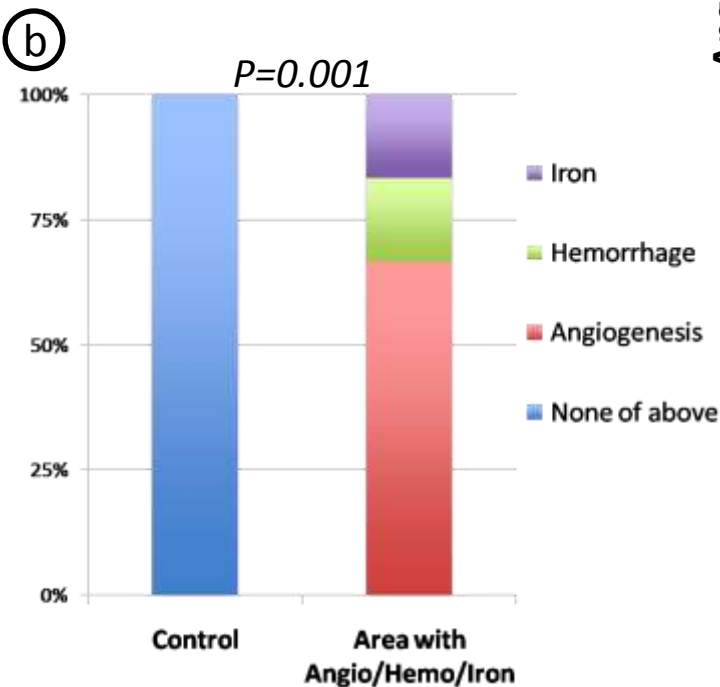
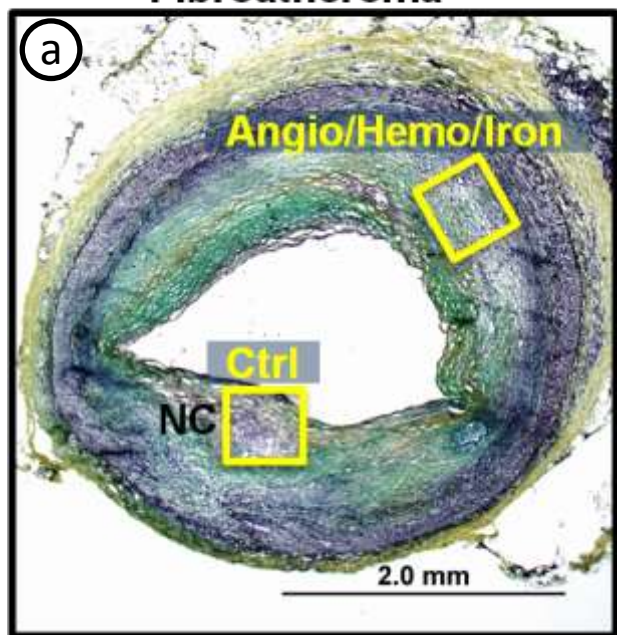


Plaque Type	GpA Score	Iron	Necrotic Core (mm ²)	Mo (mm ²)
PIT <i>no</i> core (n=129)	0.09 ± 0.04	0.07 ± 0.05	0.0	0.002 ± 0.001
FA <i>early</i> core (n=79)	0.23 ± 0.07	0.17 ± 0.08	0.06 ± 0.02	0.018 ± 0.004
FA <i>late</i> core (n=105)	*0.94 ± 0.11	*0.41 ± 0.09	*0.84 ± 0.08	*0.059 ± 0.007
TCFA (n=52)	*1.60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

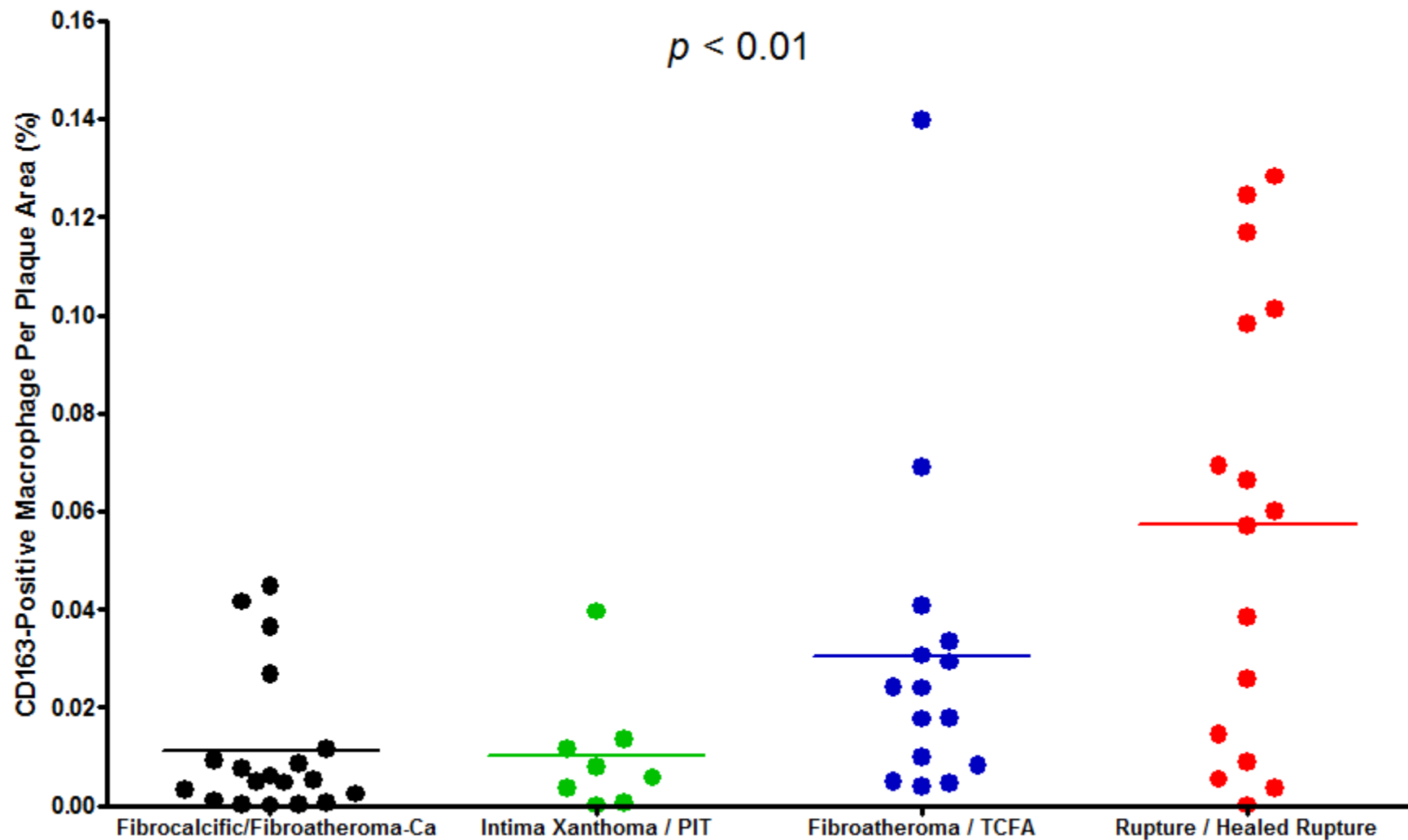
Values are reported as the means ± SE, *p < 0.001 versus early core. The number in parenthesis represent the number of lesions examined; the total number = 365. MΦ = macrophages

Kolodgie FD, et al. New Engl J Med 2003

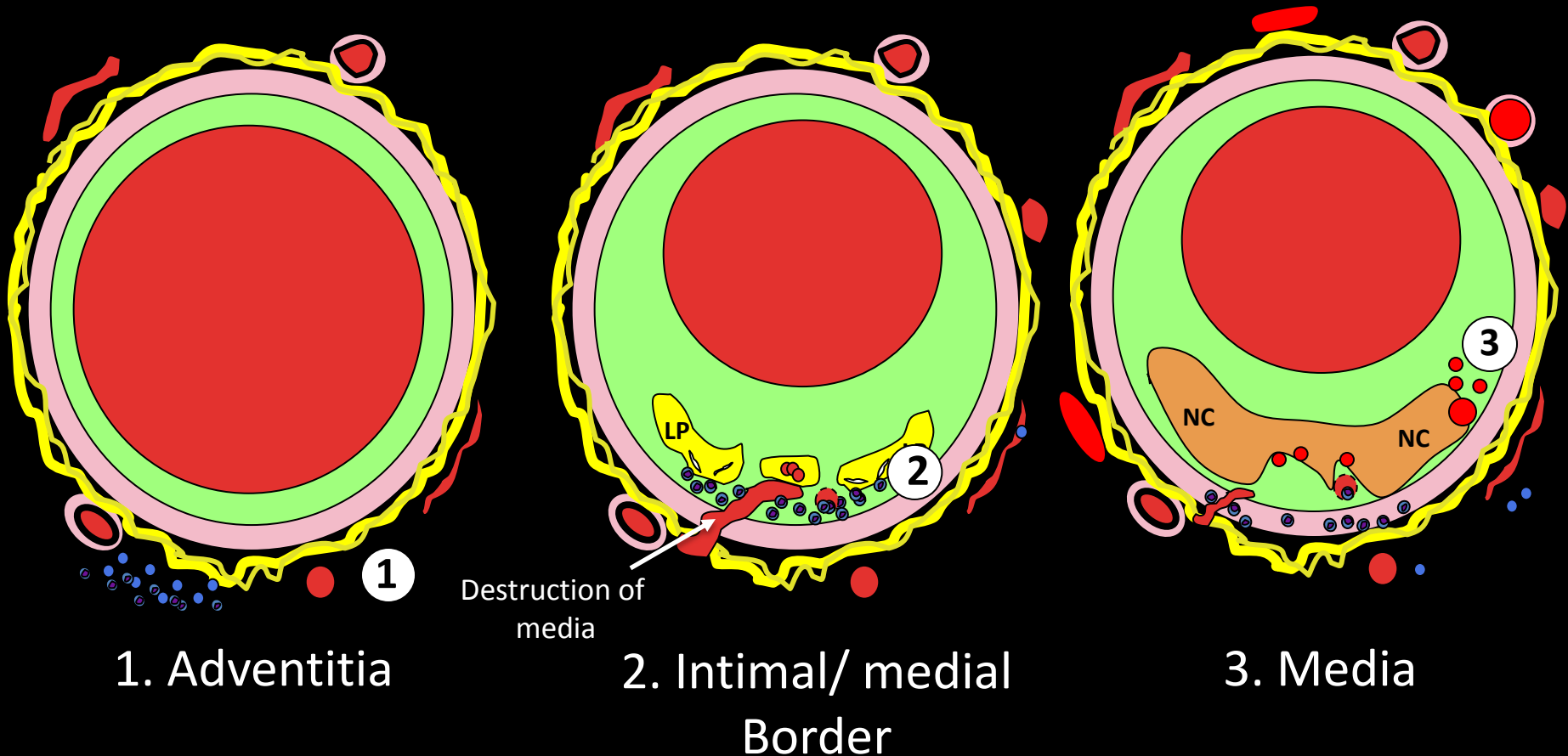
Human Coronary Fibroatheroma



CD163-Positive Macrophage in Plaque Progression



Inflammation Assessed at Three - different locations



Inflammation in Coronary Rupture vs TCFA

Combination of severity and distribution in intimal-media border

Rupture=60

TCFA=60

Distribution

	0-45	46-90	91-180	181-270	271-360
0-20	0	1	2	3	4
21-100	1	2	3	4	5
101-200	2	3	4	5	6
201-400	3	4	5	6	7
>400-	4	5	6	7	8

Severity

Severity

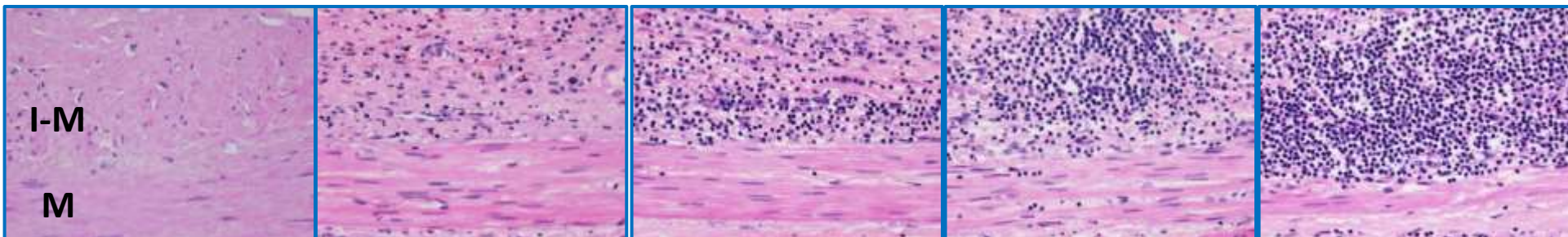
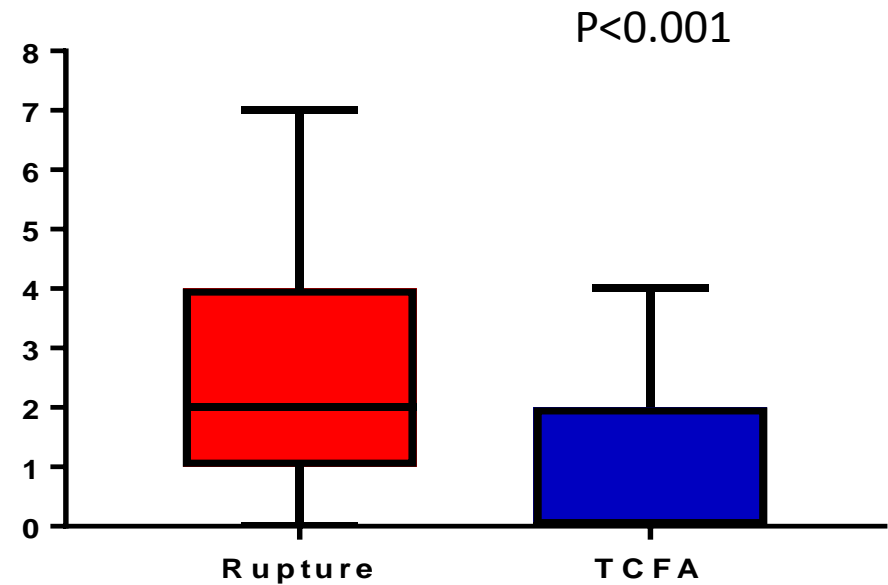
Score 1

Score 2

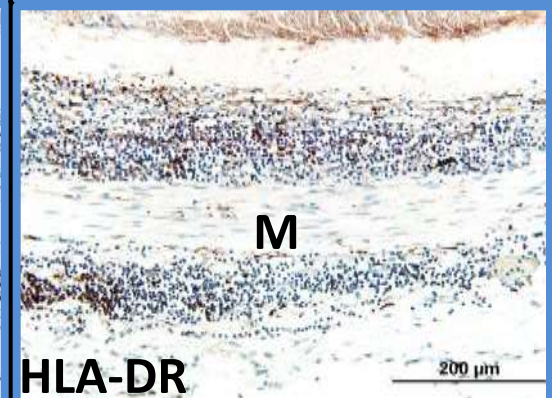
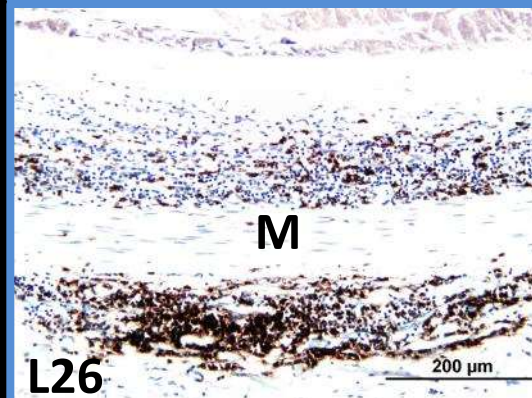
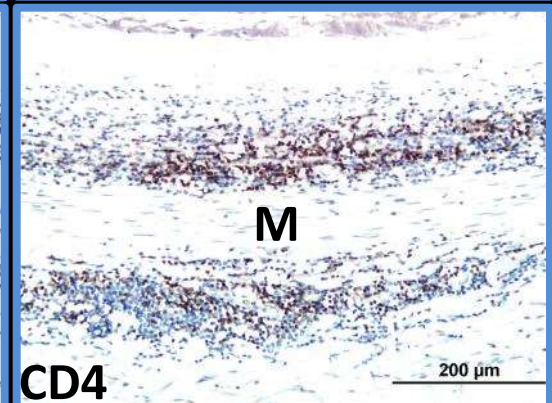
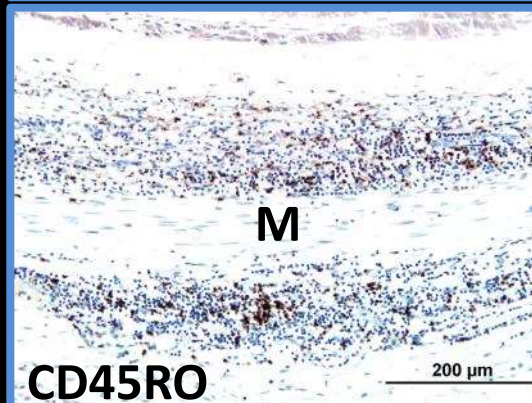
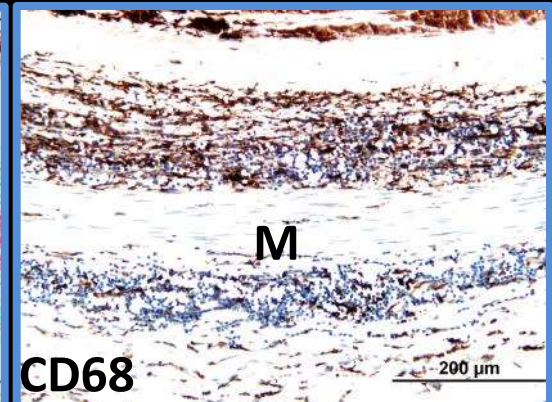
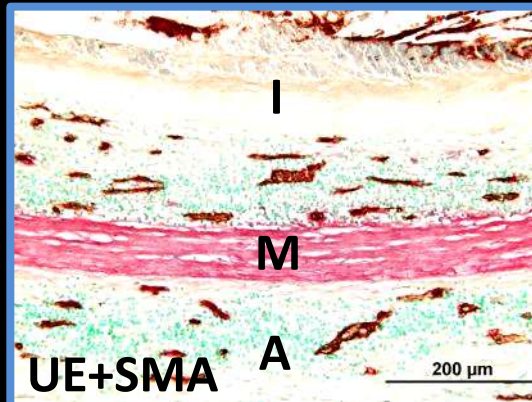
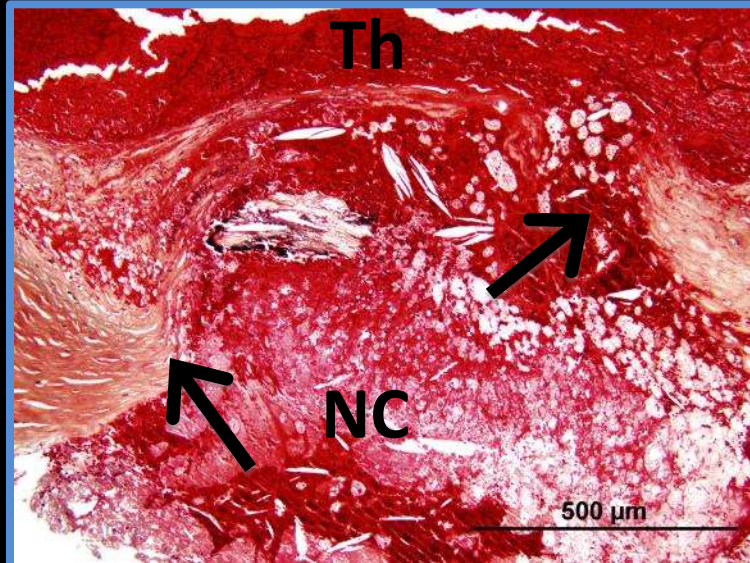
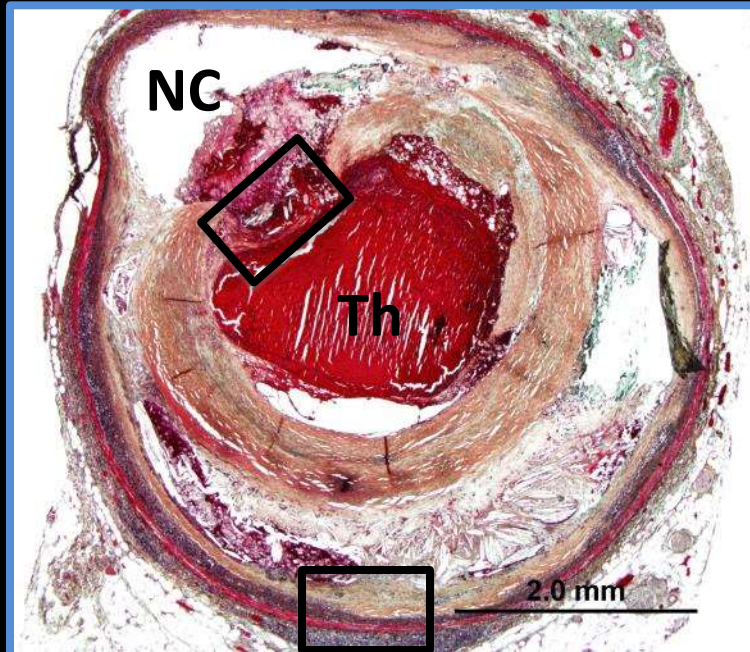
Score 3

Score 4

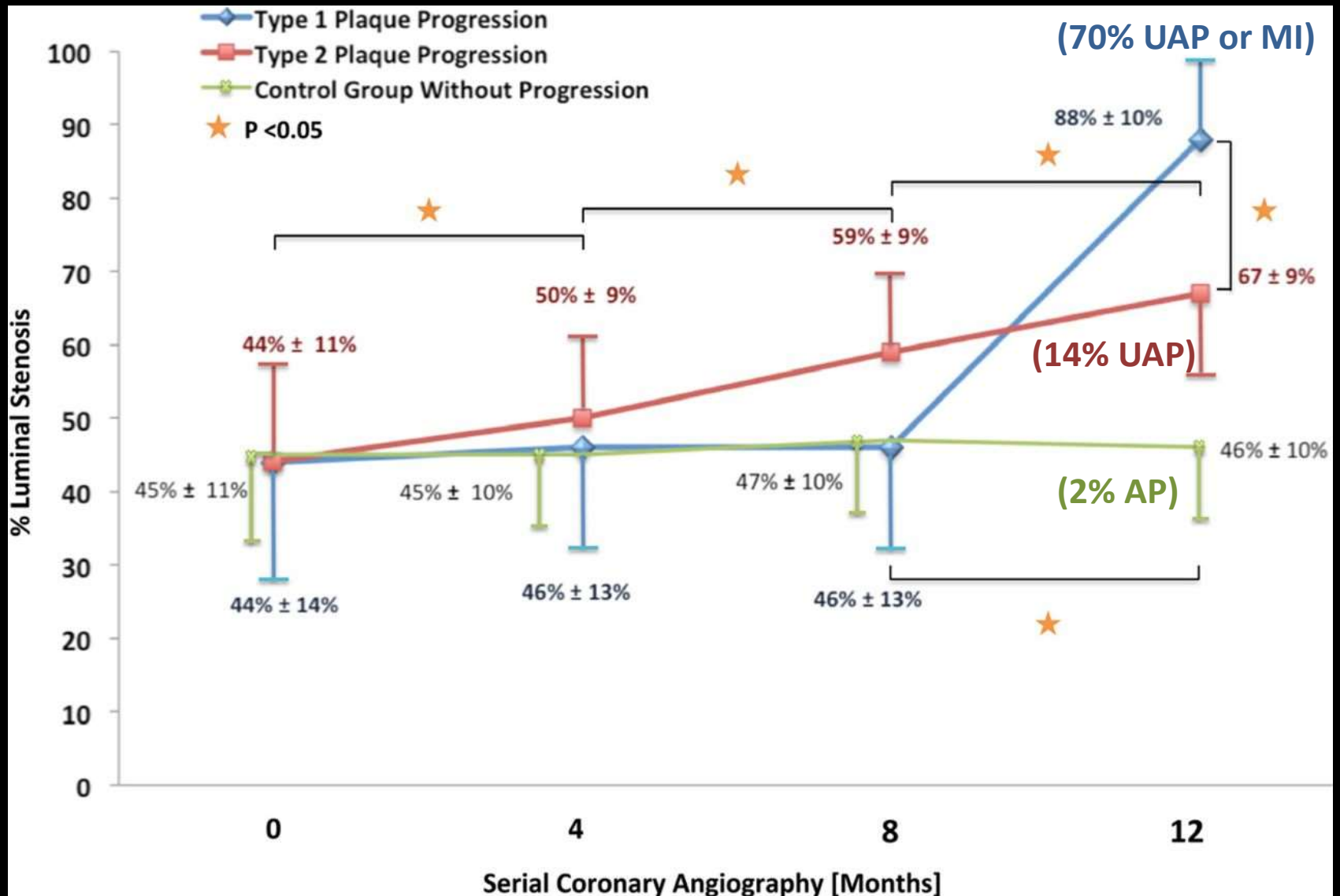
Score 5



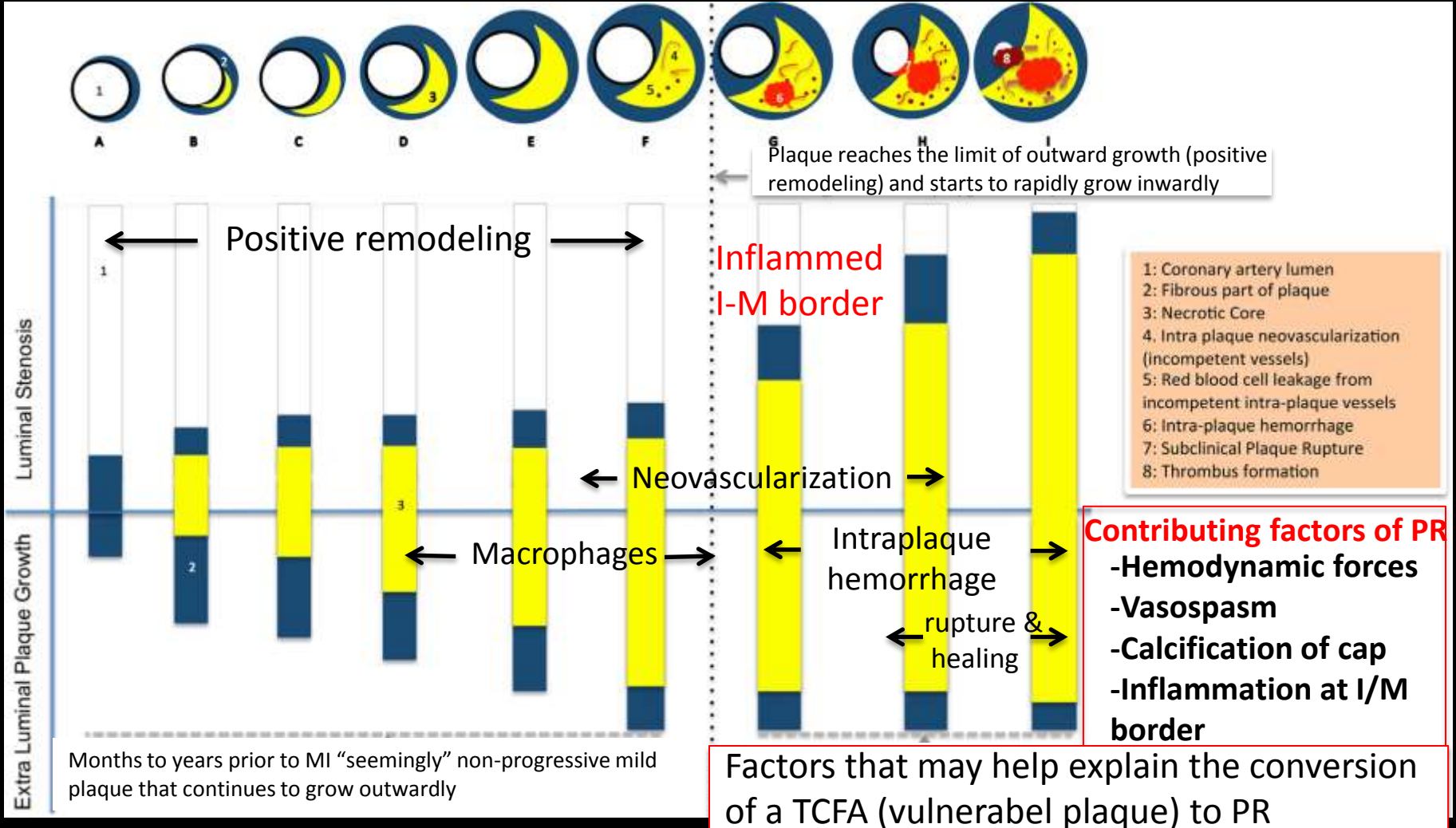
Angiogenesis and Inflammation in Coronary Plaque Rupture



Not all plaques progress the same way.



Mechanisms contributing to the rapid plaque progression before Plaque Rupture



Modified from Ahmadi et al. *Circ Res.* 2015;117:99-104

What is the vulnerable plaque? Does it exist?

From the pathological perspective

Summary

- Vulnerable plaques (TCFA) is a likely precursor lesions of rupture..
- Angiogenesis is associated with plaque progression and inflammation.
- Intra plaque hemorrhages are responsible for enlargement of necrotic core, via neoangiogenesis.
- Vulnerable plaque, plaque rupture and healed plaque ruptures occur at same sites (proximal).
- Healed ruptures are responsible for plaque progression. Rapid plaque progression before MI was considered as possible mechanism.
- Intimal-media border have greater inflammation in coronary rupture than in TCFA, may help predict which one will rupture
- **Vulnerable plaque exists, but we do not know how to predict which one will rupture, more work is needed.**

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