Vulnerable Plaque; What Is It? Pathological Perspective

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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.

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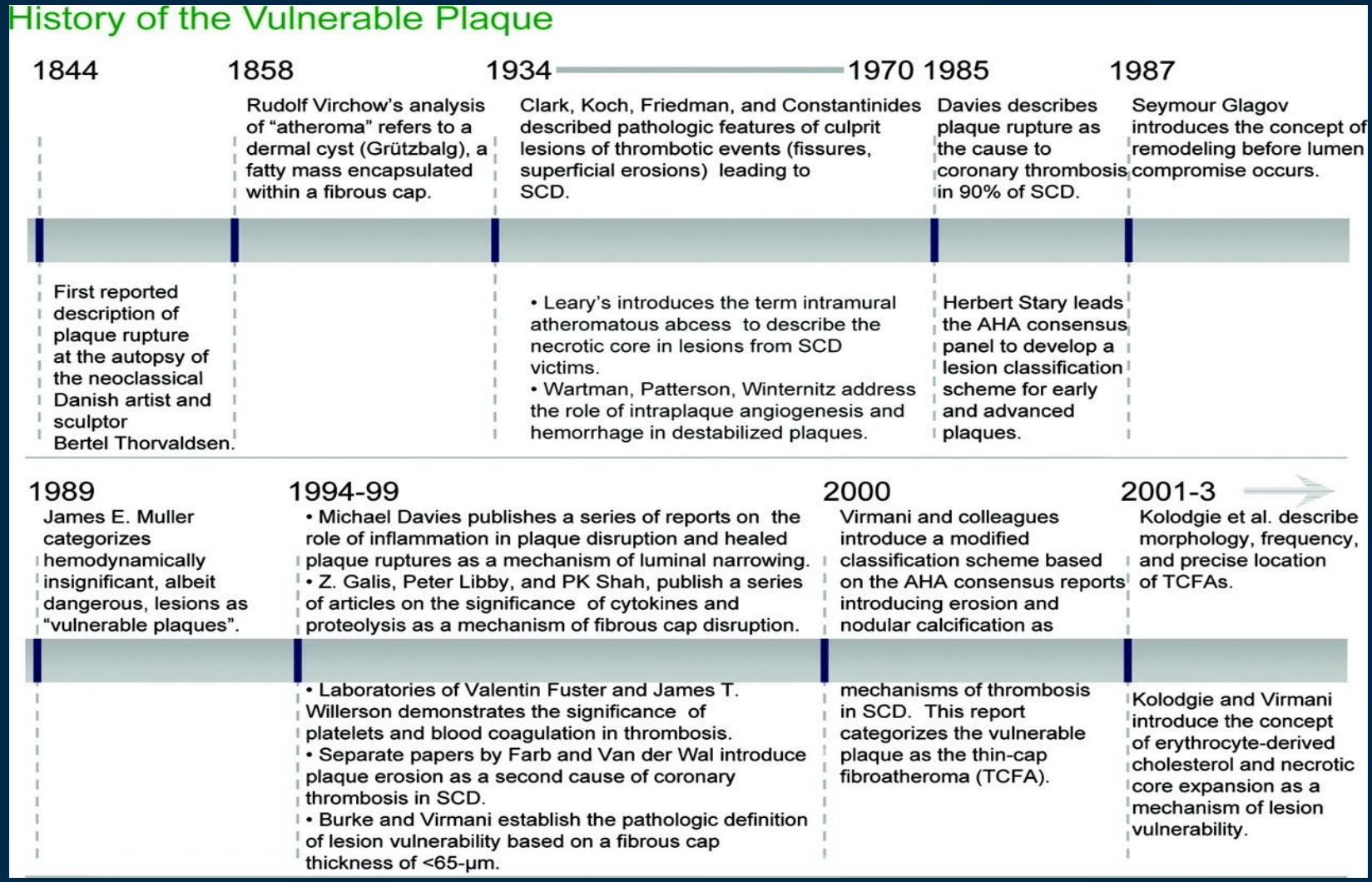
Owner of a healthcare company: No

Stockholder of a healthcare company: No

History of the Vulnerable Plaque



Aloke V. Finn. Arteriosclerosis, Thrombosis, and Vascular Biology. Concept of Vulnerable/Unstable Plaque, Volume: 30, Issue: 7, Pages: 1282-1292, DOI: (10.1161/ATVBAHA.108.179739)

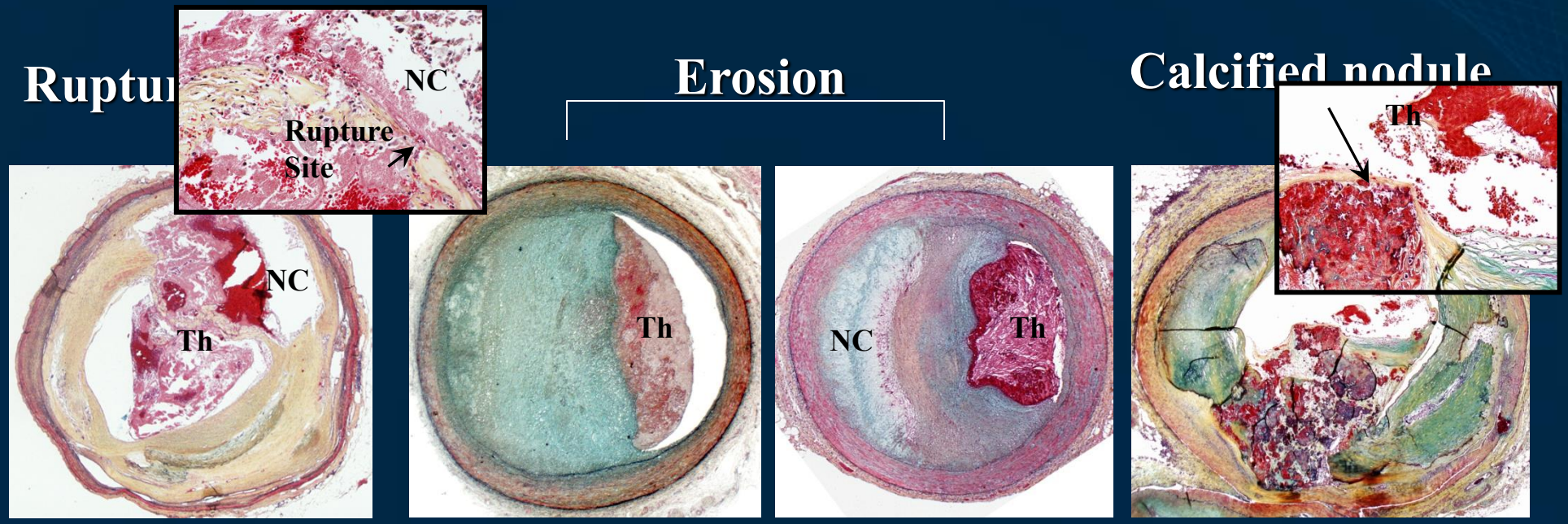
Pathology of Vulnerable Plaque

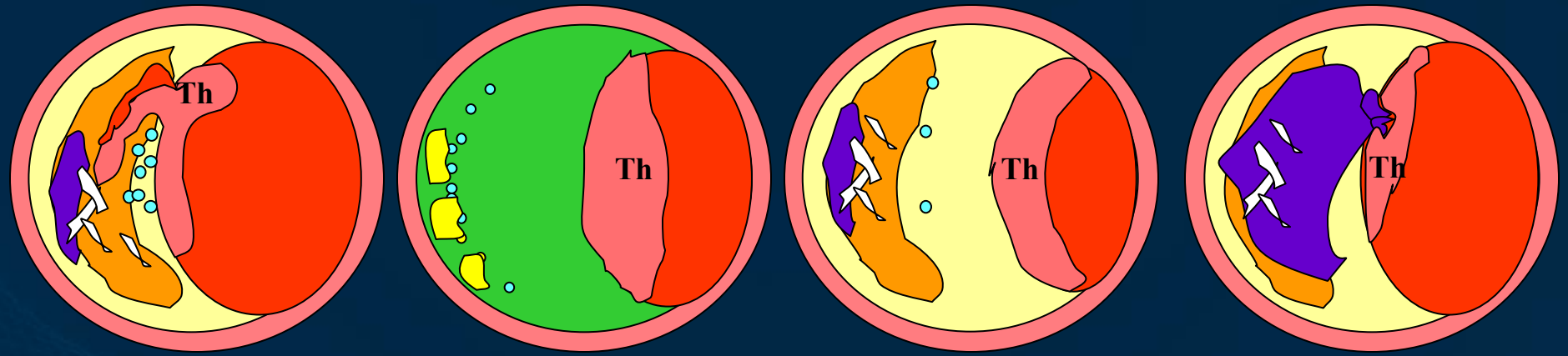
Causes of Coronary Thrombosis

Ruptur

Erosion

Calcified nodule

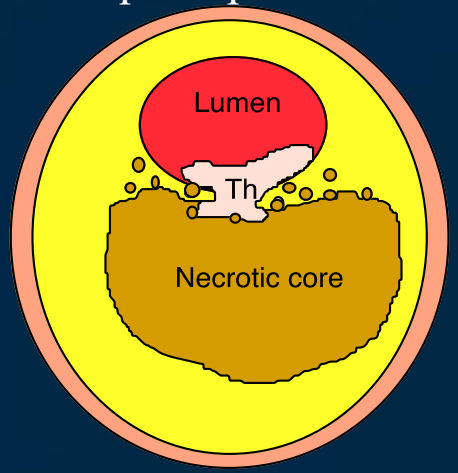
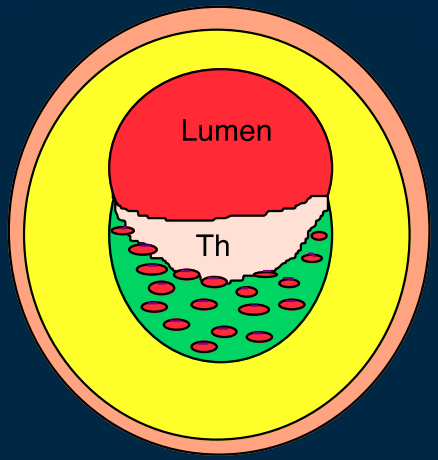
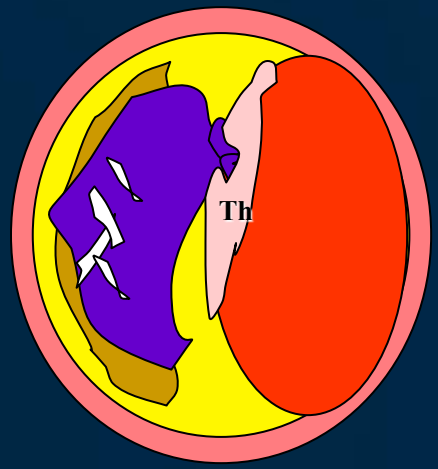




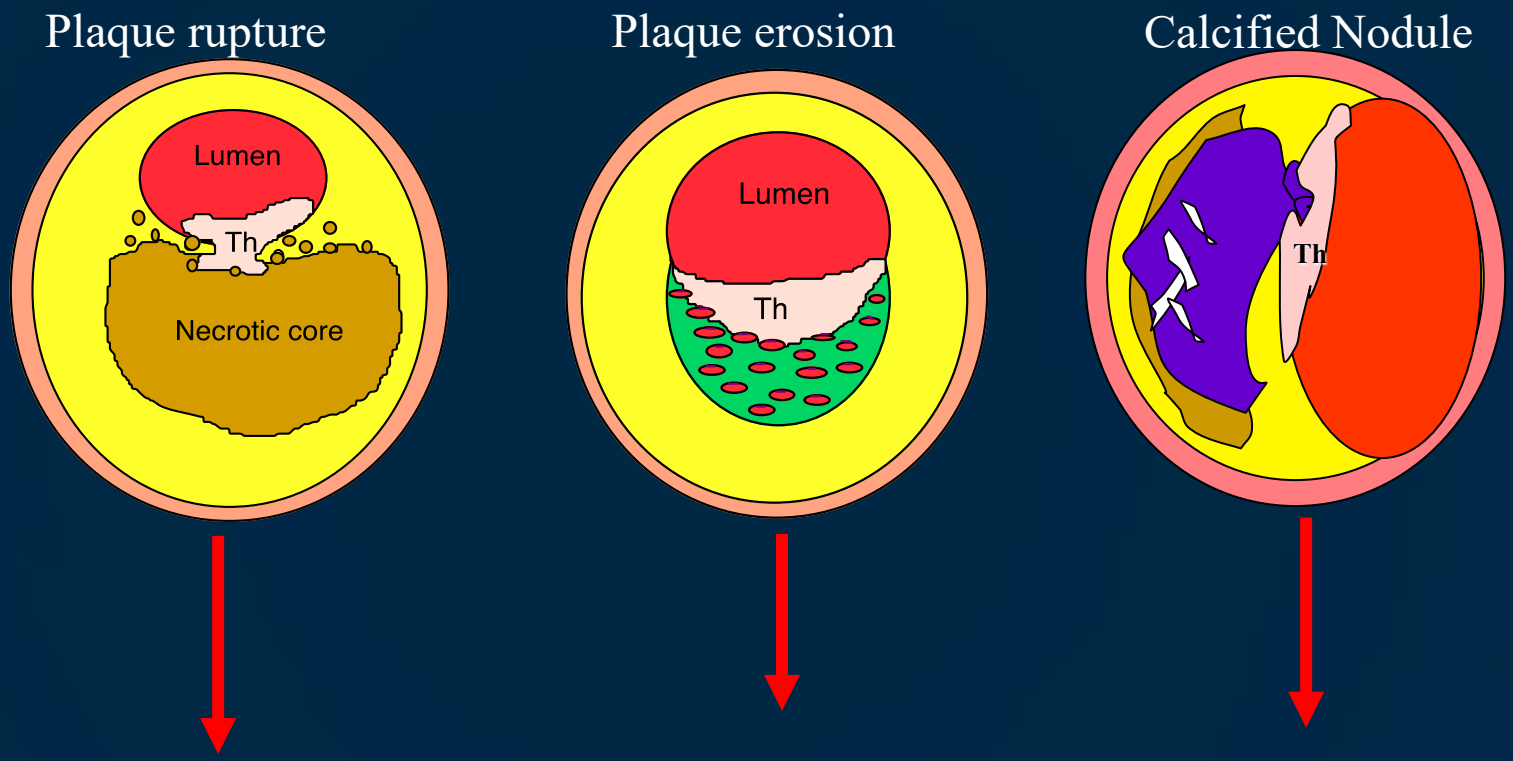
CVPath

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

Clinical and Morphologic Difference in Plaques Associated with Luminal Thrombi

Plaque rupture	Plaque erosion	Calcified Nodule
		
45-55% thrombi in SCD M>F, Older, Ca^{++} Eccentric = concentric Greater % stenosis Macs, T cells,HLADr	35-40% thrombi in SCD M=F, younger Usually eccentric Lesser % stenosis SMC rich, proteoglycans	4-7% thrombi in SCD, calcified plates M>F, older, mid RCA Usually eccentric Stenosis variable Nodules of bone

Prevention/Treatment Paradigms



Primary Targets

Lipids/inflammation

Lipids, calcification, healing?

Abnormal shear, endothelial cell dysfunction and Thrombosis?

Non-Progressive and Progressive Coronary Plaques

non-progressive → progressive

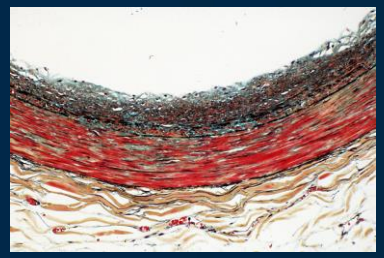
adaptive intimal thickening

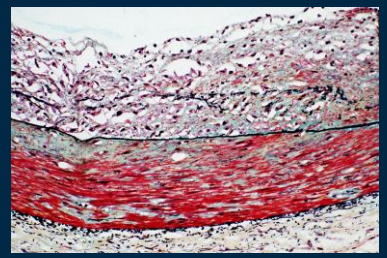
Intimal xanthoma

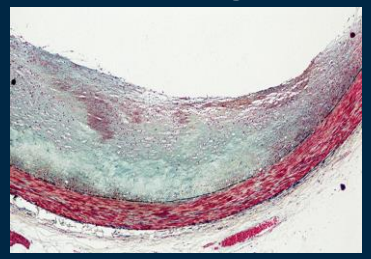
pathologic intimal thickening

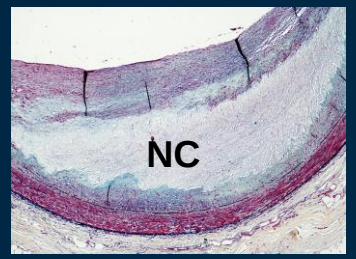
fibroatheroma

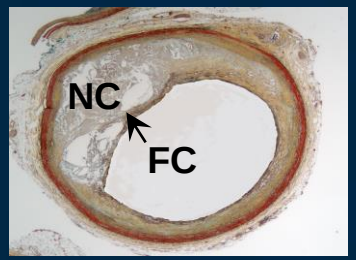
thin-cap fibroatheroma

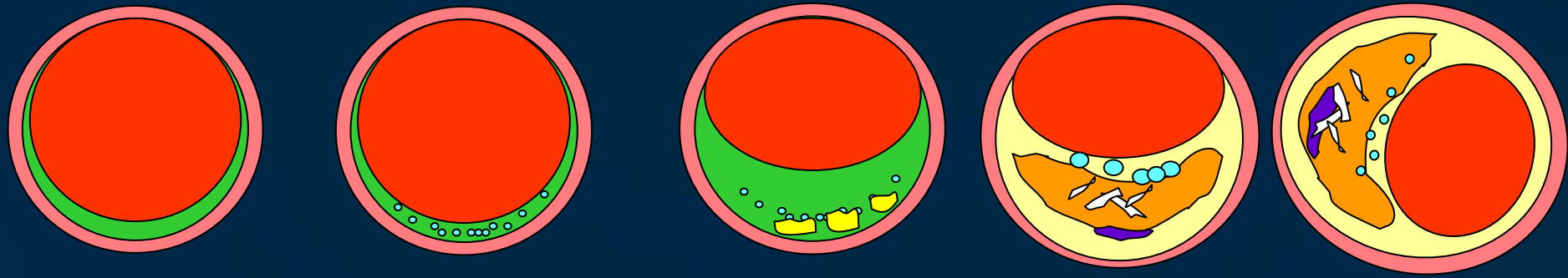












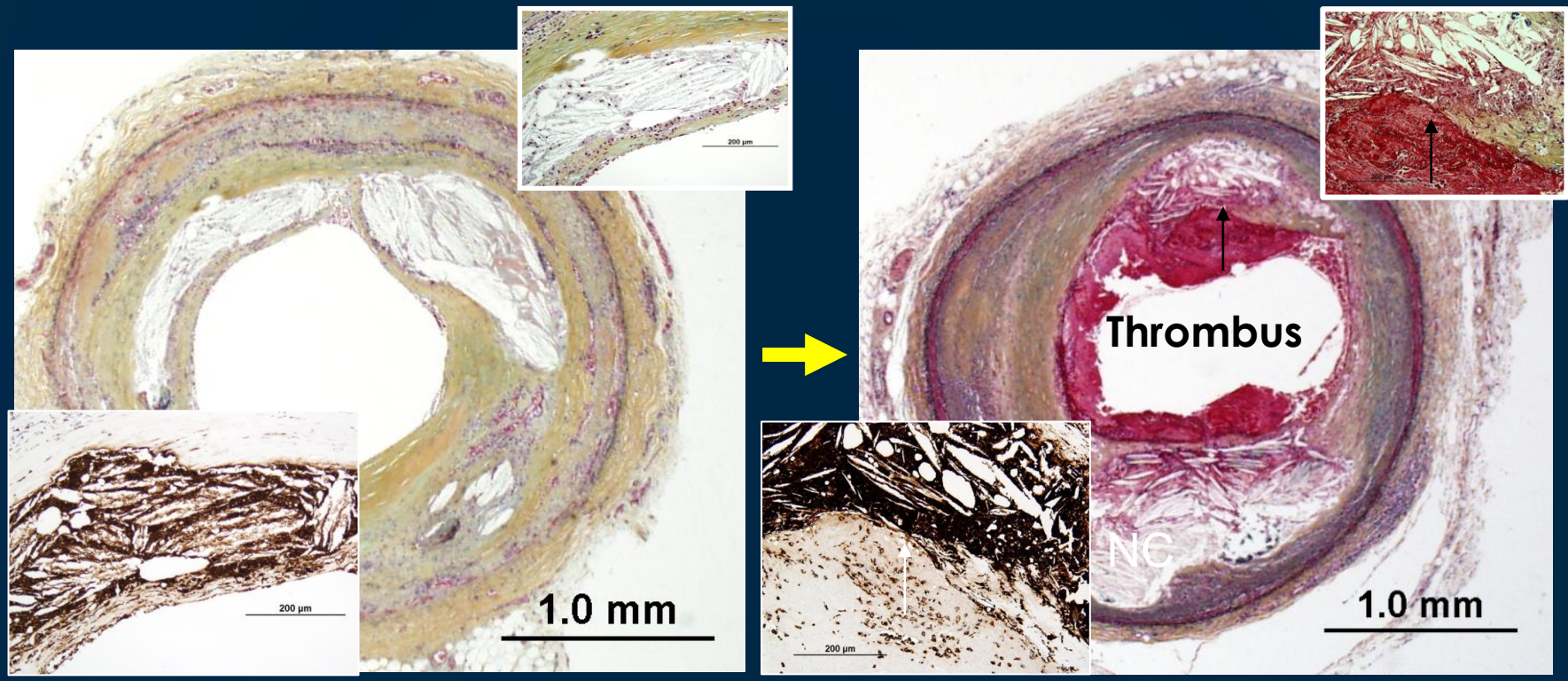
lipid pool

necrotic core

early → late necrosis

Plaque Rupture Paradigm

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



Thin cap fibroatheroma

- Necrotic core
- Thin fibrous cap (< 65 um)
- 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

Achieving Lower LDL-C Levels Was Shown to be Associated With Less Plaque Rupture

Plaque-based comparison of FD-OCT findings

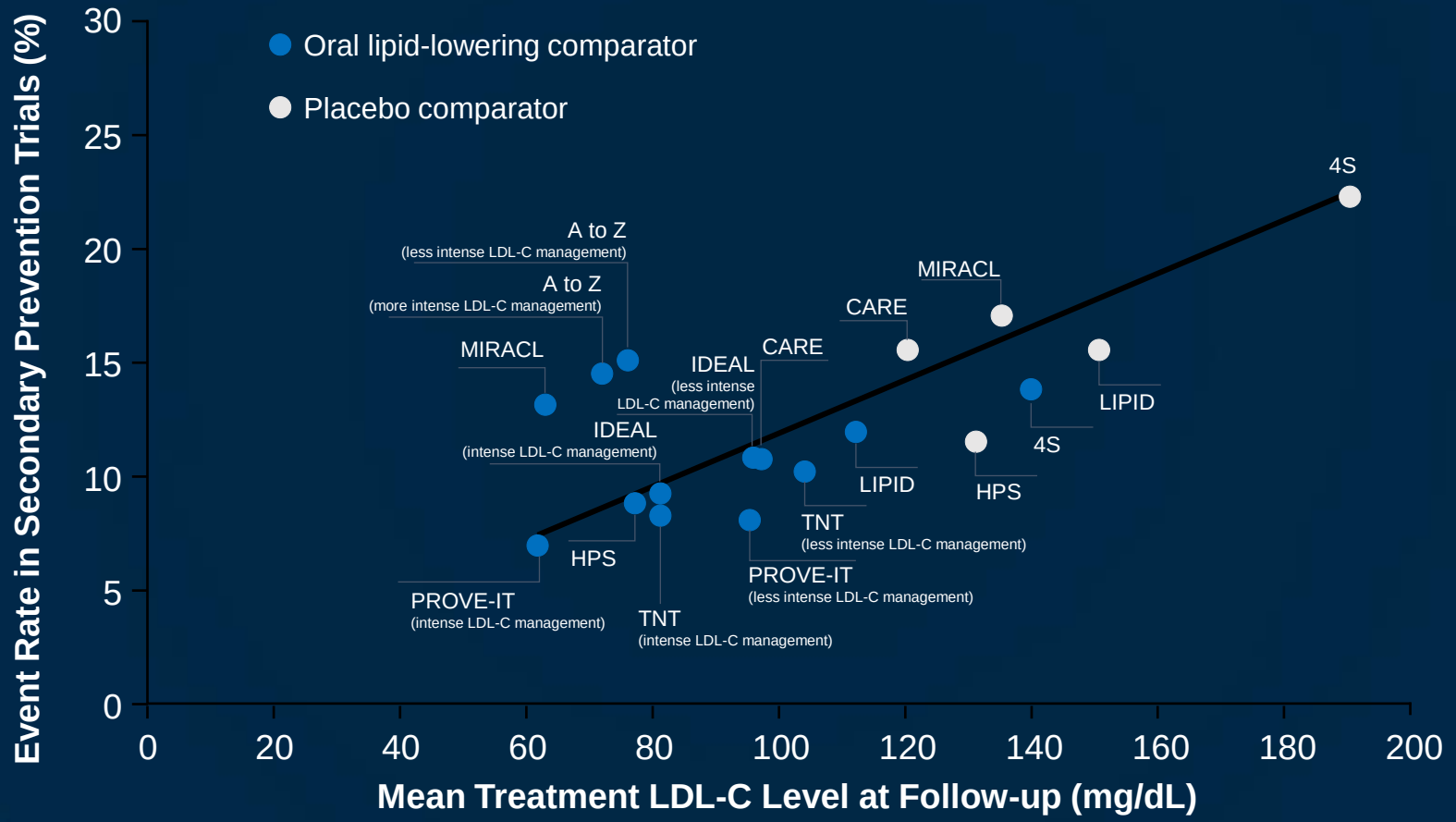
	LDL-C < 50 mg/dL (87 plaques)	LDL-C 50–70 mg/dL (81 plaques)	LDL-C 70–100 mg/dL (117 plaques)	LDL-C > 100 mg/dL (130 plaques)	*P*-value
Plaque location					
LAD, n (%)	40 (46.1)	40 (49.3)	68 (58.1)	67 (51.5)	0.48
LCX, n (%)	23 (26.4)	25 (30.9)	29 (24.7)	43 (33.1)	0.50
RCA, n (%)	24 (27.5)	16 (19.8)	20 (17.2)	20 (15.4)	0.89
Characteristics of plaques					
Fibrous Plaque, n (%)	**45 (51.7)**	**35 (43.2)**	**26 (22.2)**	**16 (12.3)**	**0.01**
Lipid plaques, n (%)	**42 (48.2)**	**46 (56.7)**	**91 (77.7)**	**114 (87.6)**	**0.01**
Lipid content at lipid plaques (n = 293)					
Averaged lipid Arc (°)	**173 ± 76**	**175 ± 88**	**196 ± 102**	**234 ± 85**	**0.01**
Lipid length (mm)	5.9 ± 6.1	5.8 ± 7.0	6.2 ± 5.8	6.7 ± 6.8	0.12
Plaque microstructures at lipid plaques (n = 293)					
Fibrous cap thickness (um)	**139.9 ± 93.9**	**103.1 ± 66.4**	**92.5 ± 48.5**	**92.1 ± 47.8**	**0.001**
TCFA, n (%)	**2/42 (4.7)**	**4/46 (8.6)**	**15/91 (16.4)**	**29/114 (25.4)**	**0.01**
Microchannel, n (%)	3/42 (7.1)	7/46 (15.2)	15/91 (16.4)	24/114 (21.1)	0.14
Plaque rupture, n (%)	1/42 (2.3)	2/46 (4.3)	7/91 (7.6)	12/114 (10.5)	0.17
Thrombus, n (%)	0/42 (0.0)	1/46 (2.1)	2/91 (2.1)	3/114 (2.6)	0.18

FD-OCT = frequency-domain optical coherence tomography, LAD = left anterior descending artery, LCX = left circumflex artery, LDL-C = low-density lipoprotein cholesterol, RCA = right coronary artery, TCFA = thin-cap fibroatheroma.

Kataoka Y, et al. *Atherosclerosis*. 2015;242:490-495.

There Is a Linear Correlation Between LDL-C Lowering and Lowering Risk of CV Events in Statin Trials[1,2]

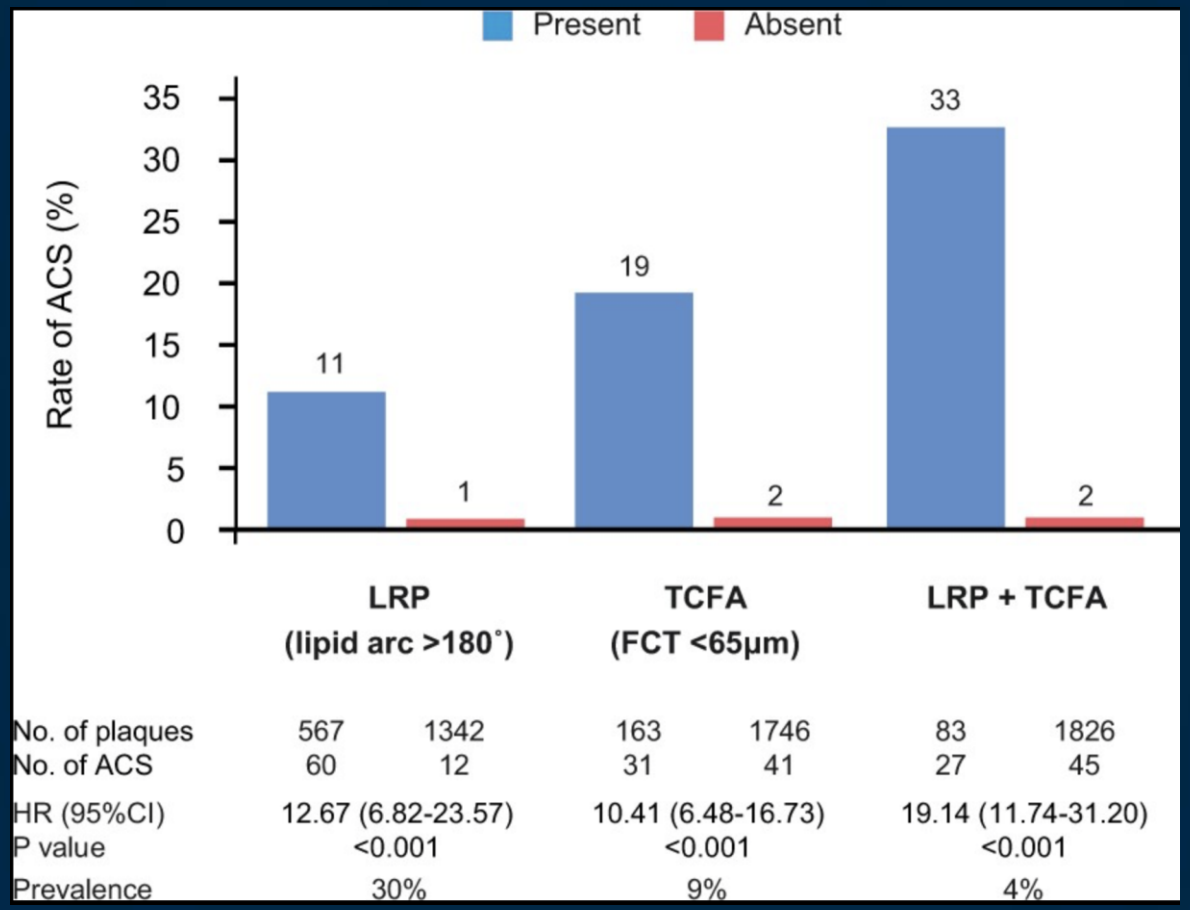
CTTC Meta-analysis of major lipid secondary prevention statin trials conducted in 2010: Median follow-up ~ 5 years, N = 169,138[2]



CTTC = Cholesterol Treatment Trialists' Collaboration.

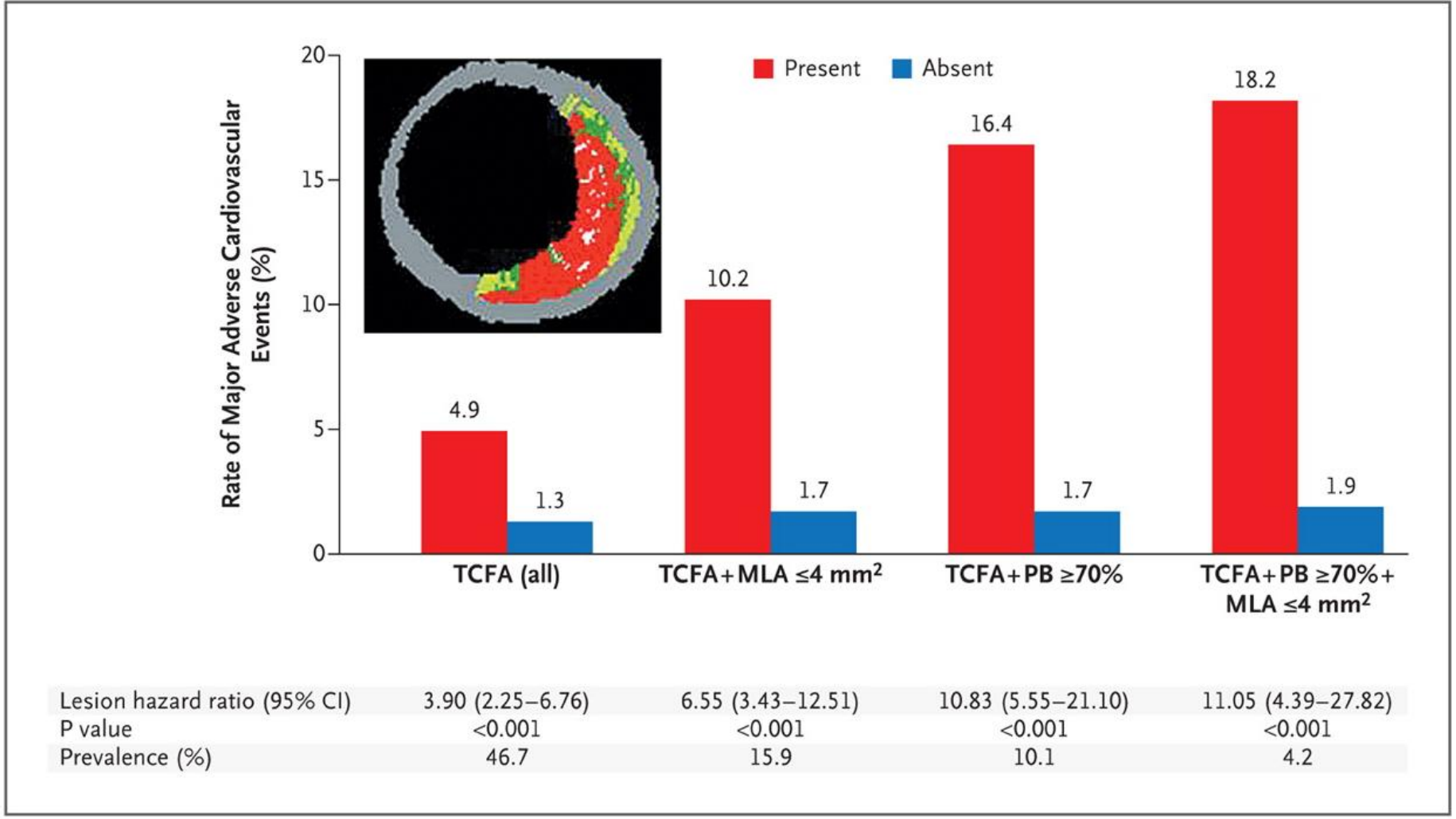
1. Raymond C, et al. *Clev Clin J Med*. 2014;81:11-19. 2. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2010;376:1670-1681.

Characteristics of non-culprit plaques which went on to cause events



No. of plaques	567	1342	163	1746	83	1826
No. of ACS	60	12	31	41	27	45
HR (95%CI)	12.67 (6.82-23.57)		10.41 (6.48-16.73)		19.14 (11.74-31.20)	
P value	<0.001		<0.001		<0.001	
Prevalence	30%		9%		4%	

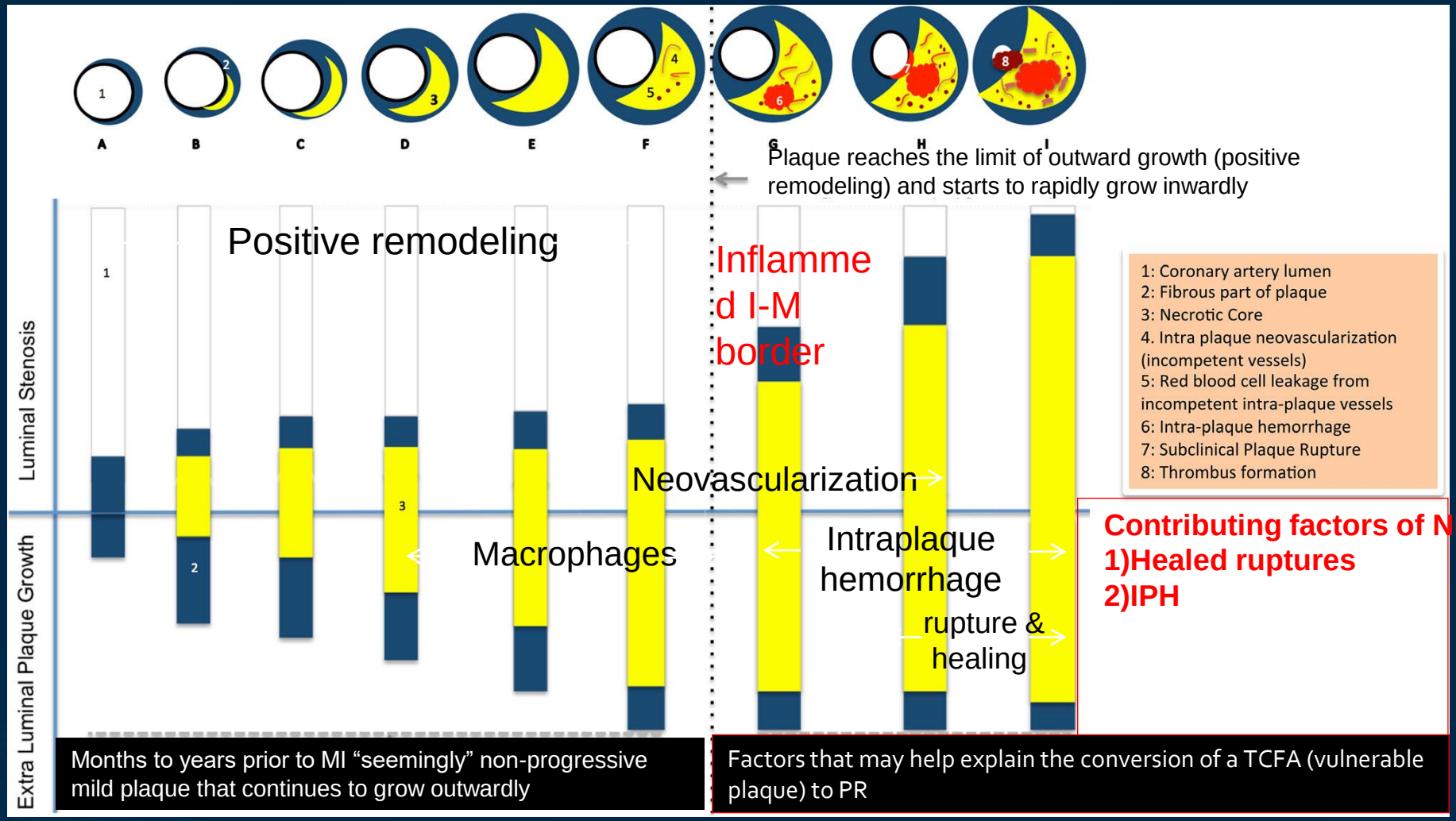
Kubo T, Ino Y, Mintz GS, et al. Optical coherence tomography detection of vulnerable plaques at high risk of developing acute coronary syndrome. *Eur Heart J Cardiovasc Imaging*. 2021. 10.1093/ehjci/jeab028; PMID: 33619524



Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

TCFA+PB>70%+MLA<4md conferred a hazard ratio of 11.05
yet 88.2 percent of patients with similar plaques did not have a MACE events
Most of these events were for angina not MI– and in the vast majority of so called high risk plaque there was no events at all!
Event rate in plaques without these features was also not insubstantial

Mechanisms contributing to the rapid plaque progression before Plaque Rupture

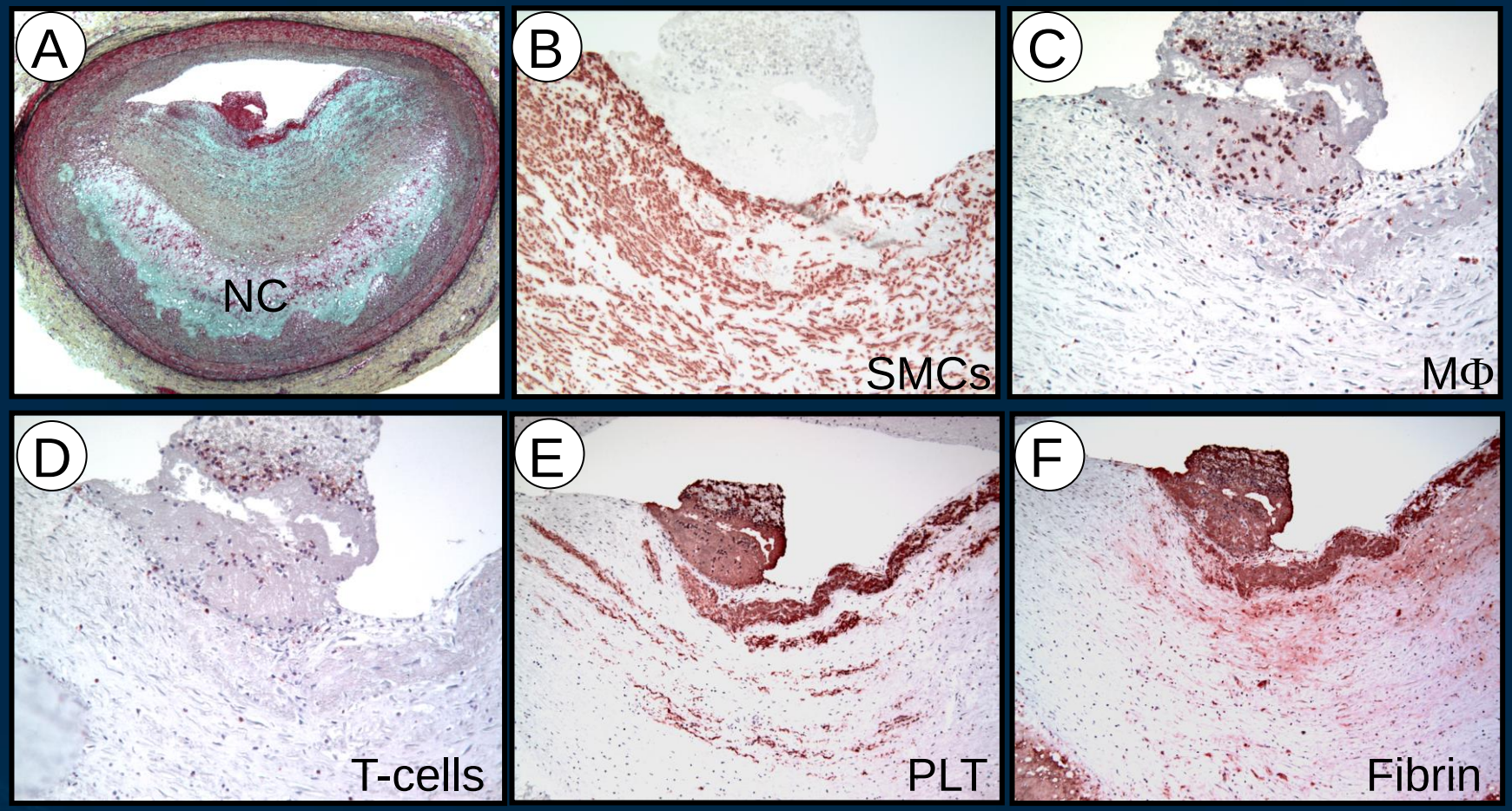


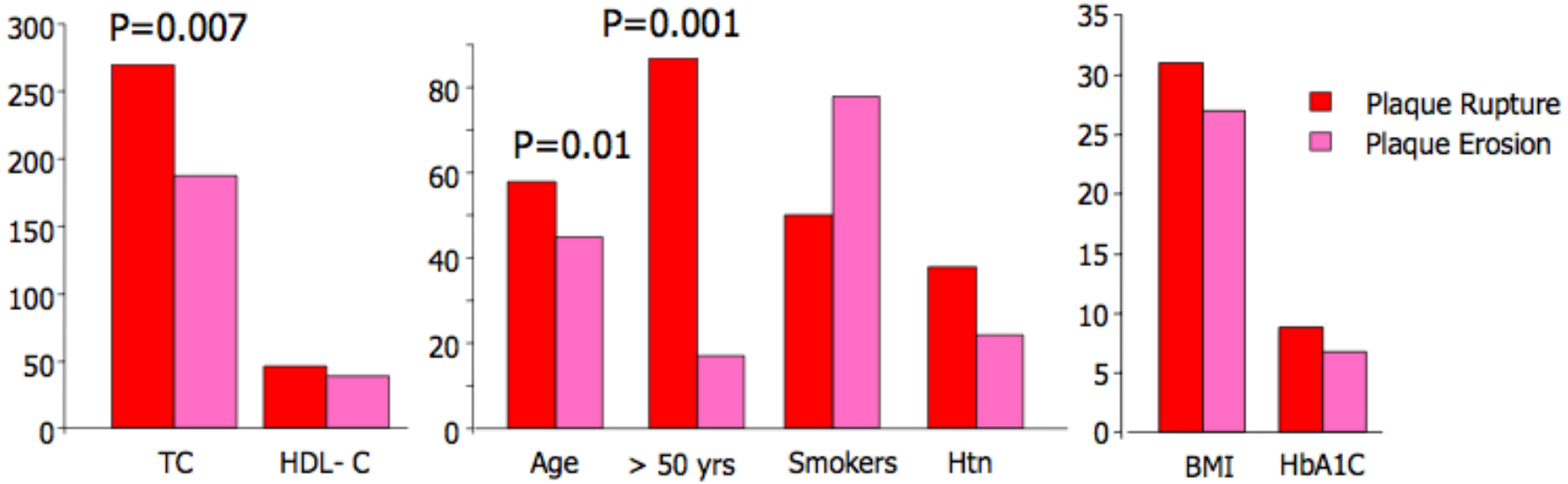
Modified from Ahmadi et al. Circ Res. 2015;117:99-104

Plaque Erosion

Plaque Erosion: 30-35% of thrombi in SCD

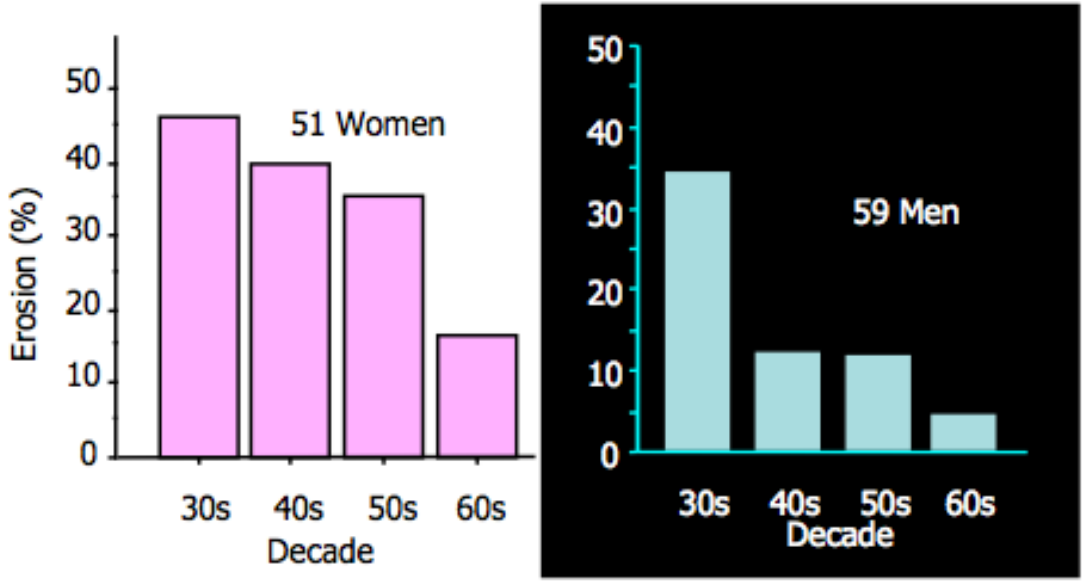
Plaque erosion in a 33 year-old female complaining of chest pain for two-weeks and discharged from the emergency room with a diagnoses of anxiety.



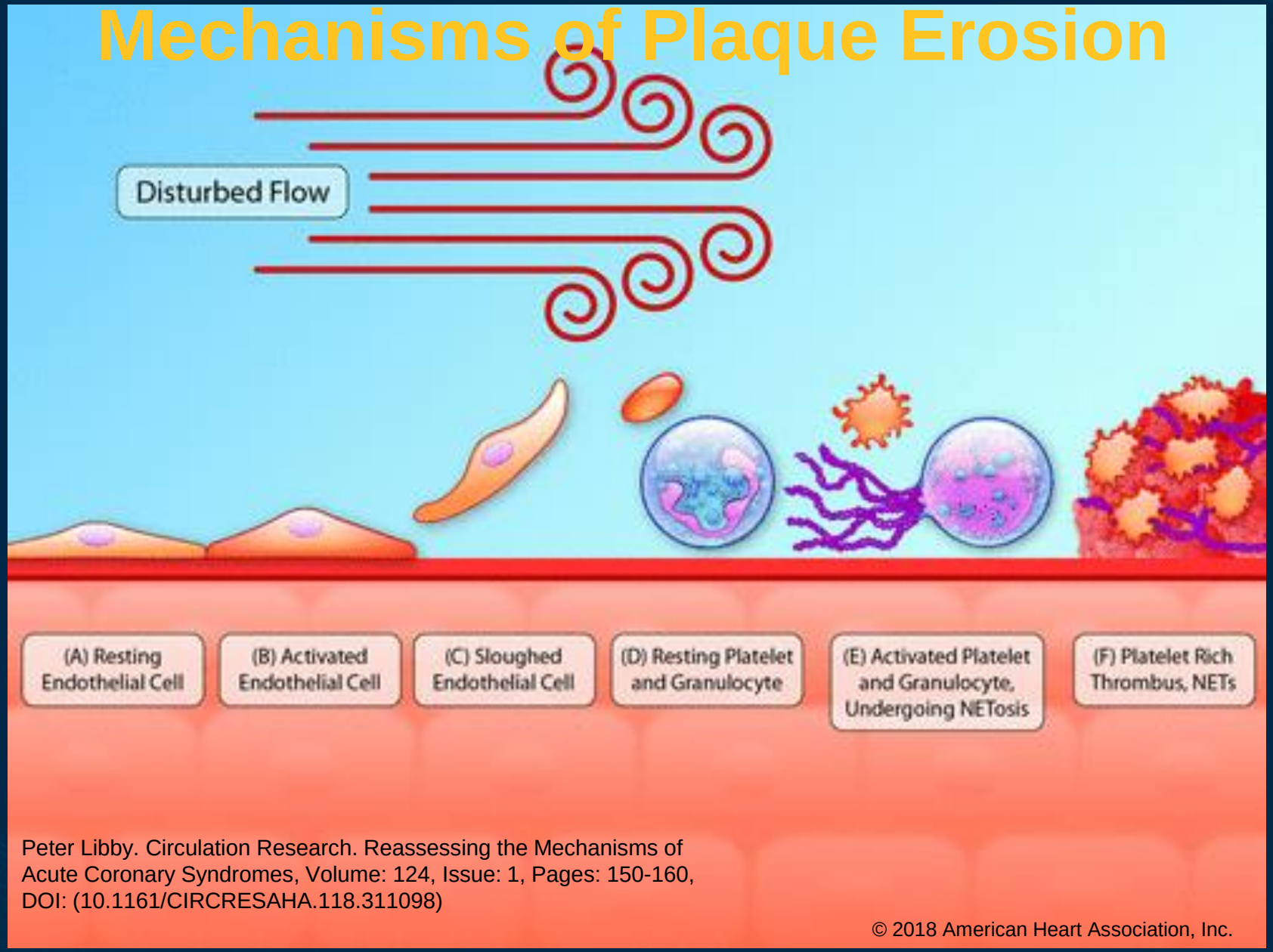


Women with Severe Coronary Atherosclerosis

Burke et al. Circulation 1999



Mechanisms of Plaque Erosion

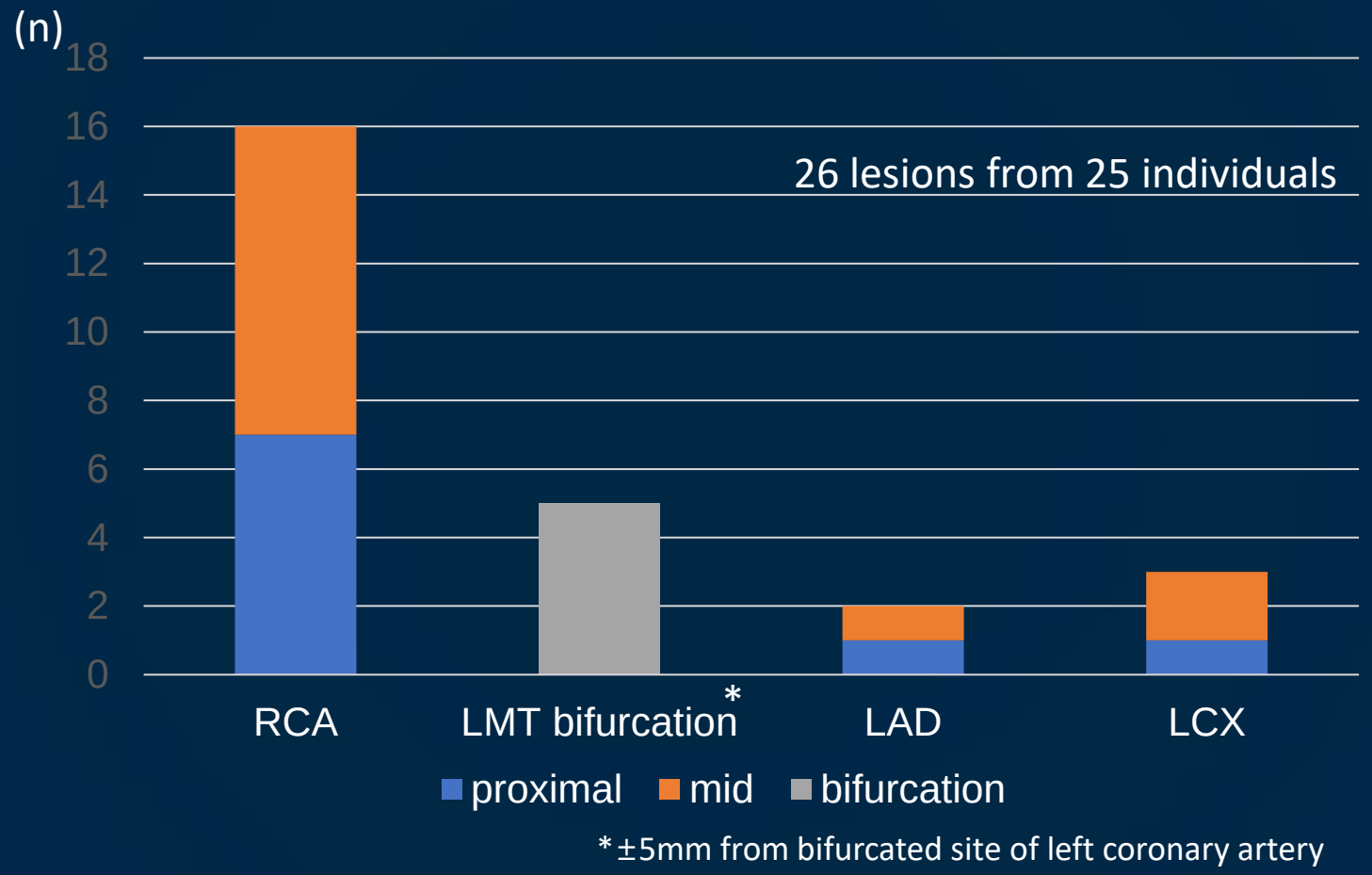


Peter Libby. Circulation Research. Reassessing the Mechanisms of Acute Coronary Syndromes, Volume: 124, Issue: 1, Pages: 150-160, DOI: (10.1161/CIRCRESAHA.118.311098)

Calcified nodules

2-7% of thrombi in SCD

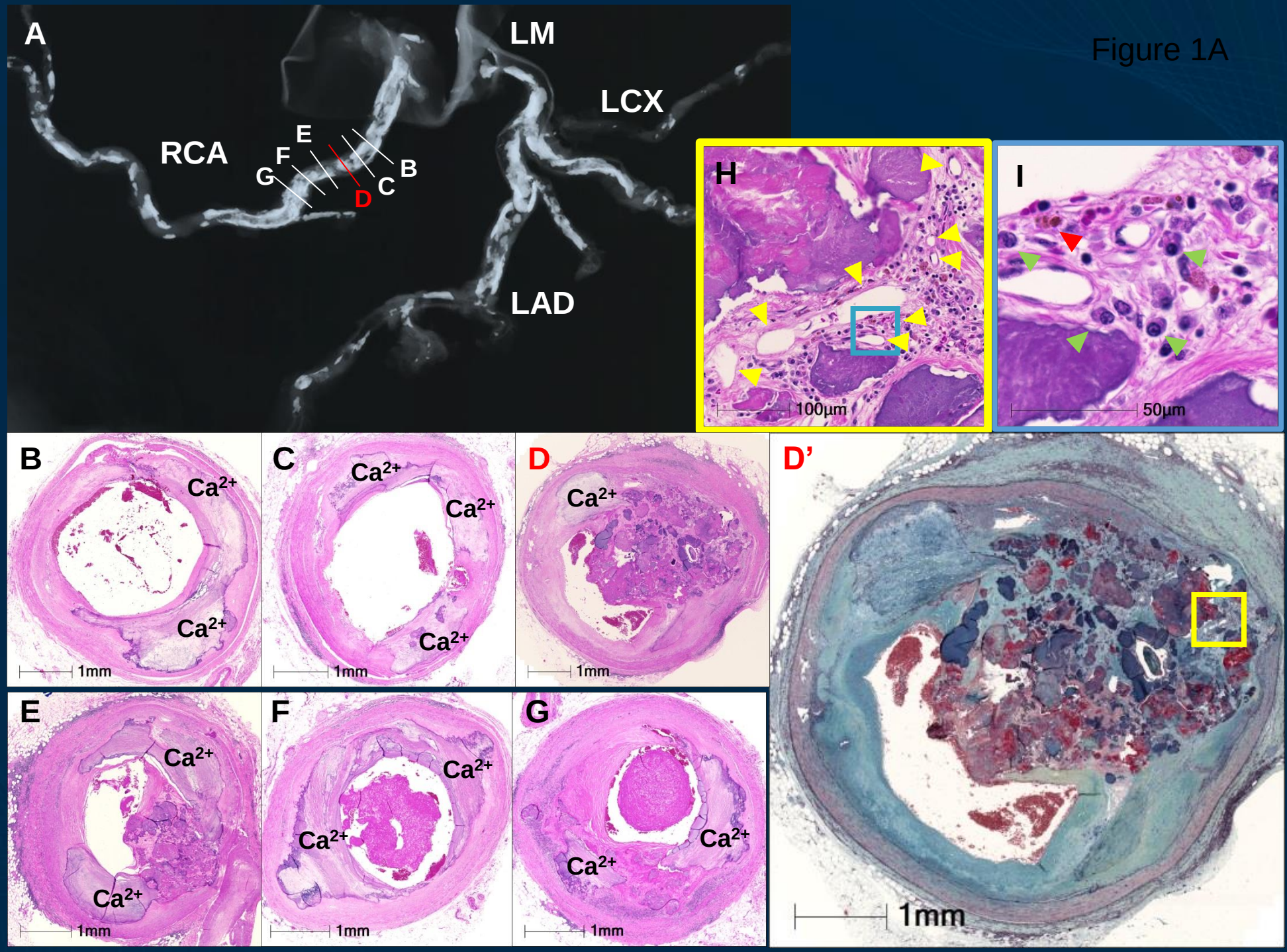
Coronary distribution of calcified nodule lesions



*±5mm from bifurcated site of left coronary artery

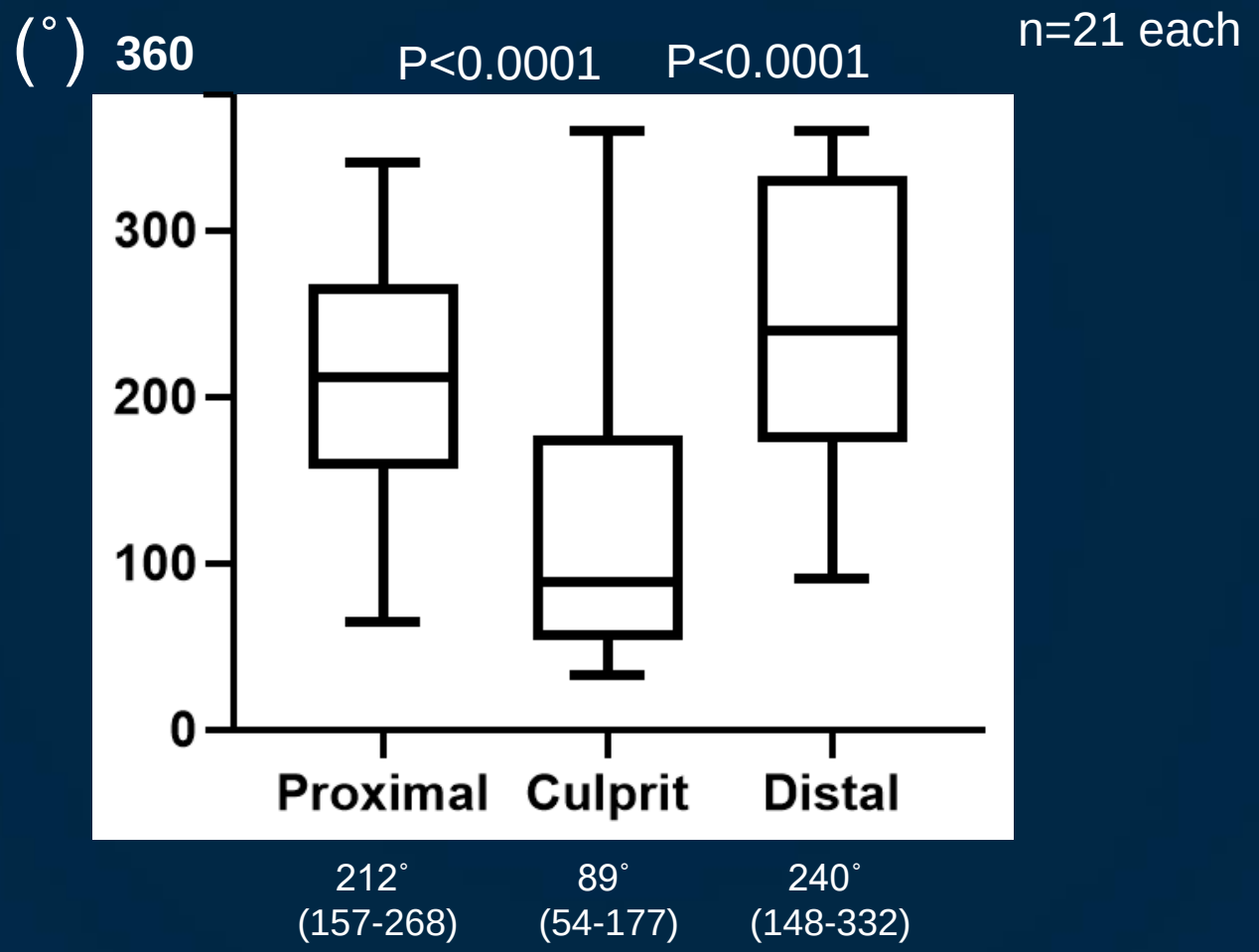
Figure 1A

A 79-year-old woman with a past medical history of hypertension, diabetes, coronary artery disease, and congestive heart failure, who died suddenly



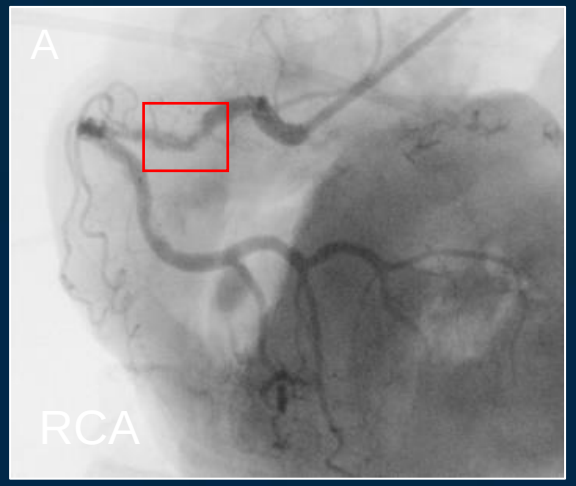
Degree of circumferential sheet calcification in proximal, culprit, and distal section of calcified nodule

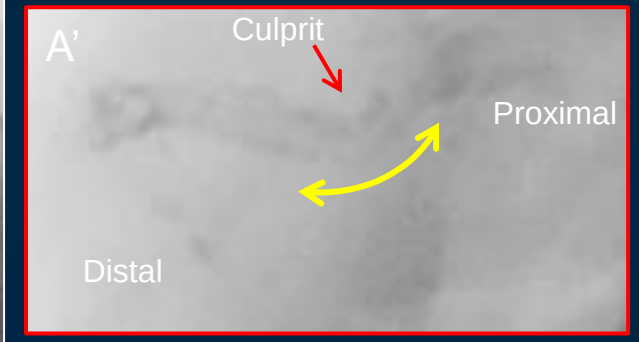
Figure 1B

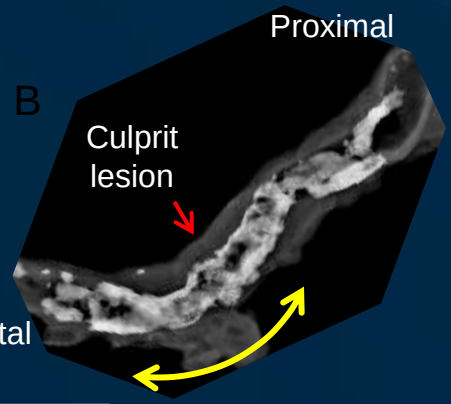


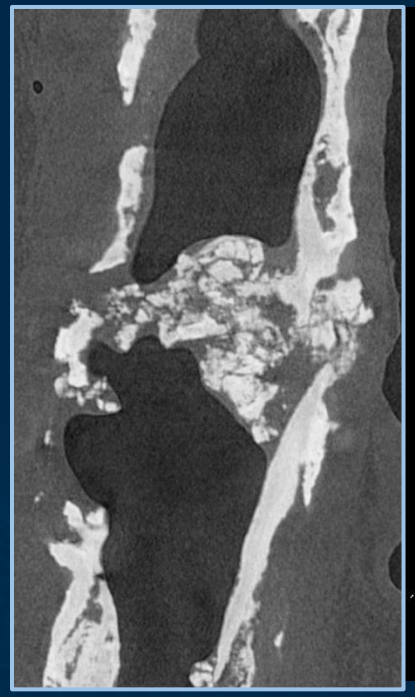
Heart without consecutive vessel section (n=4), or post stent implantation (n=1) were excluded.

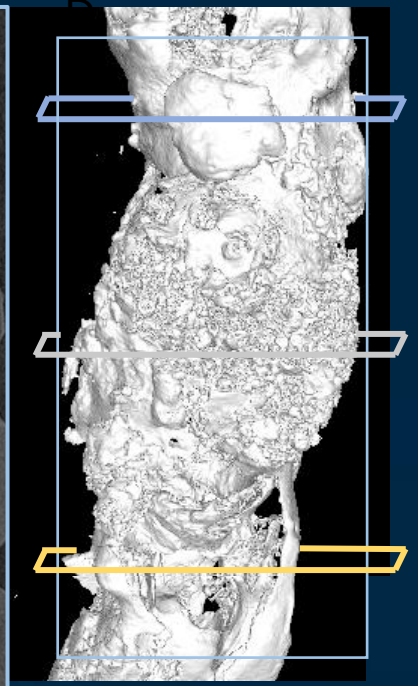
Proximal and distal sections are taken from the maximum value within 1 cm (1-3 sections) from the culprit site

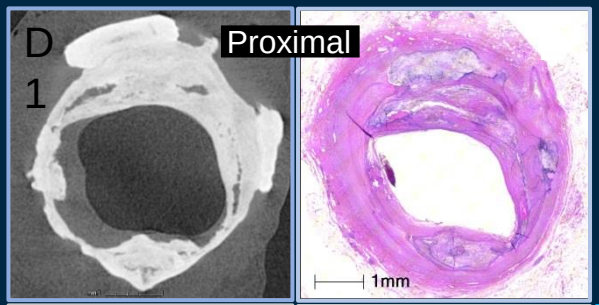

A
RCA


A'
Culprit
Proximal
Distal

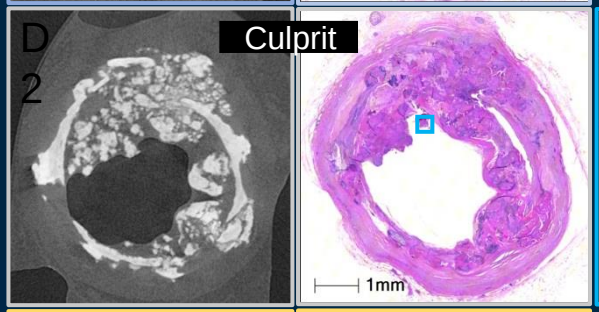

B
Proximal
Culprit lesion
Distal


C
Proximal
Distal

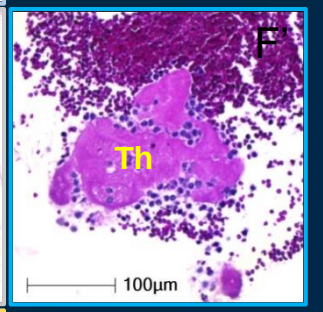

D
Proximal
Distal

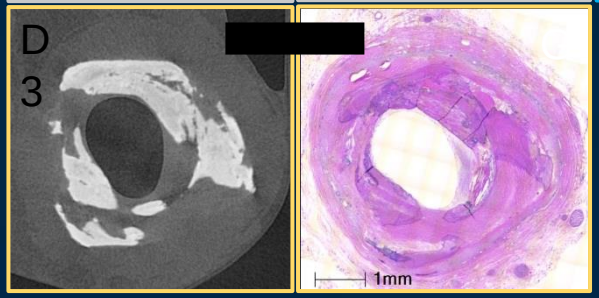

D
1
Proximal

1mm


D
2
Culprit

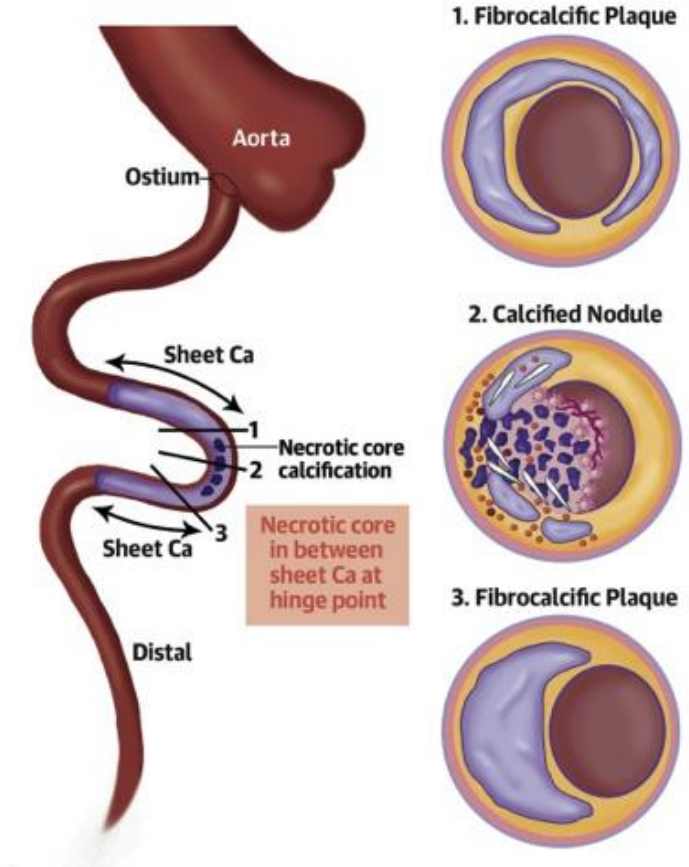
1mm

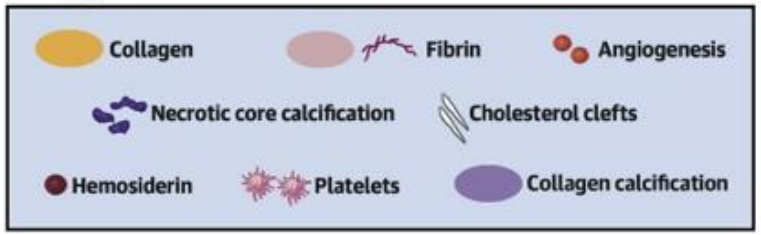

F'
Th
100μm


D
3

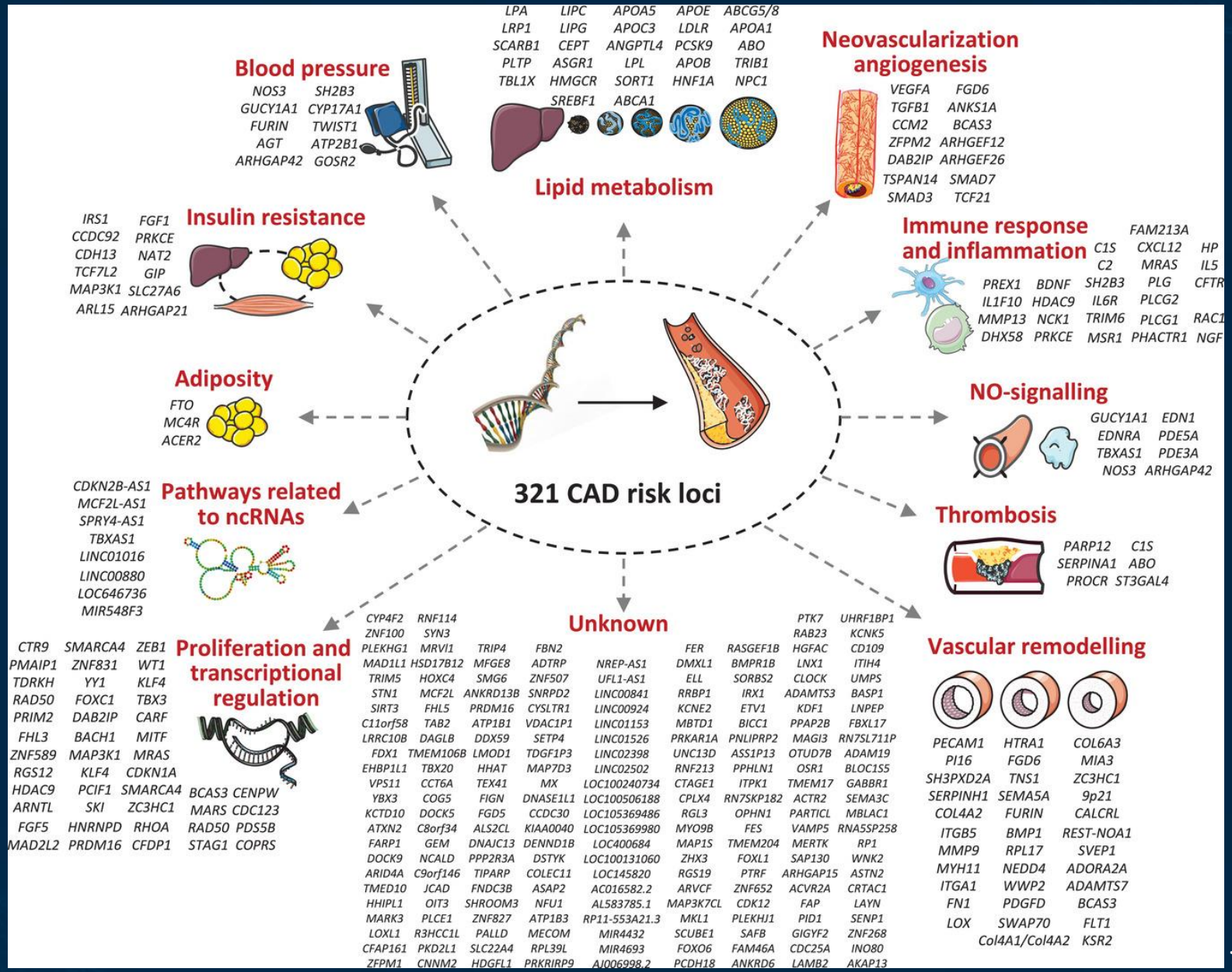
1mm

CENTRAL ILLUSTRATION: Proposed Mechanism of the Occurrence of Calcified Nodule



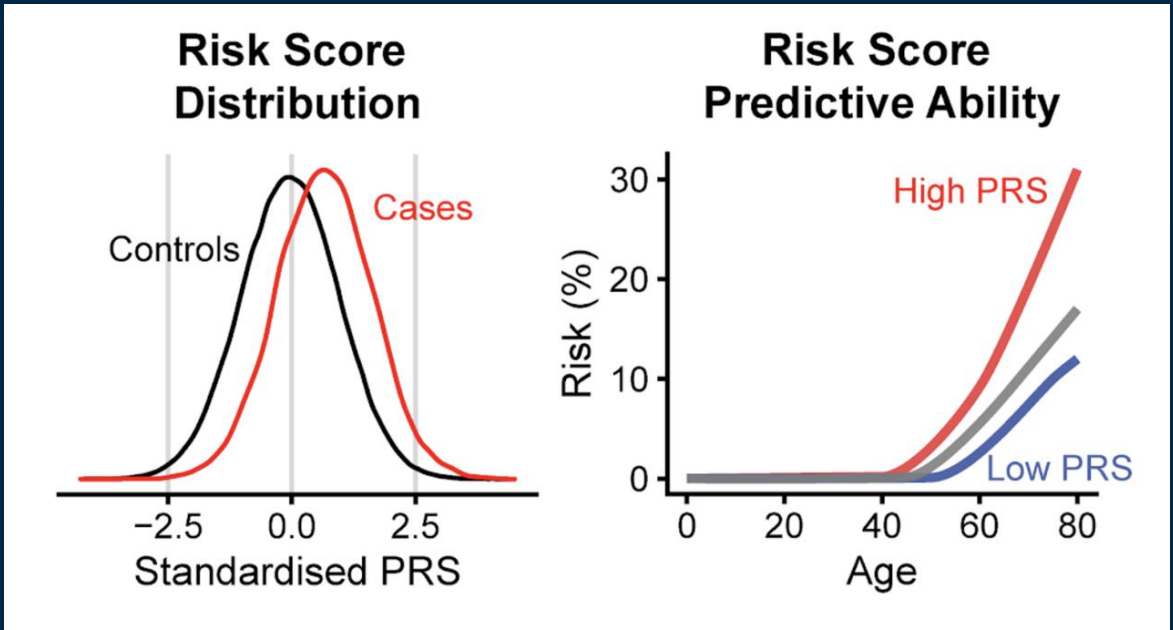


Torii, S. et al. J Am Coll Cardiol. 2021;77(13):1599-611.



Chen & Schunkert,
Journal of Internal Medicine, 2021

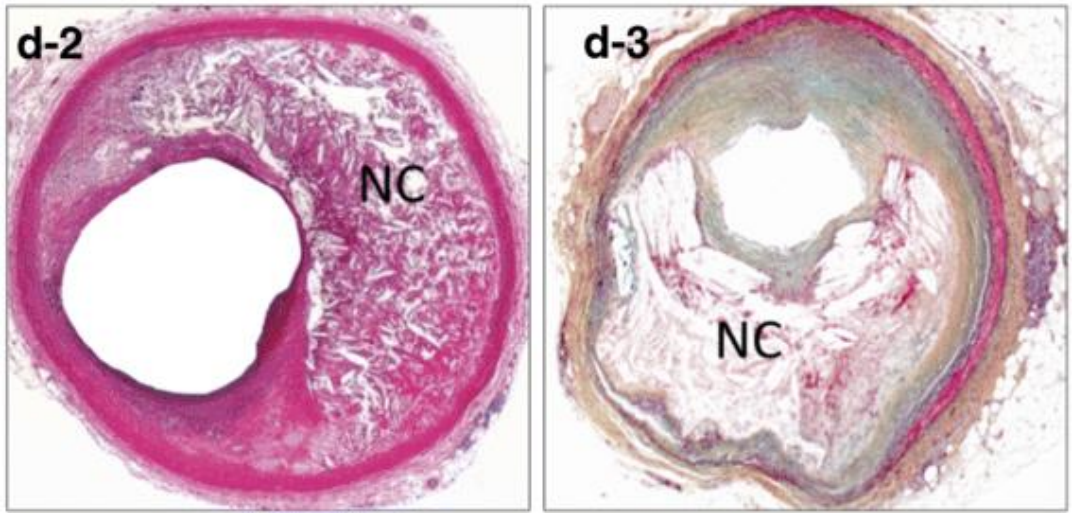
Polygenic Risk Scores and Cardiovascular Diseases

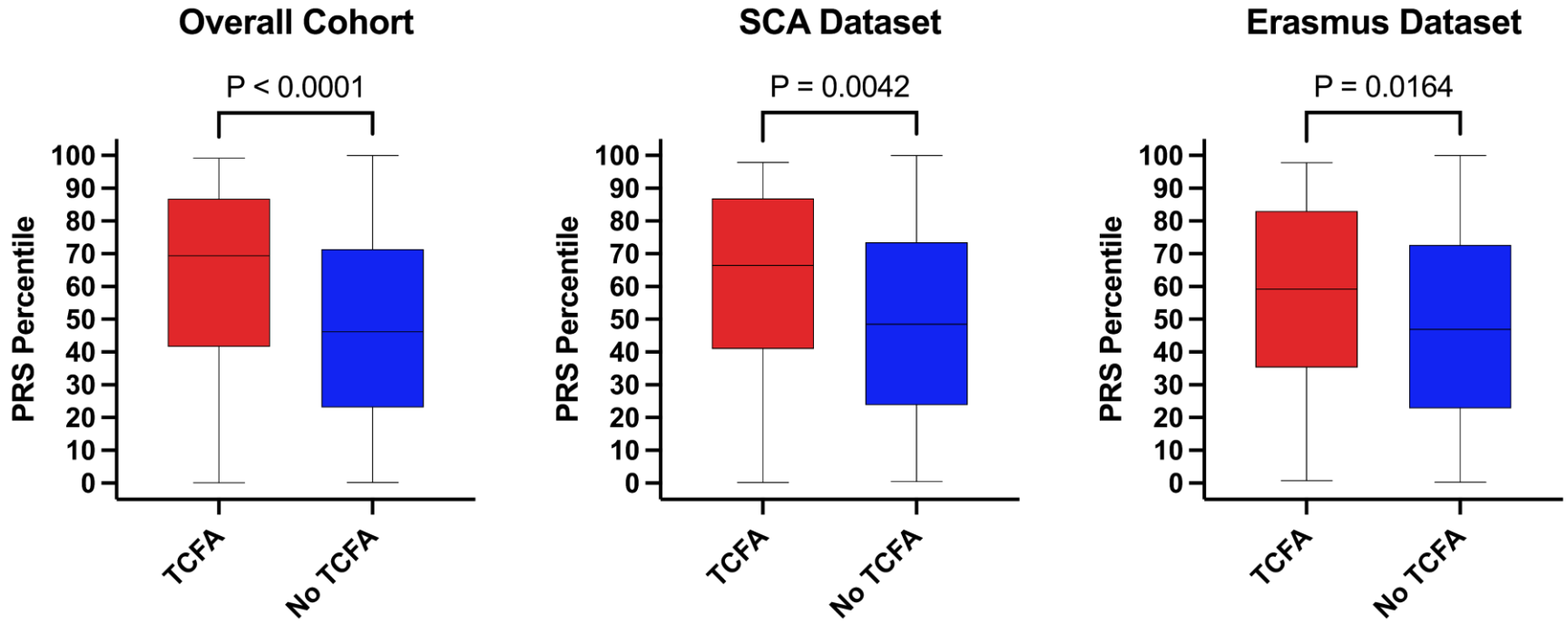


Polygenic Risk Scores (PRS)…

- summarize the estimated effect of a number of genetic variants on an individual's phenotype
- typically calculated as a weighted sum of trait-associated alleles
- generated from genome-wide association study (GWAS) data

Associations with Thin-Cap Fibroatheroma





New Insights into Plaque Vulnerability

- Plaque rupture, Plaque erosion, and Calcified Nodule are all causes of intracoronary thrombosis
- Vulnerable plaques (TCFA) is a likely precursor lesions of rupture. Lipid Metabolism and inflammation play an important role in plaque progression towards rupture.
- Intraplaque hemorrhages are responsible for enlargement of necrotic core, plaque progression and may be an important target for imaging.
- The risk factors for plaque erosion remain poorly understood but the pathophysiology of this disease involves shear induced alternations in endothelial function leading to endothelial damage and thrombus formation
- Calcified nodule is a poorly understood entity. Our data suggests that fibrous cap disruption in calcified nodule and overlying thrombosis is initiated through the fragmentation of calcified necrotic cores which is flanked between areas of hard circumferential sheet calcification in highly tortuous coronary arteries.
- Genetic Risk Scores will play an important role in primary prevention in the future and may help to decrease the incidence of vulnerable plaques prone to plaque rupture through early access to medical therapies