Can We Predict the Fate of Vulnerable Plaque: Progression or Regression?

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Non-Progressive and Progressive Coronary Plaques
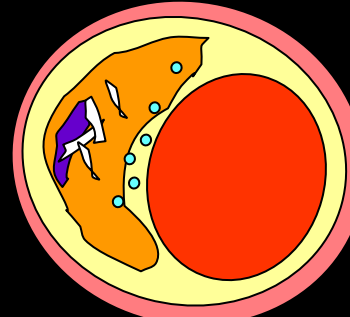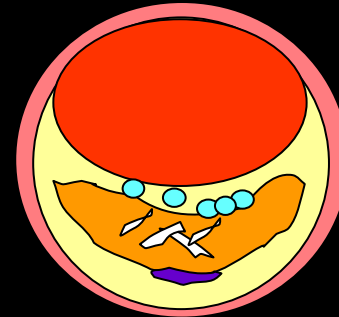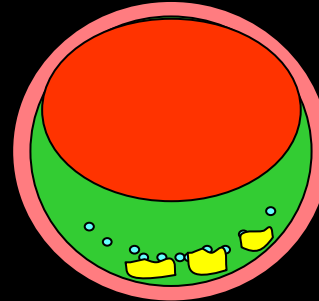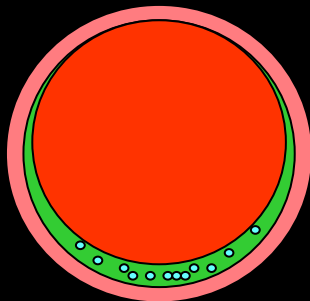

non-progressive

progressive

adaptive intimal thickening

Intimal xanthoma

pathologic intimal thickening

fibroatheroma

thin-cap fibroatheroma

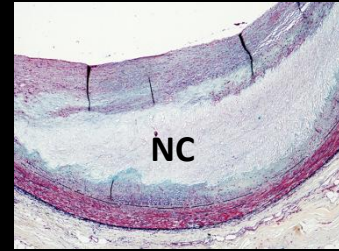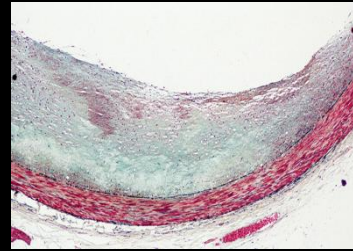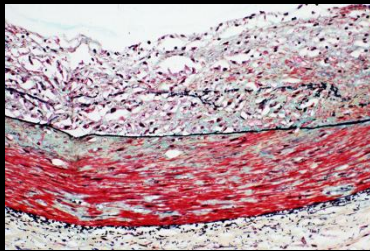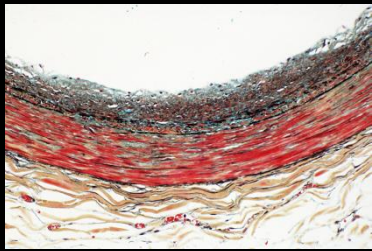NC

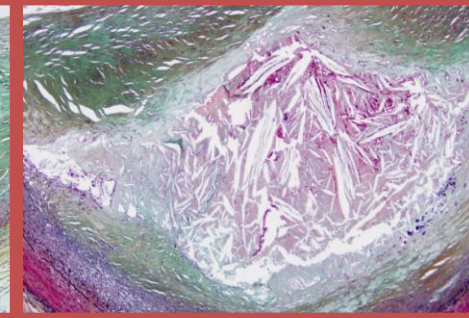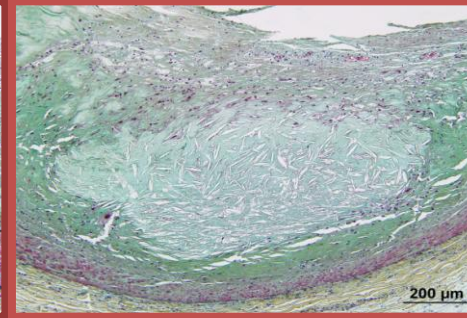NC

FC
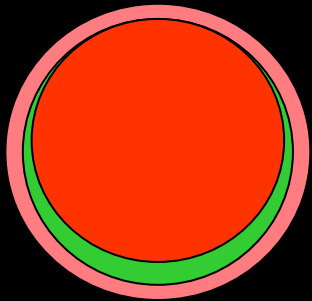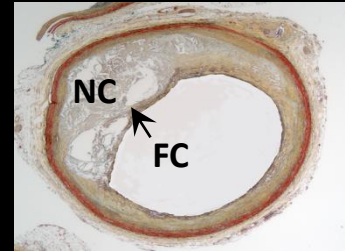
lipid pool

necrotic core
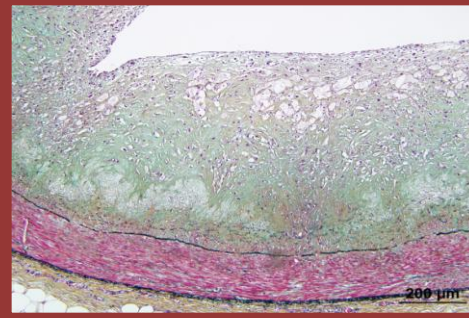
early ⟶ late necrosis

Histomorphometric Analysis of Plaque Component
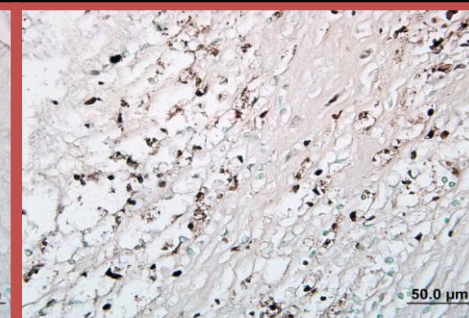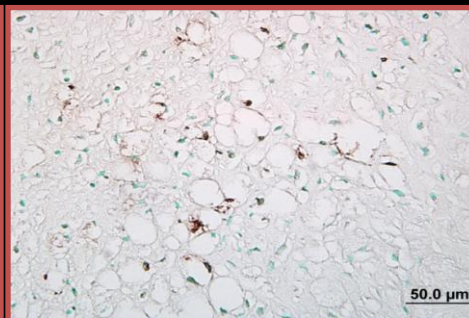
| PIT (no Macs) | PIT (+ Macs) | Early FA | Late FA |

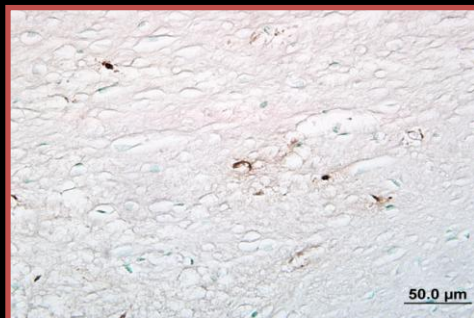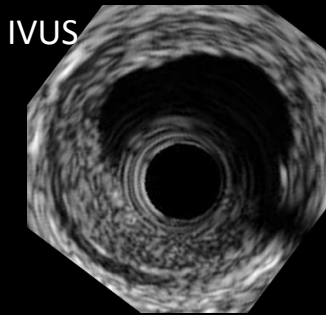## Macrophage (KP-1.CD68)

In-Situ End Labeling (DNA fragmentation, apoptosis)

Plaque Progression: From PIT (LP) to Fibroatheroma (NC)
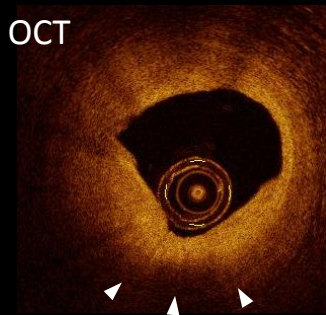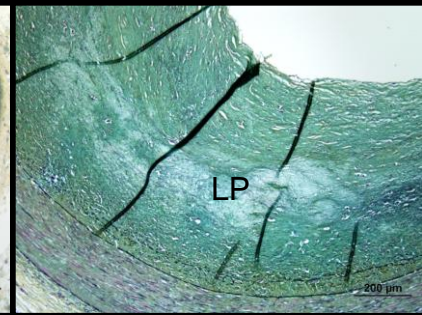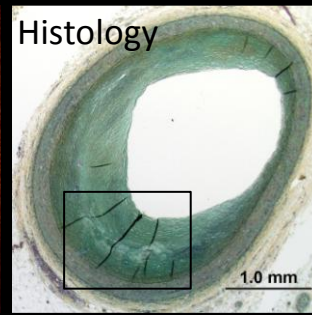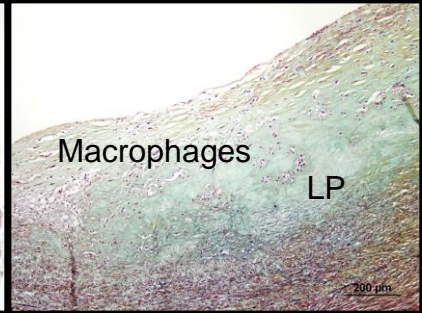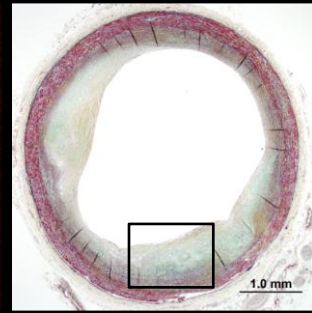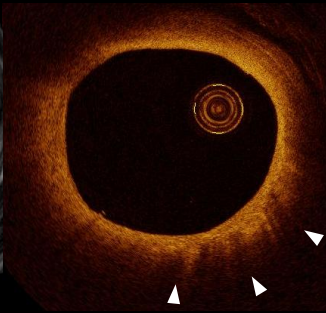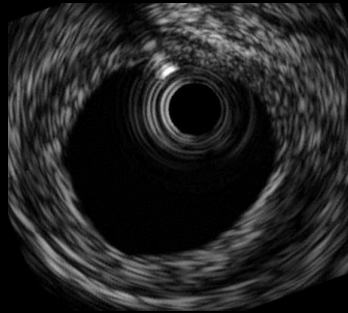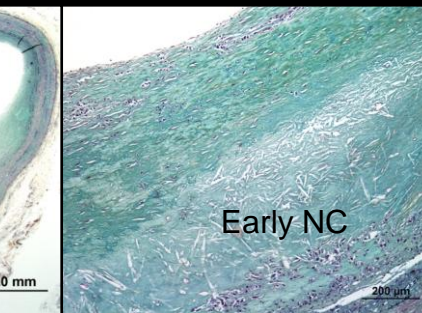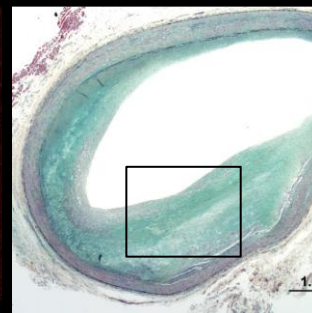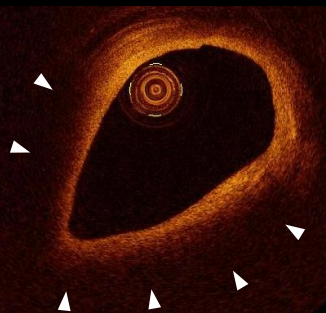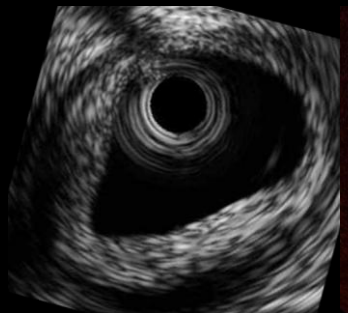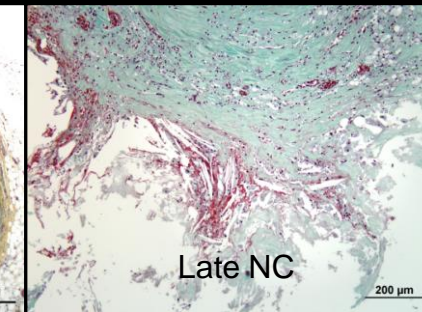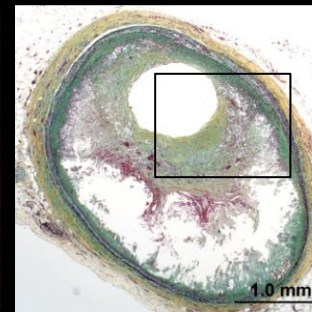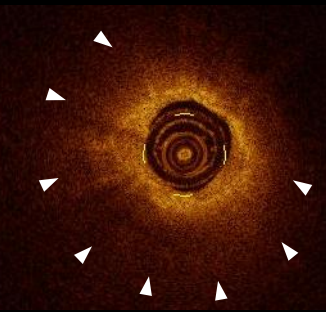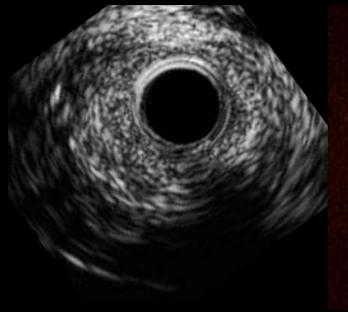
FA=fibroatheroma; LP=lipid pool; NC=necrotic core; PIT=pathologic intimal thickening

Causes of Coronary Thrombosis

Rupture 60 to75%
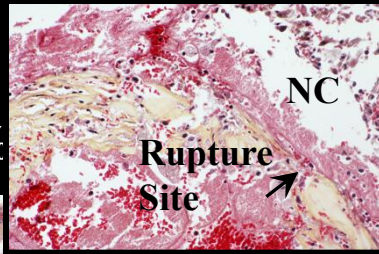
Erosion 30-35%

Calcified nodule (2 to 7%)

Virmani R, et al. Arterioscler Thromb Vasc Biol 2000;20:1262
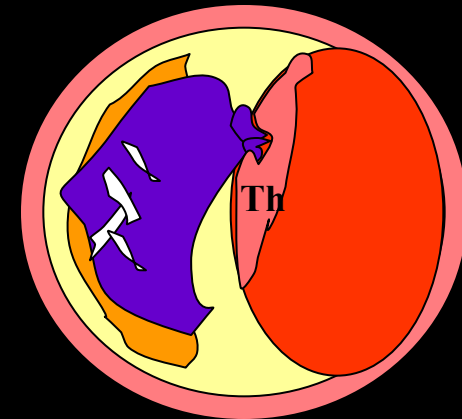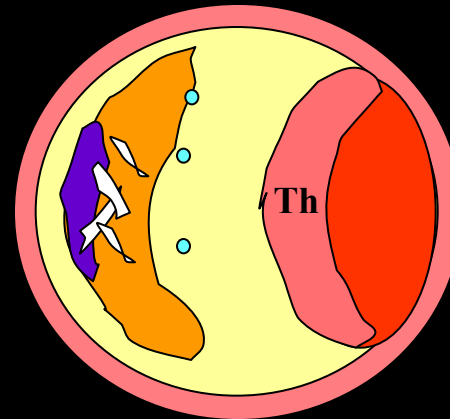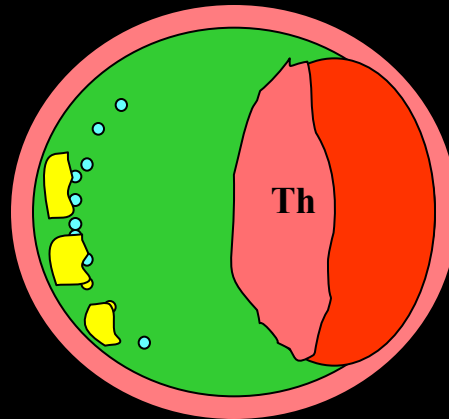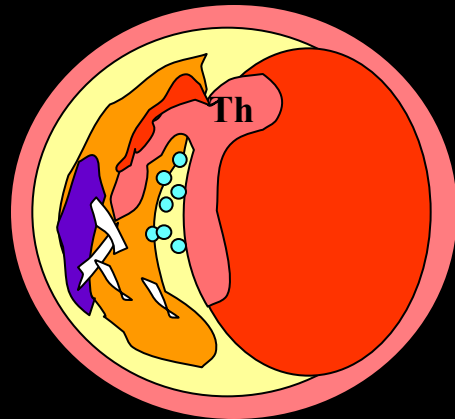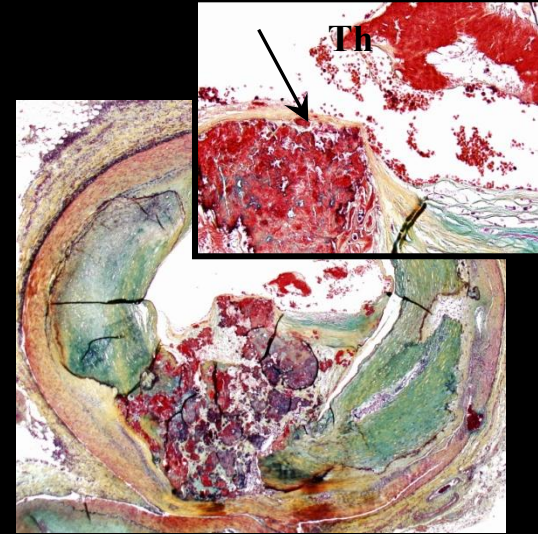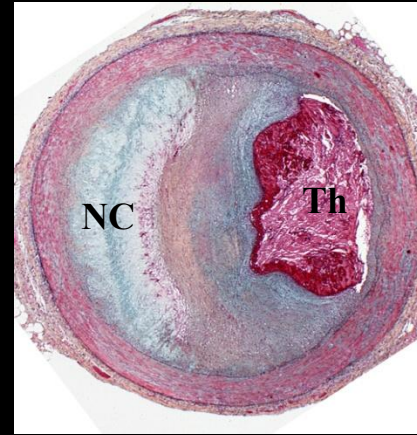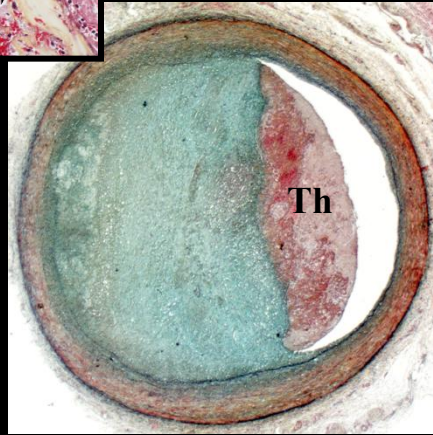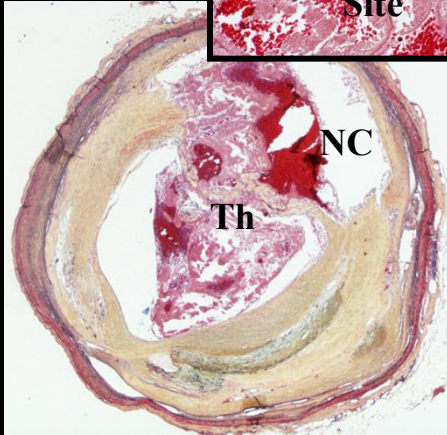
Can we better characterize the differences between these three types of plaques?
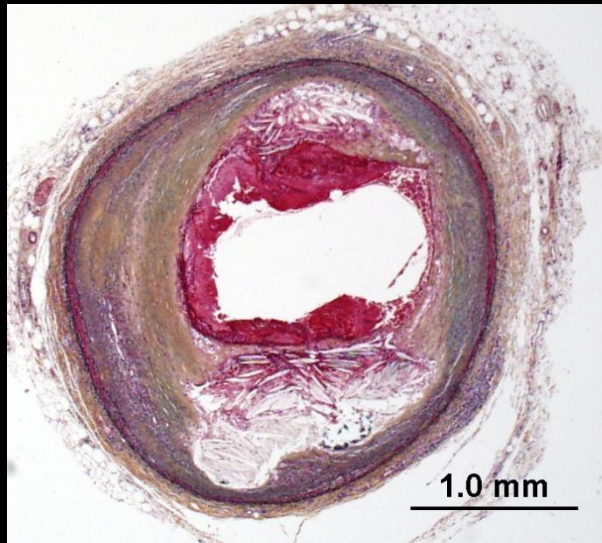
Plaque Rupture	Thin cap fibroatheroma	Fibroatheroma -SP
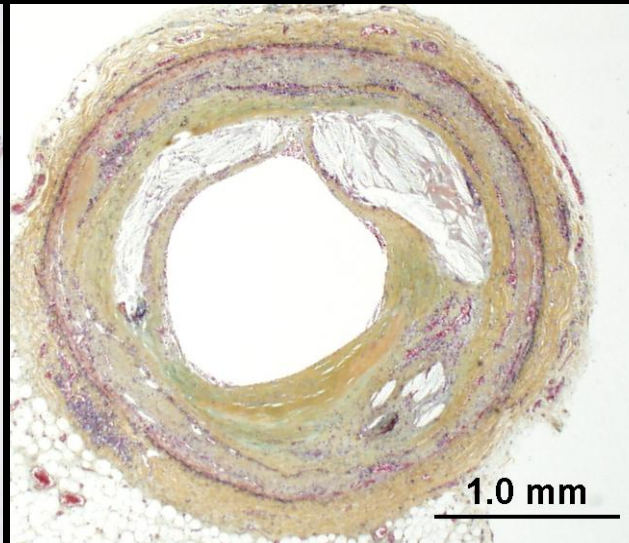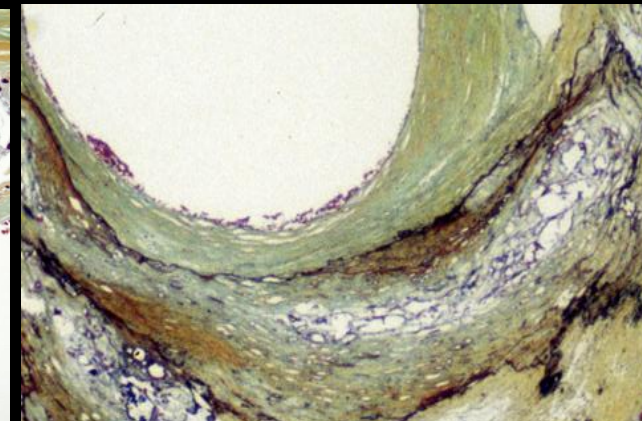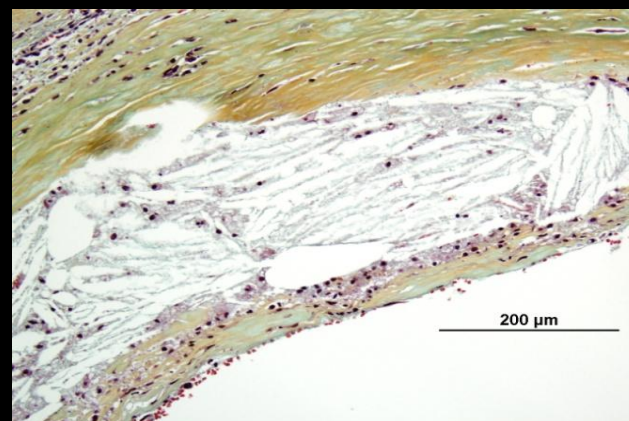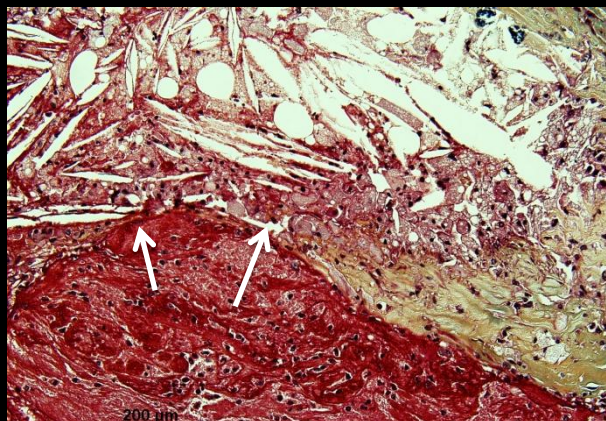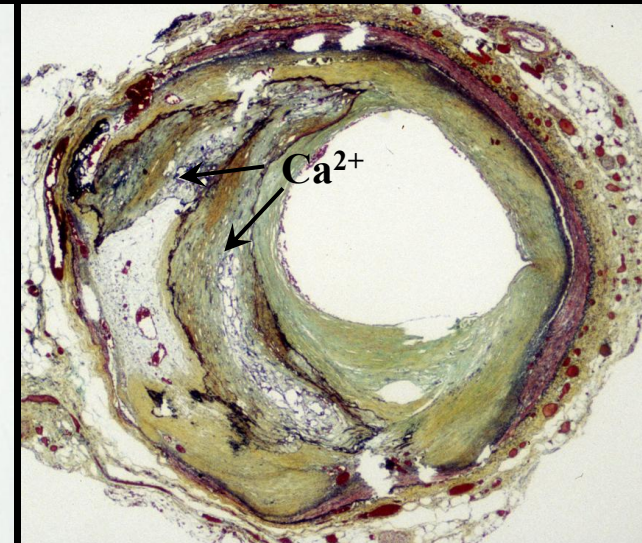
Plaque Rupture and TCFA with Varying Luminal Stenosis
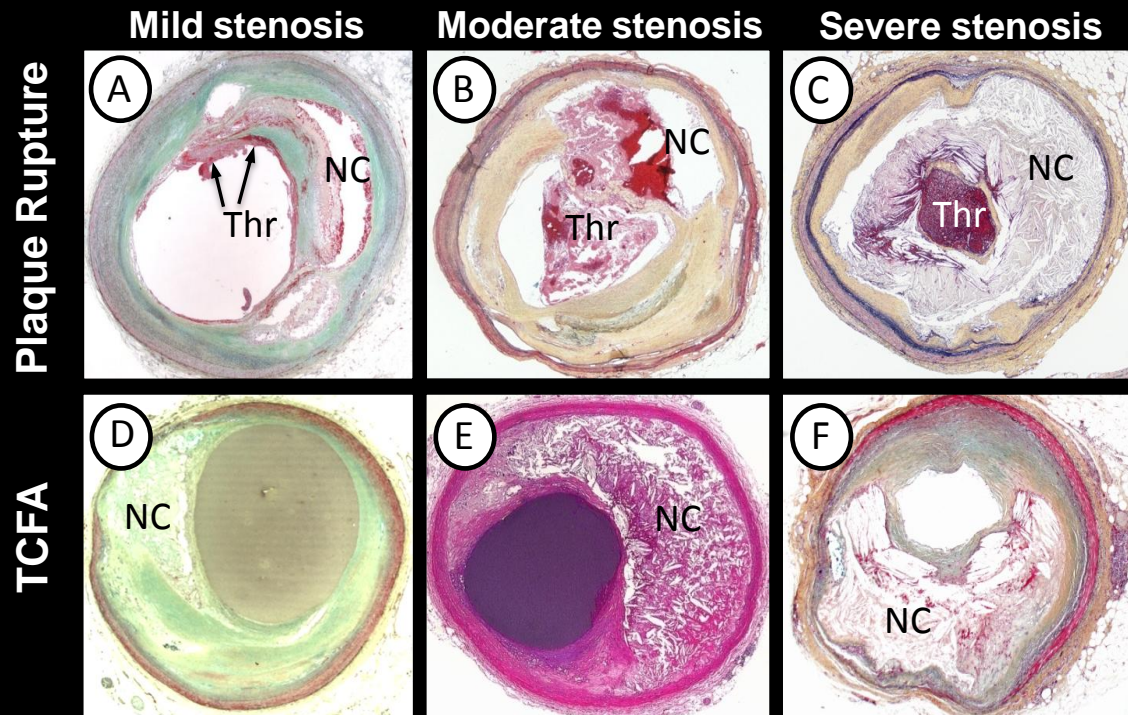
Narula J, Nakano M, et al.
J Am Coll Cardiol 2013;61:1041-51.
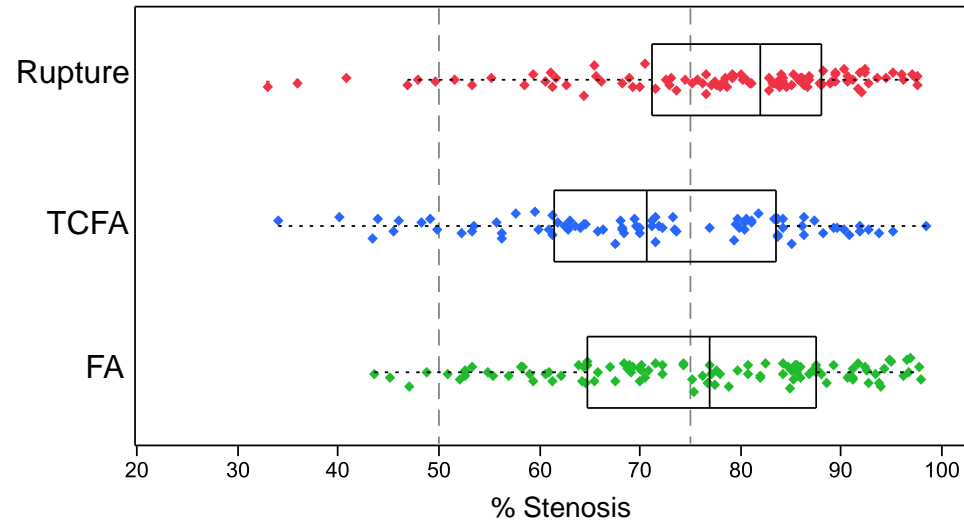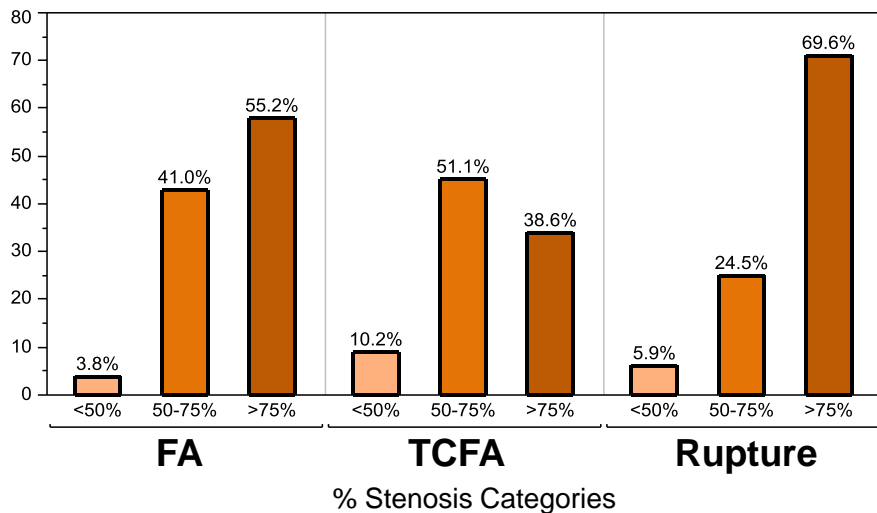
Gross and Light Microscopic Features of Plaque Rupture

60% of Thrombi in Sudden Coronary Death occur form Plaque Rupture
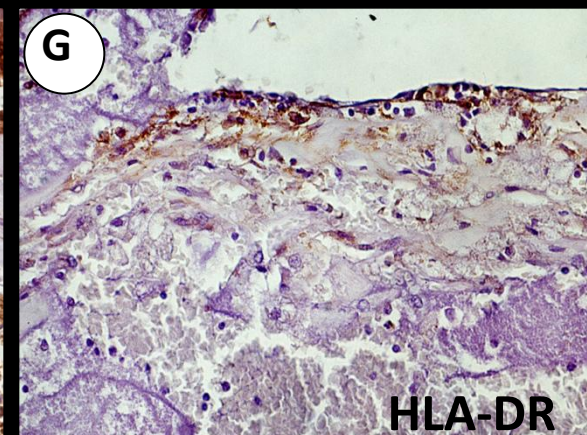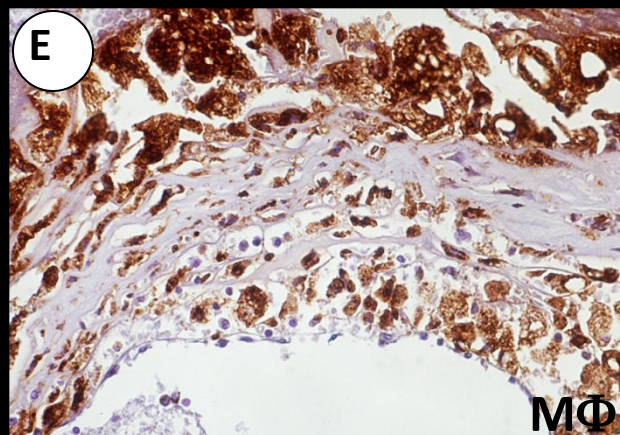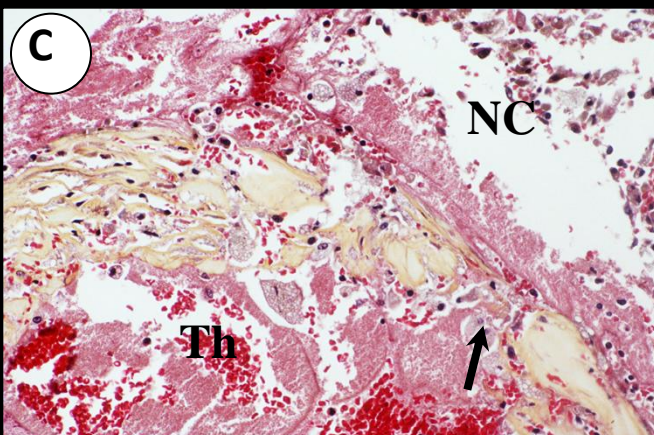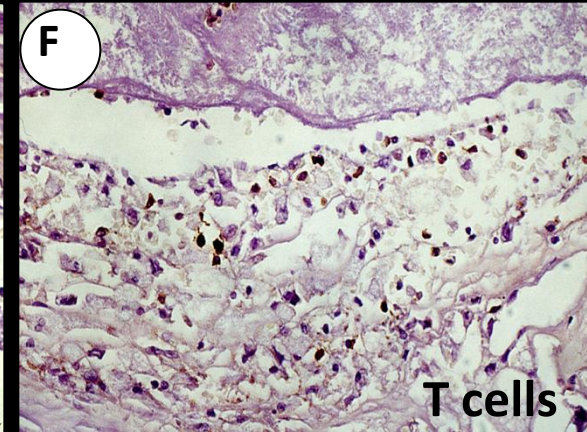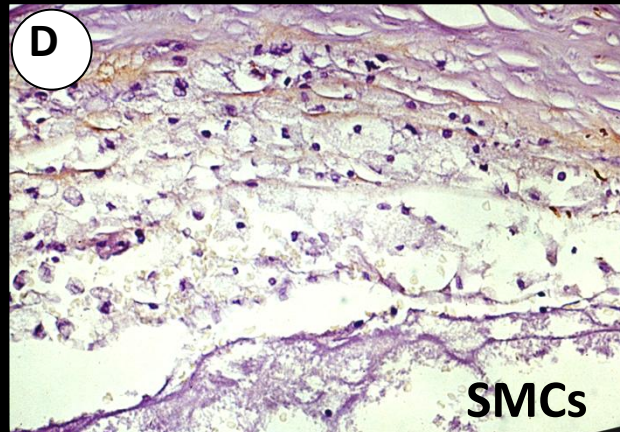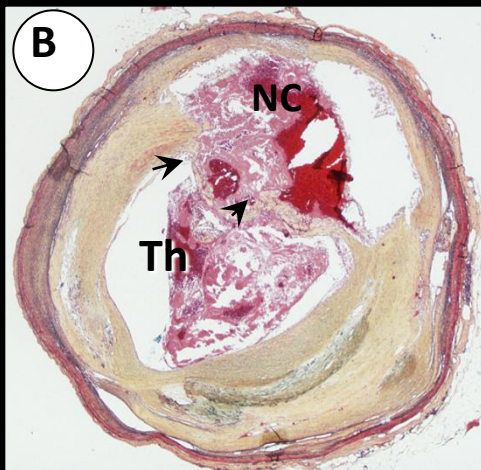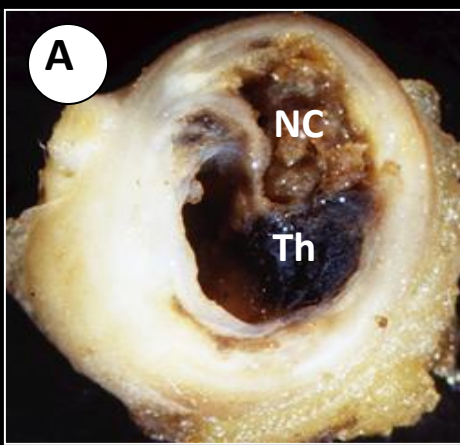
Do TCFA (vulnerable plaques) Continue to Progress and Rupture?
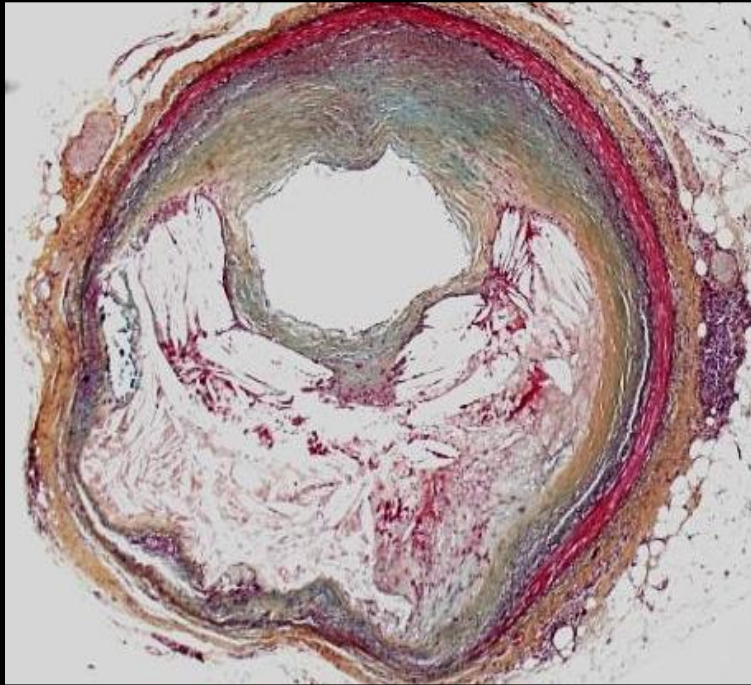
Thin cap fibroatheroma

- **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**
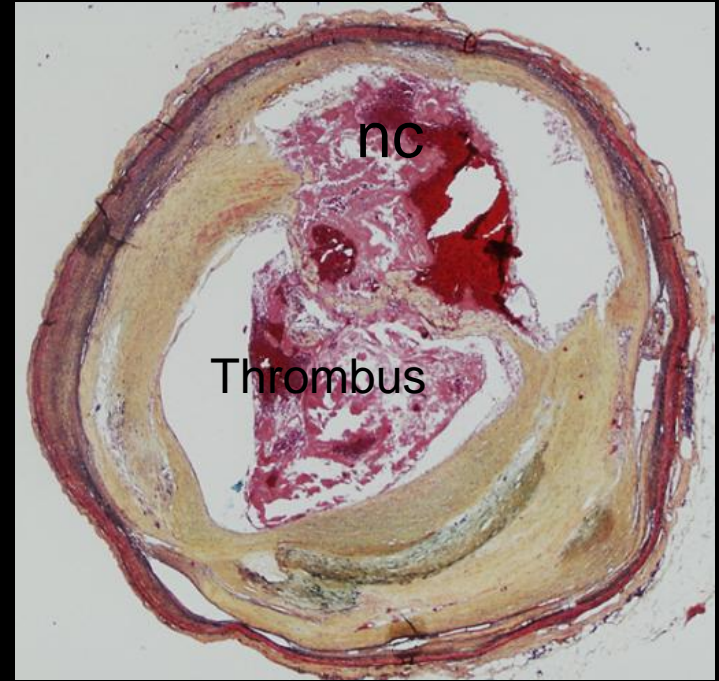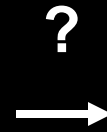
Plaque Rupture

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

Remodeling in Varying Coronary Lesion Morphologies
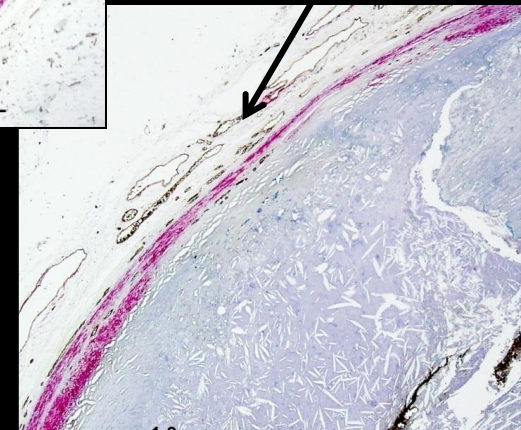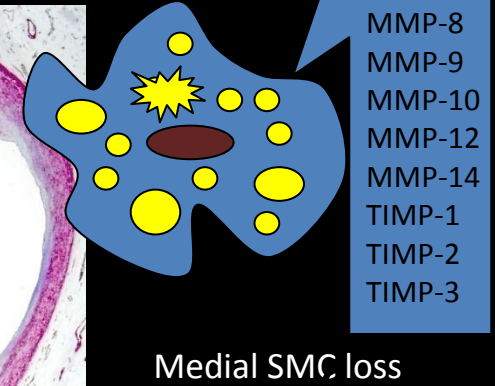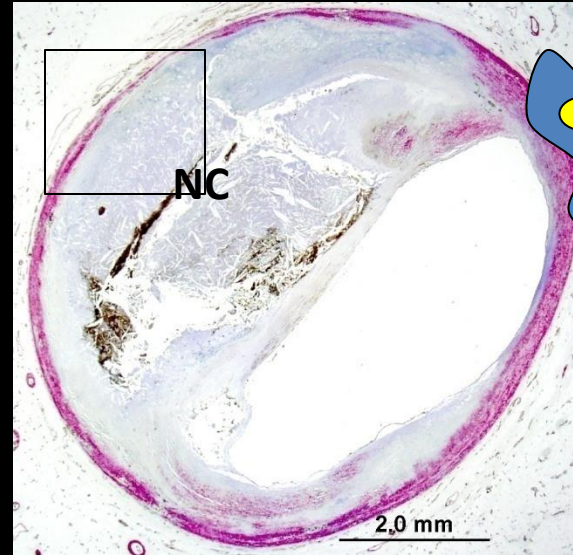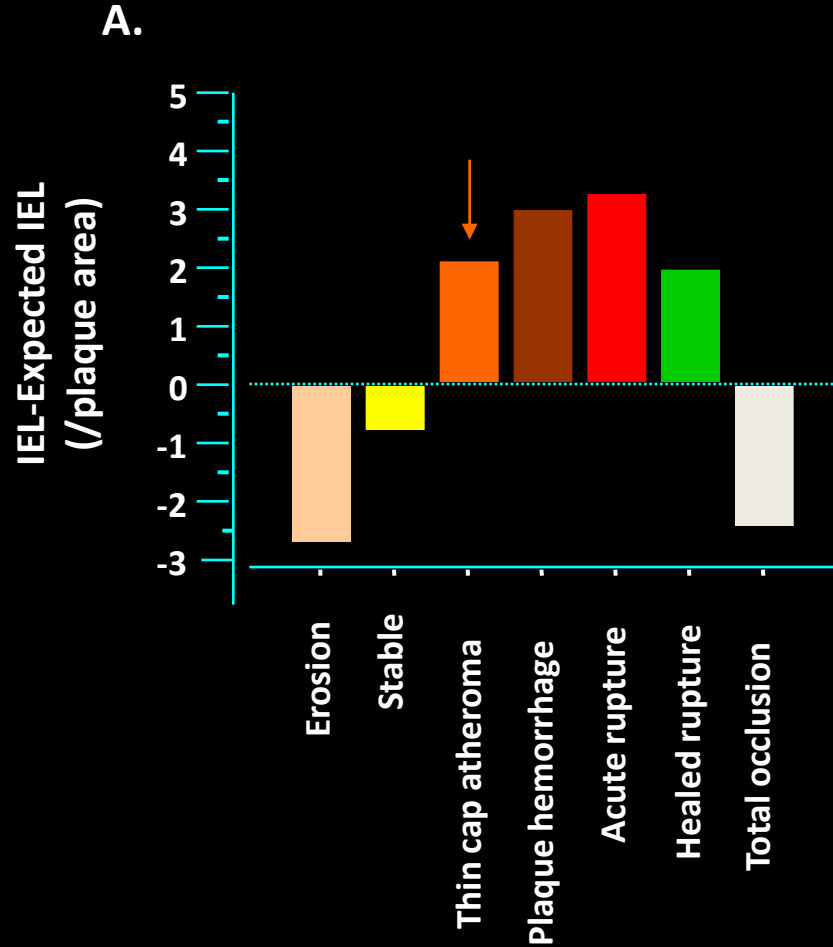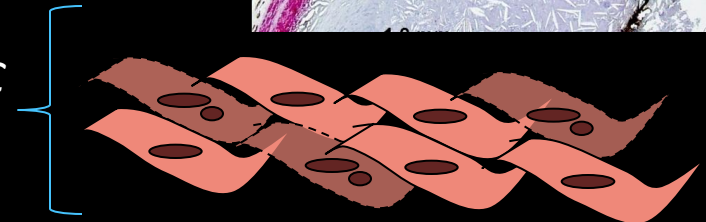
Relationship of Fibrous Cap Thickness to Macrophage Infiltration

P = 0.03

P = 0.06

Cell Mean for % Kp-1

6
5
4
3
2
1
0

Less than 65 μm

66 – 200 μm

201 - 300 μm

More than 300 μm

Modified from Newby AC. ATVB 2008

LPS
IL-1β
TNFα

Collagen
Laminin
Fibronectin
SIKVAV
EMMPRIN

PS

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

MMP-2
MMP-14
TIMP-2

MMP-2
TIMP-2

SMC death

PS = P-Selectin

Unstable plaque
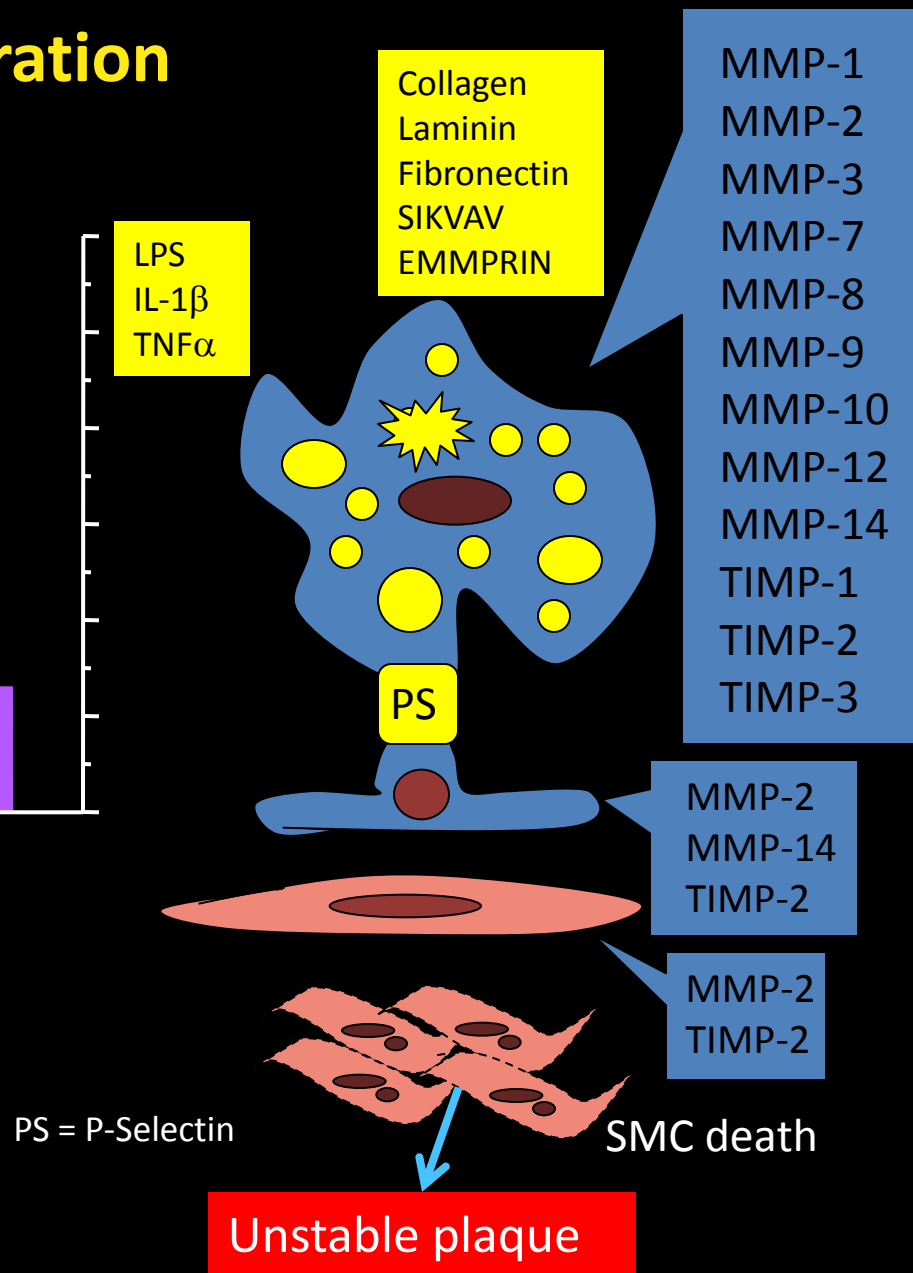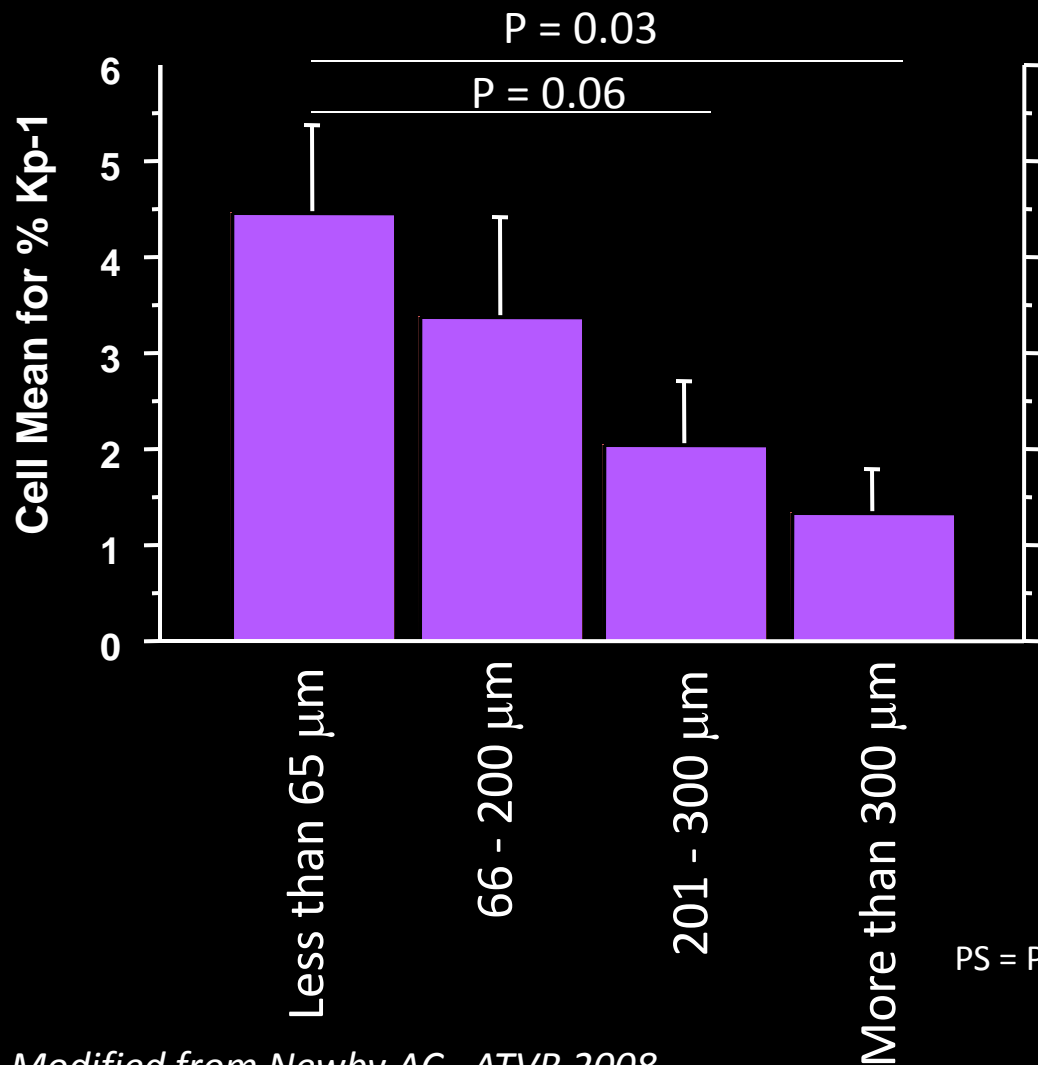
Independent Morphological Predictor of Rupture
50-75% cross-sectional stenosis
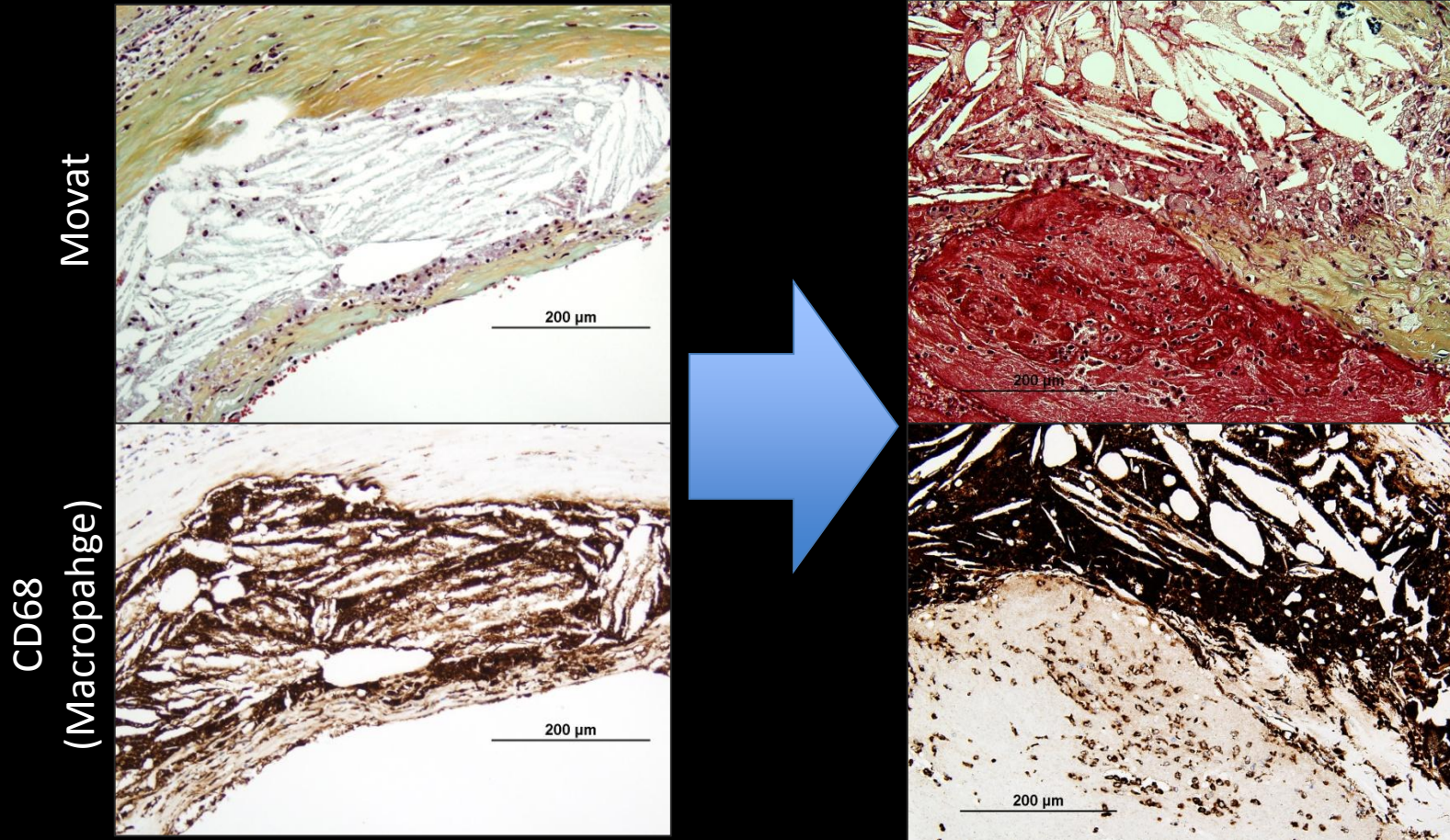
	P Value	Odds Ratio	95% CI
Cap thickness	0.005	0.35	0.16 – 0.69
%NC	0.02	2.0	1.1 – 3.7
%Macrophage	0.052	1.8	0.99 – 3.2

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

Kolodgie F, et al. Current Opinion in Cardiology 2001;16:285
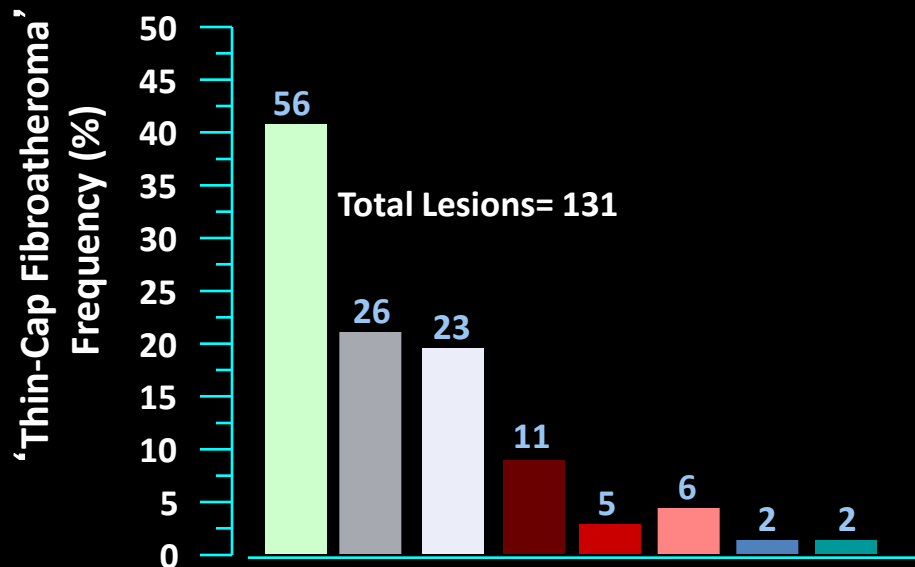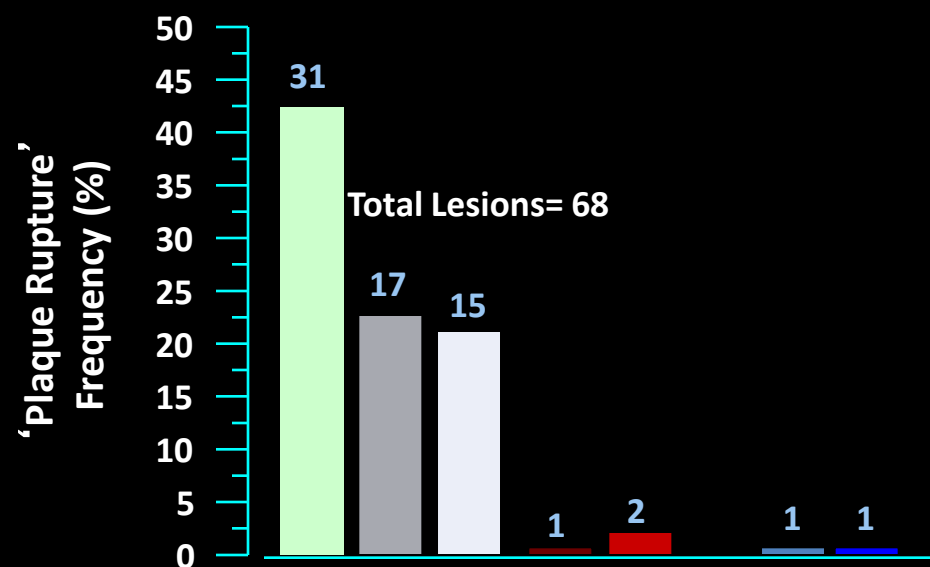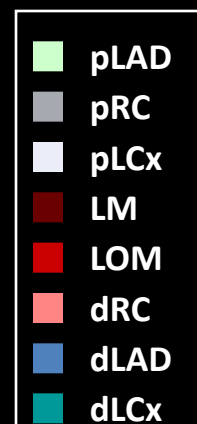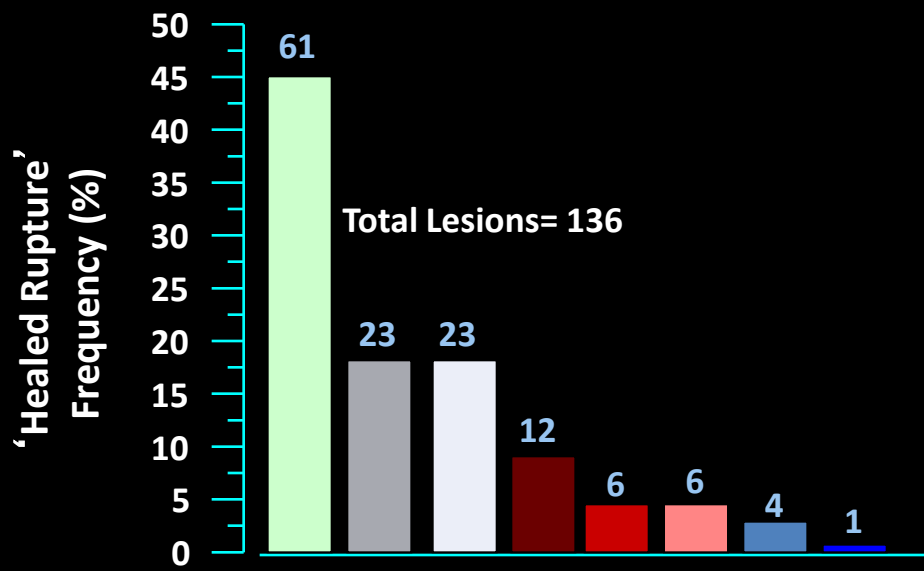
Plaque Rupture with Acute Thrombus

OCT

IVUS

Histology

Necrotic core
(NC)

Thrombus

Movat

1.0 mm
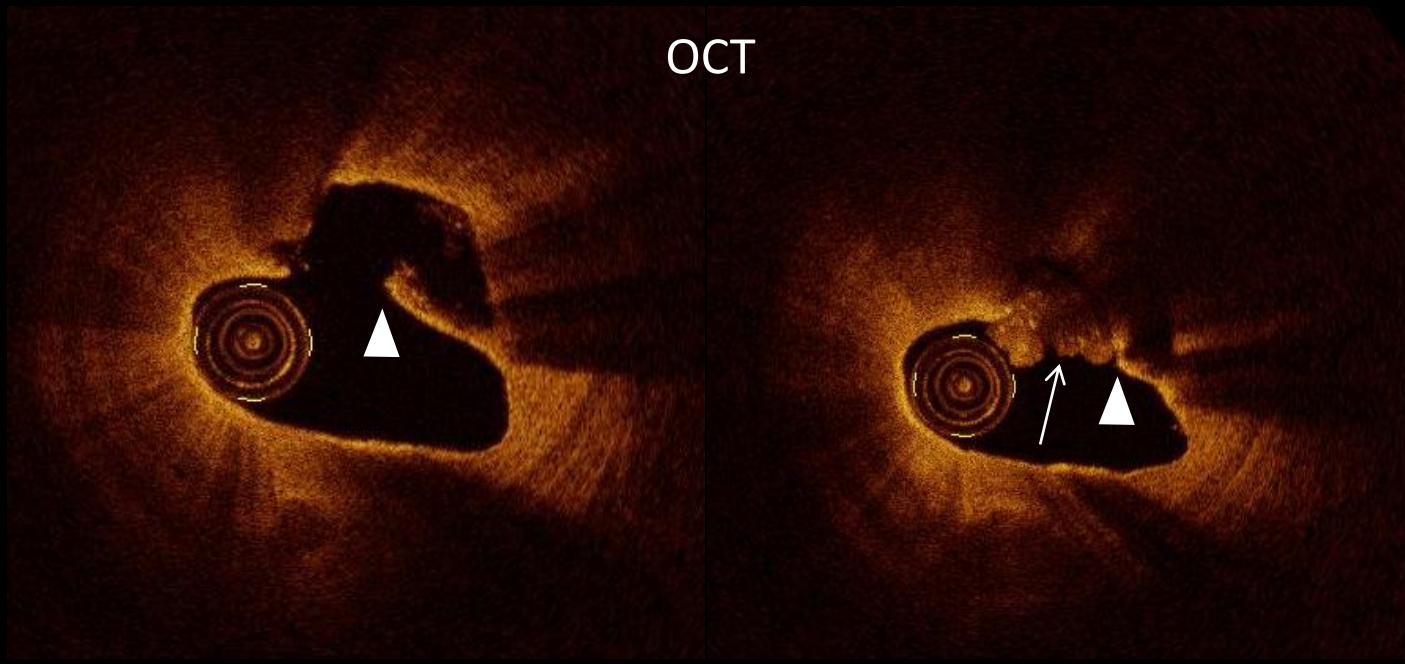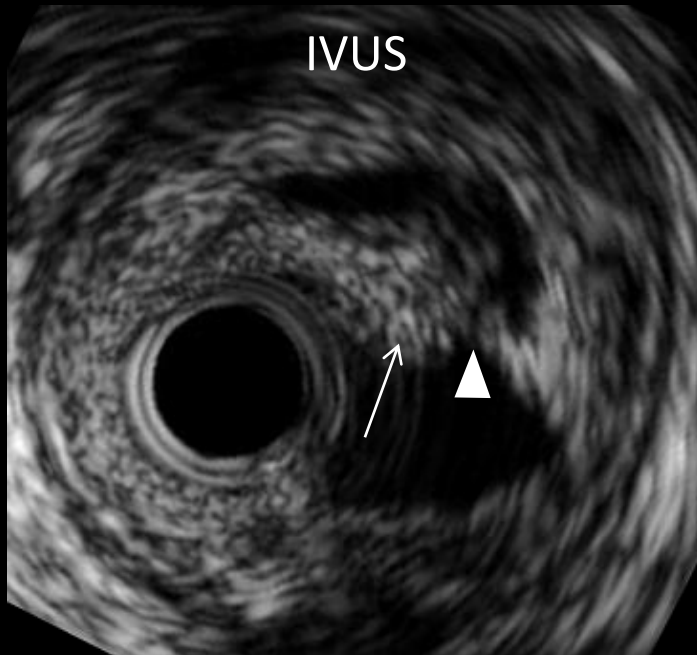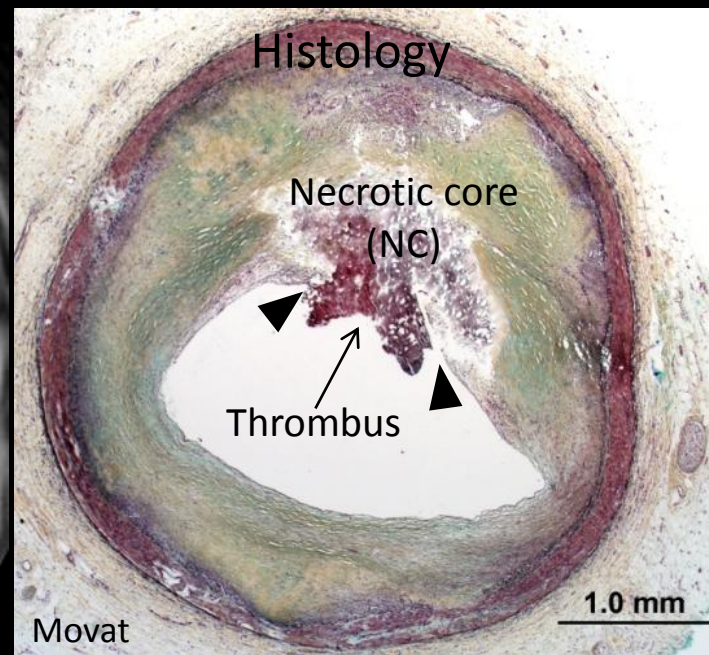
Healed Plaque Rupture

IVUS

OCT

Signal-rich with attenuation

Layered pattern

Signal-poor

Histology

1.0 mm

Foamy macrophage accumulation

200 μm

Newly formed intima

Old fibrous cap

NC

200 μm

Type III collagen

Type I collagen

Sirius red (polarized)

NC

200 μm
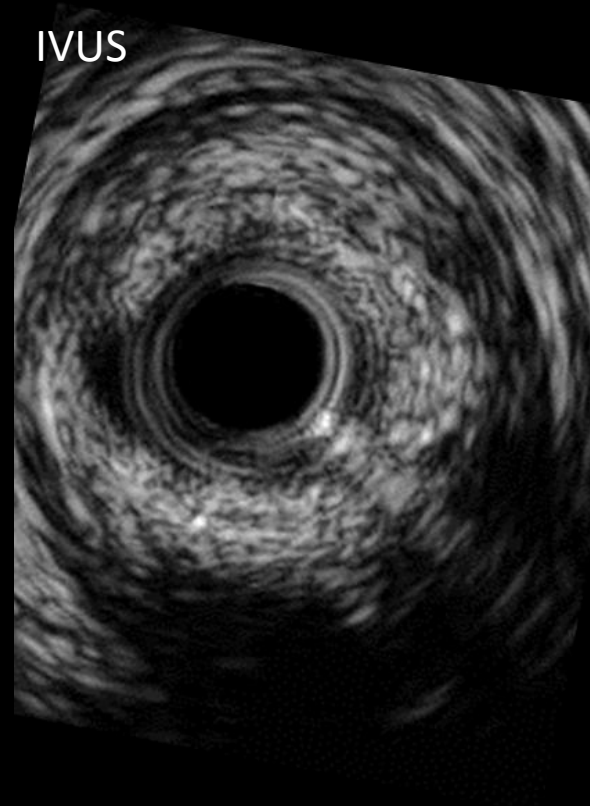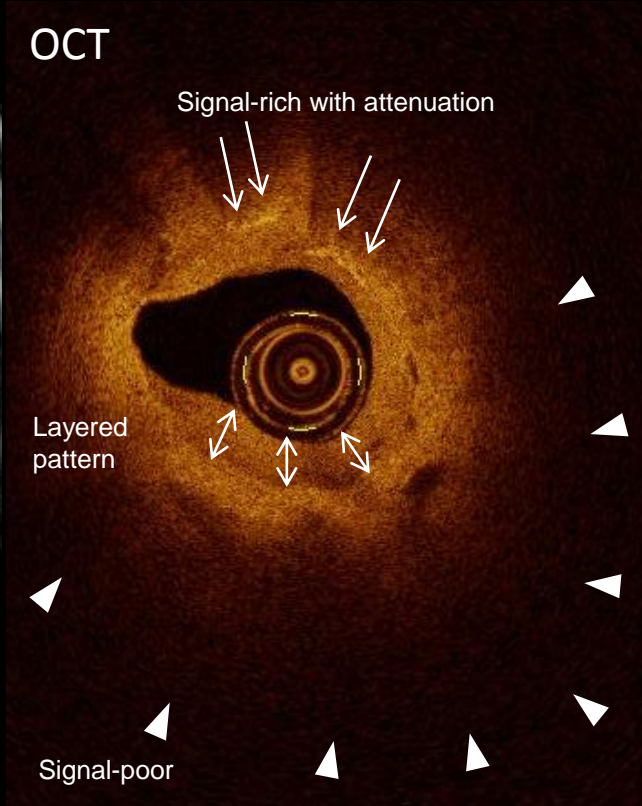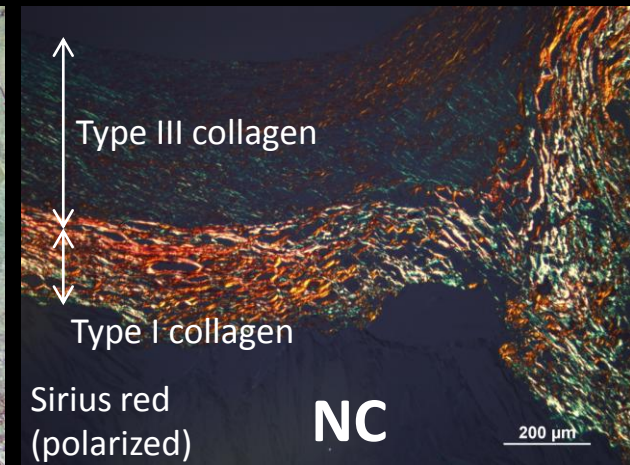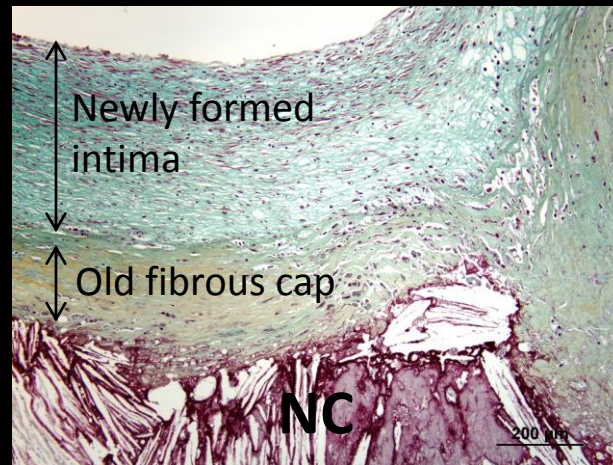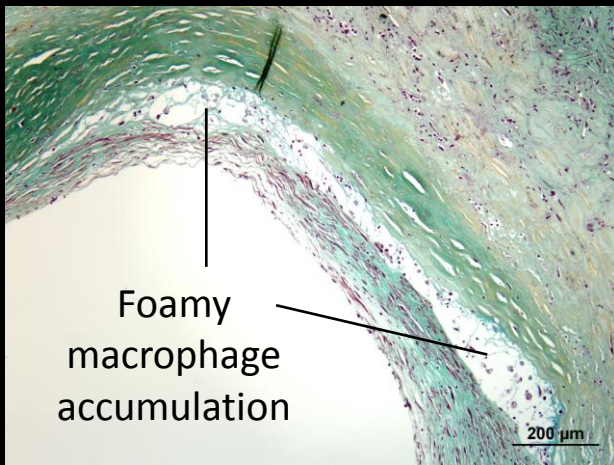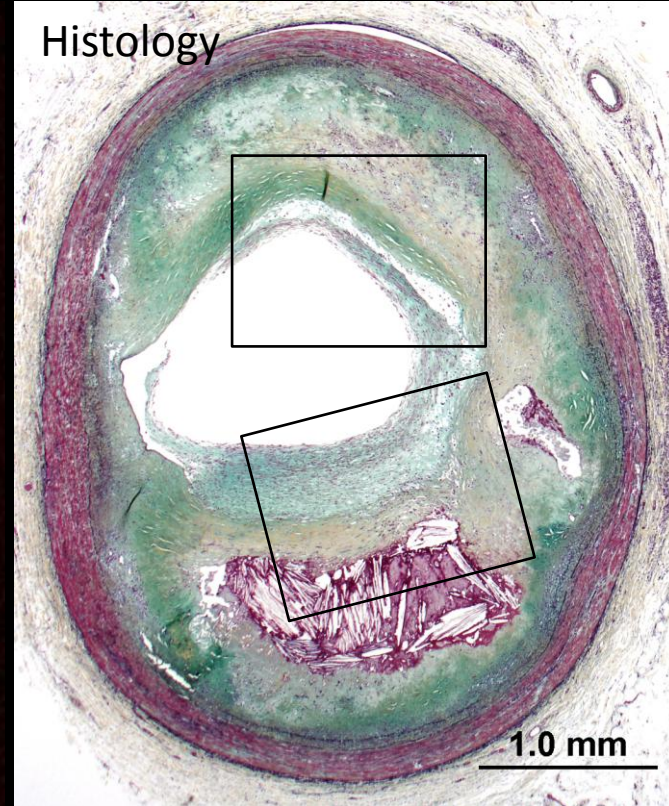
Features of ruptured plaques

- 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

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.
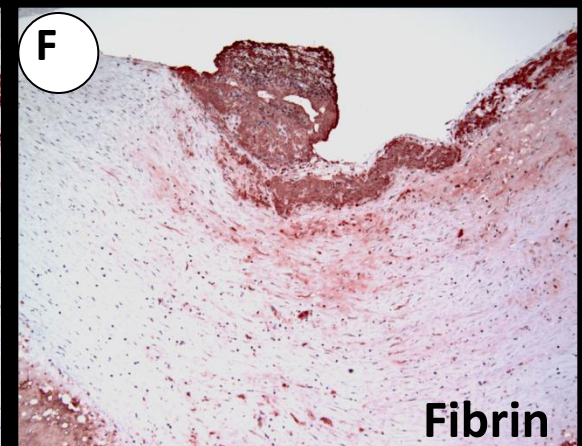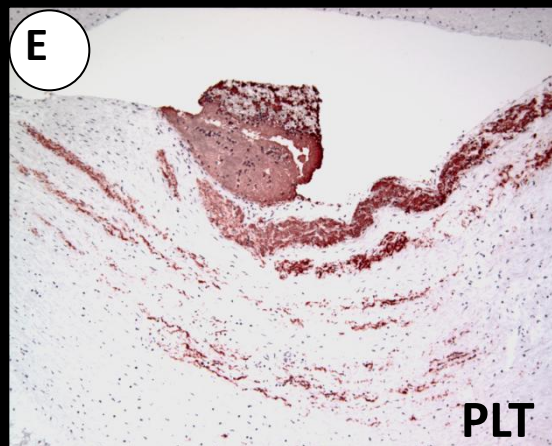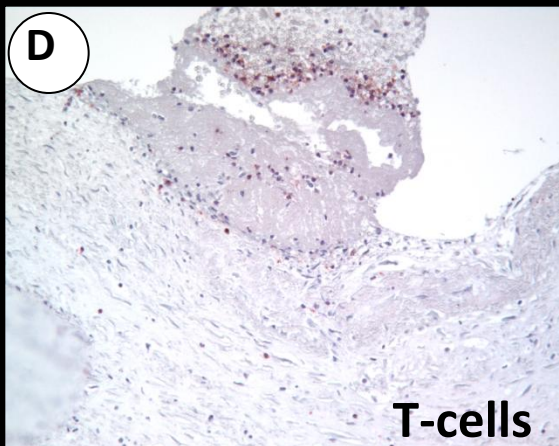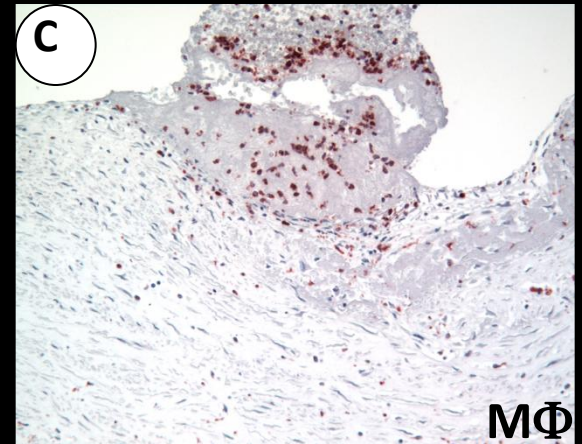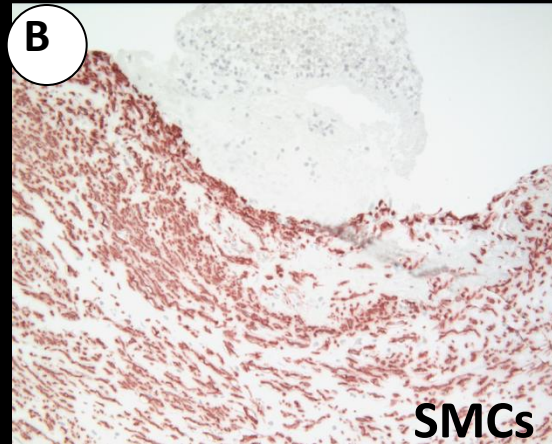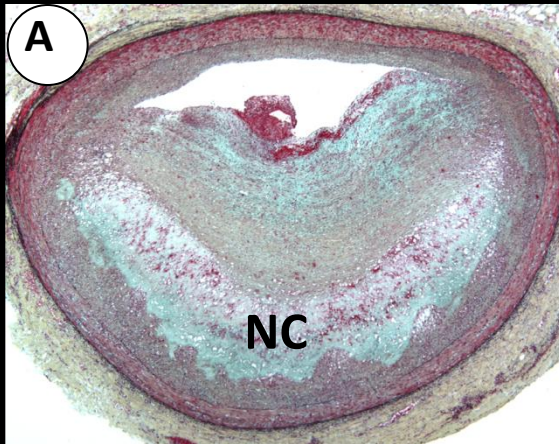
Can plaque erosion be identified by OCT/OFDI?

51F presented with STEMI

Luminal thrombus without plaque rupture

Sub-occlusive thrombus

A Proximal RCA

Thr →

Thr →

B Mid RCA

mm

A

B

m
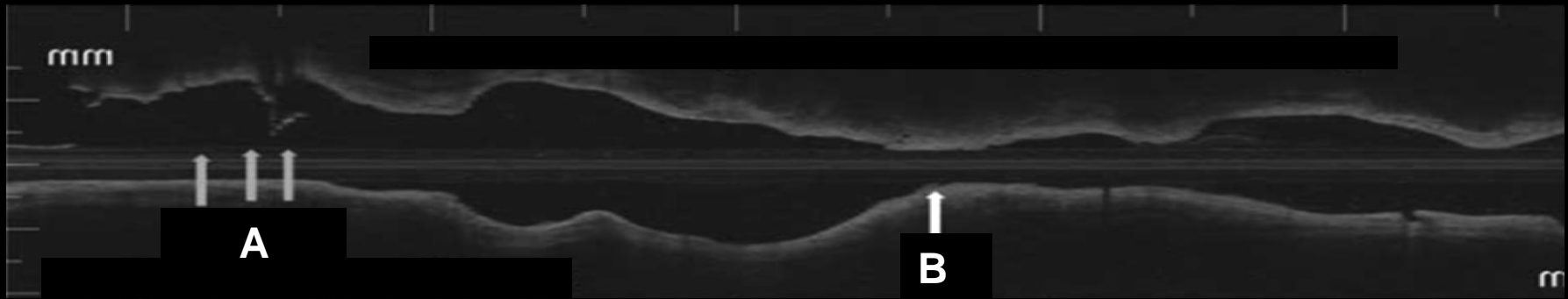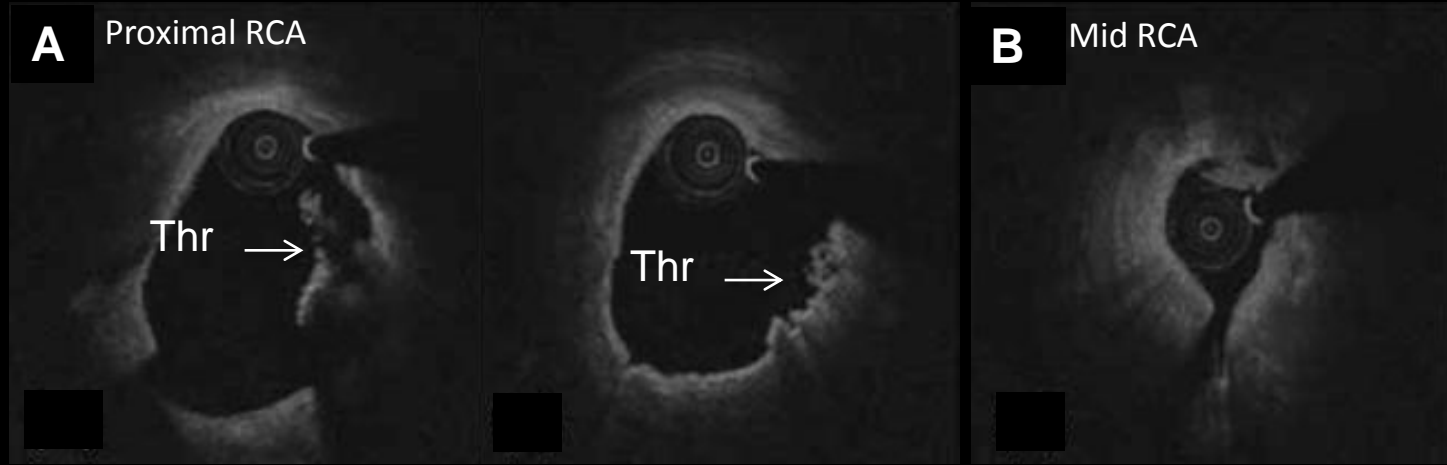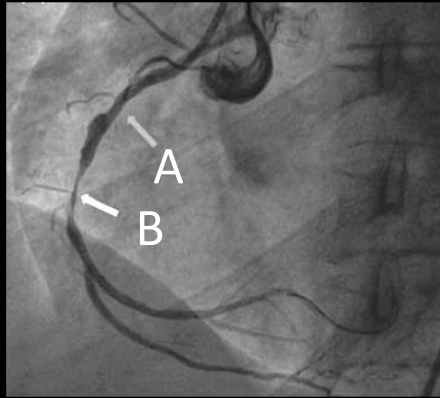
Fineschi M, J Cardiovasc Med 2013 [Epub ahead of print]

❖ Thrombus may obscure the underlying plaque morphology.
❖ Currently, no distinct morphological features of erosion-prone plaques have been identified.

Plaque Erosions in Men and Women Stratified by Age

Men

Women
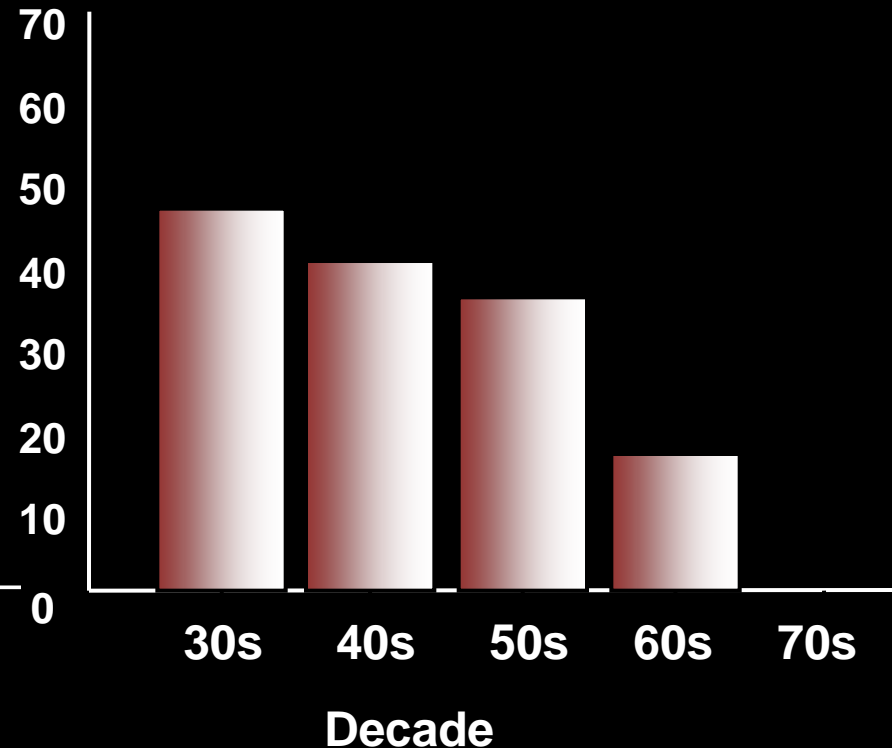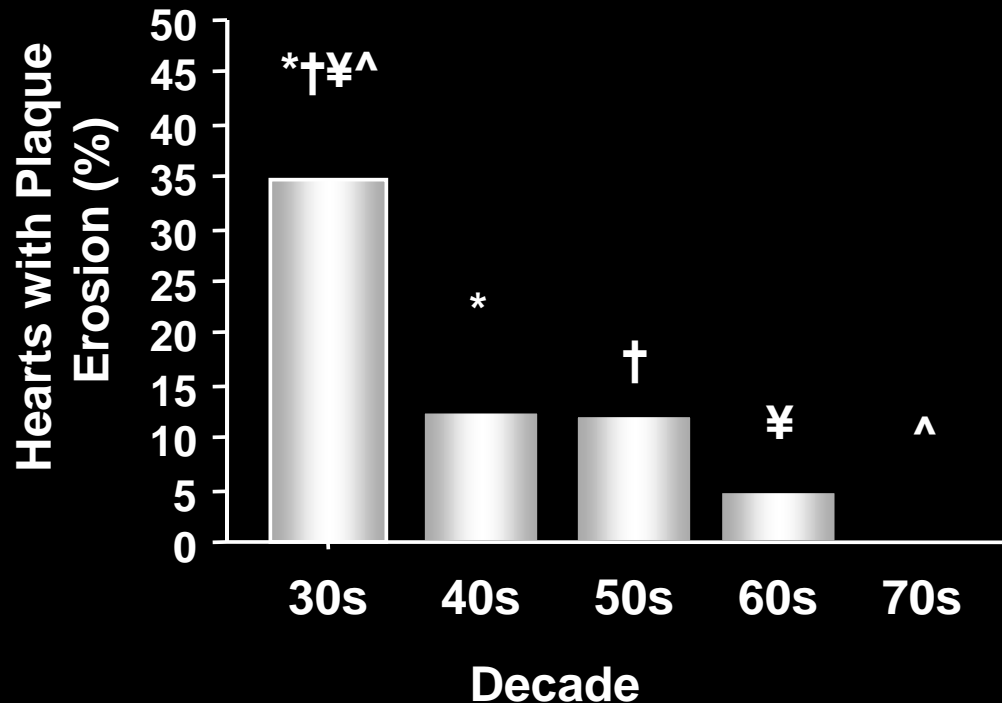
*P=0.01,†P=0.02,¥p=0.01,^P=0.03

All P > 0.05

Kolodgie FD, et al. Plaque erosion. 2008

Calcified Nodule

A

Calcified
plate

B

* Nodule

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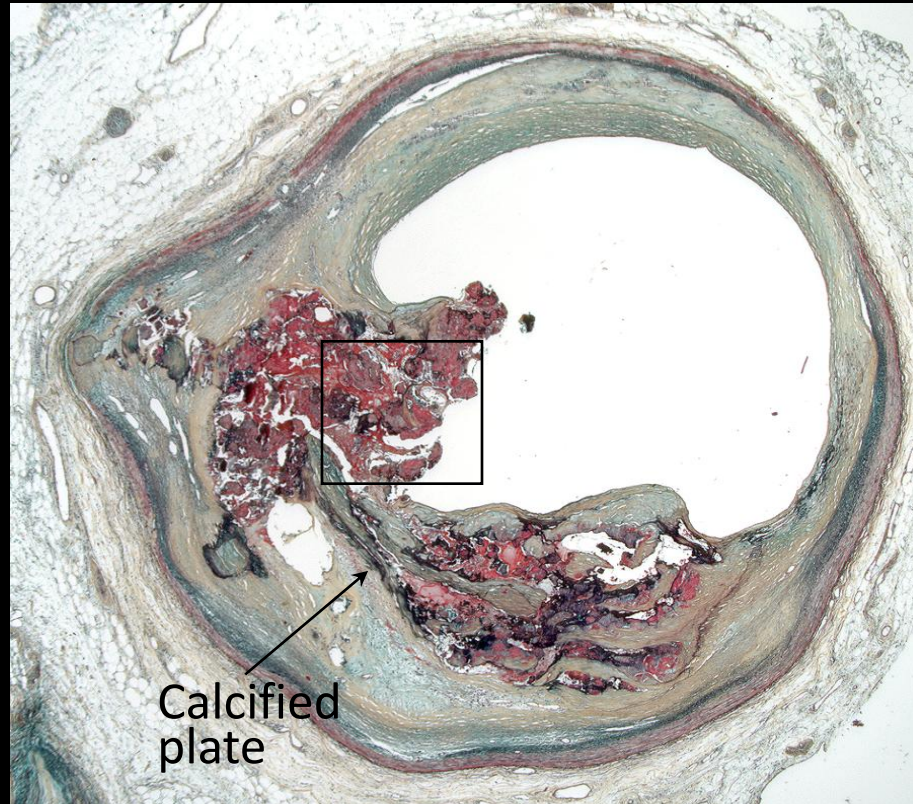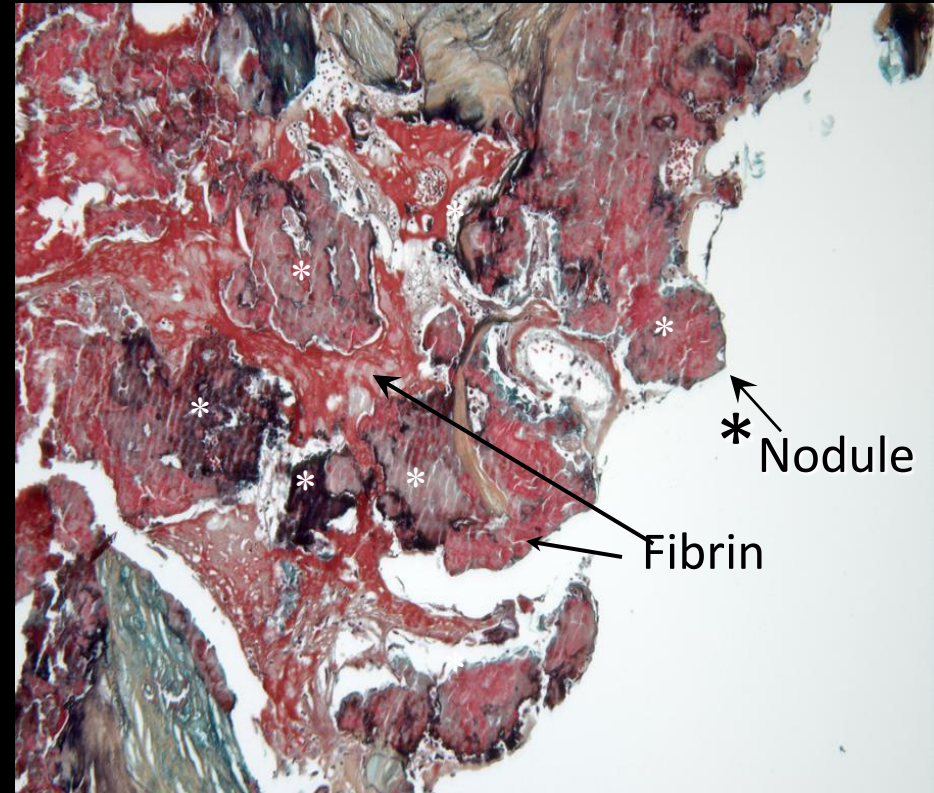
**Frequency 2-7% of SCD, Older individuals, usually Men,
equally common in tortuous right and left coronary arteries**

Nodular Calcification and Calcified Nodule on OCT/OFDI

Sheet Ca^{++} Nodular Ca^{++} Sheet Ca^{++}

OFDI

Sheet Ca^{++} Sheet Ca^{++}

Nodular Ca^{++}

Slightly brighter region with attenuation

IVUS
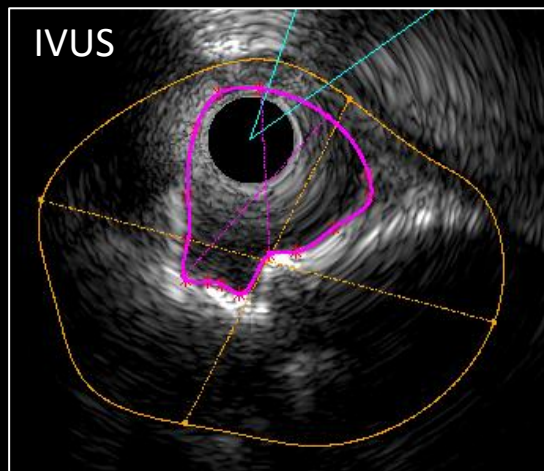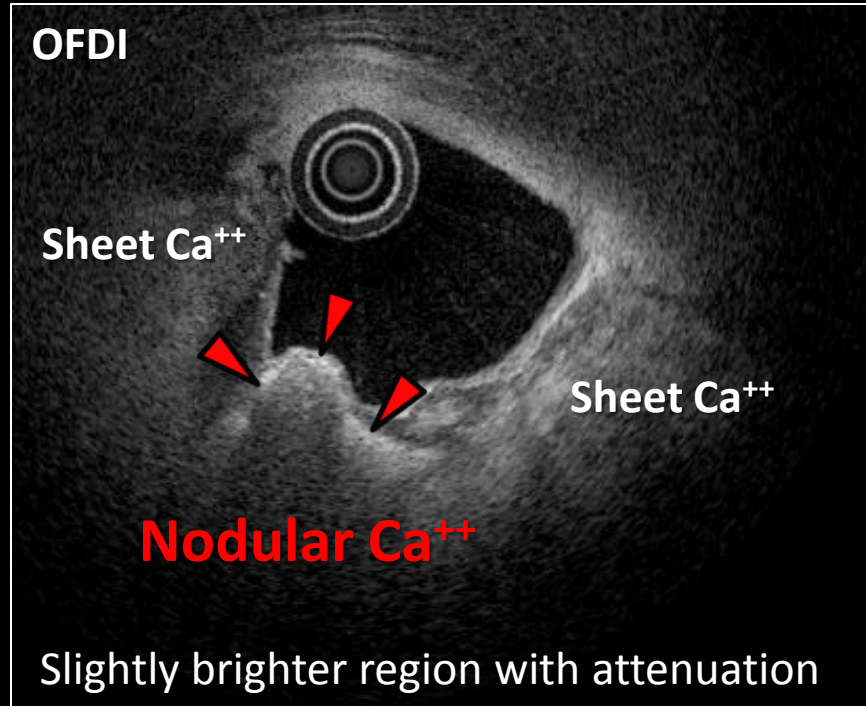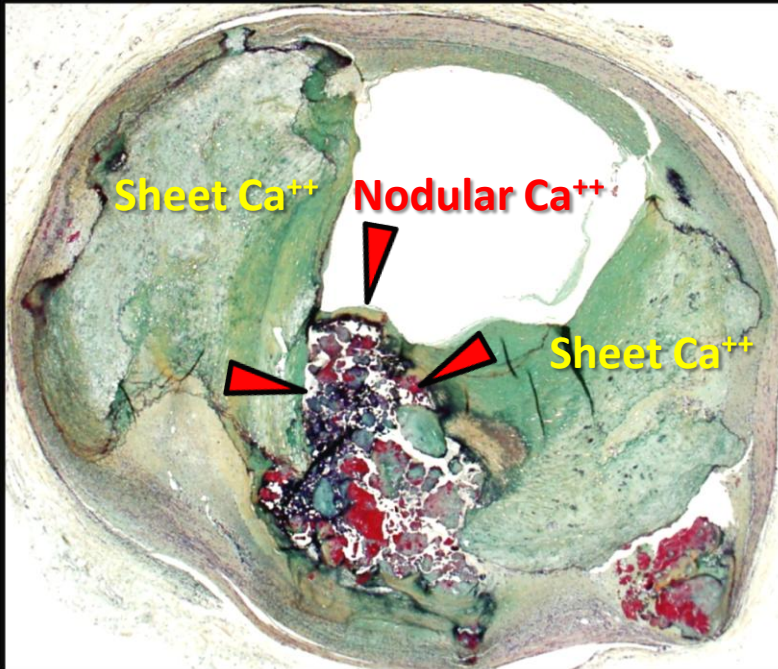
Calcified Nodule as Detected by OCT

1 mm
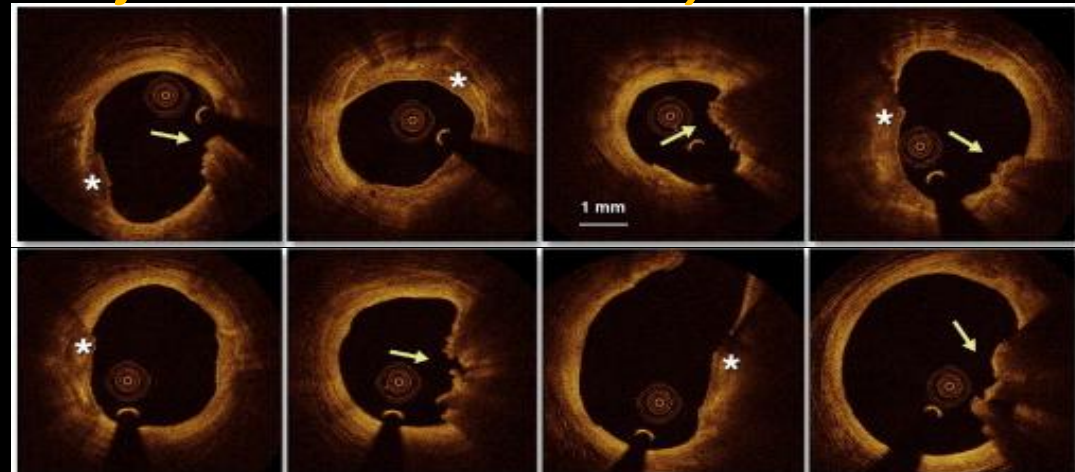
However, the precursor lesions of calcified nodule remain to be clarified.

Karanasos A, et al. JACC: Cardiovascular Imaging 2012;5:1071-1072

Plaque Fissure

Plaque Rupture

Th

Healed Plaque Rupture

Fibrocalcific Plaque
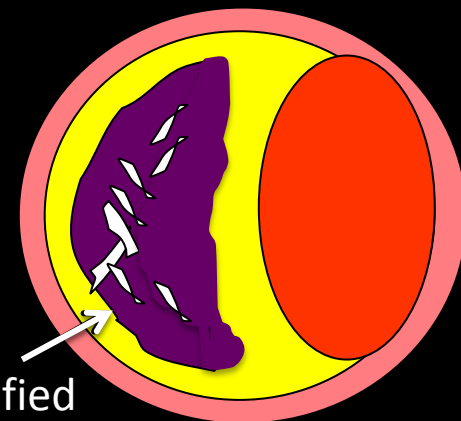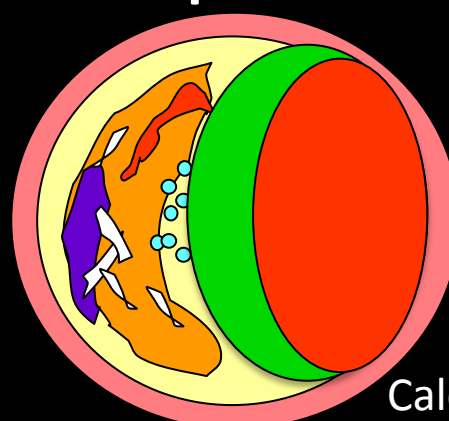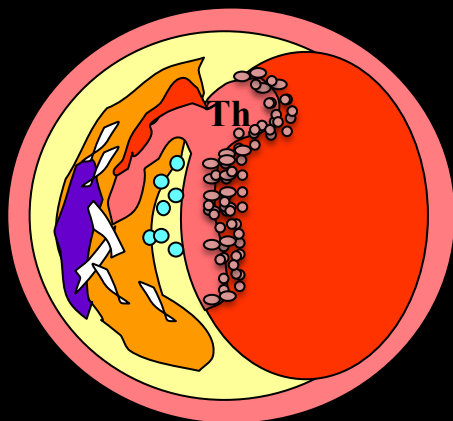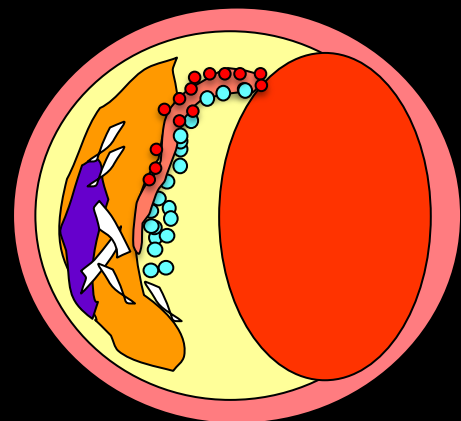
Calcified plate

Calcified Plate Fragmentation

Calcified Plate fragmenation from artery tortuosity and beating heart

Nodular Calcification

Fibrin

Nodules of calcium Destroying the media

Calcified Nodule with luminal thrombus

Medial destruction

Luminal thrombus surrounded by Fibrin and platelet

Macrophage Diversity around Angiogenesis, Plaque Hemorrhage and Iron deposits - Markers of Plaque Progression ?

Intraplaque Hemorrhage

▲ Angiogenesis
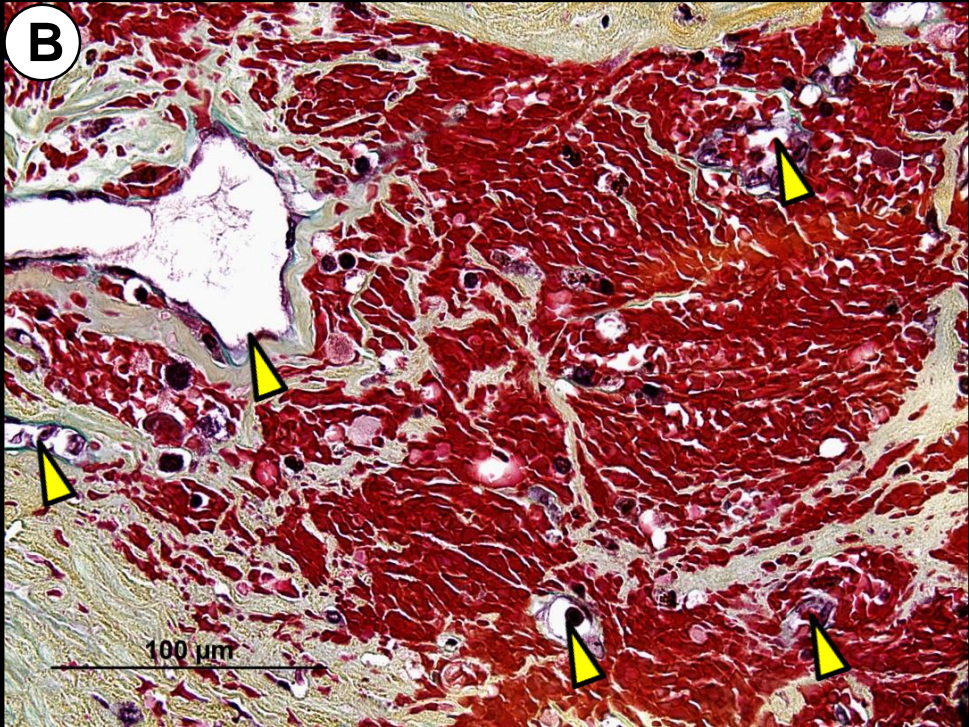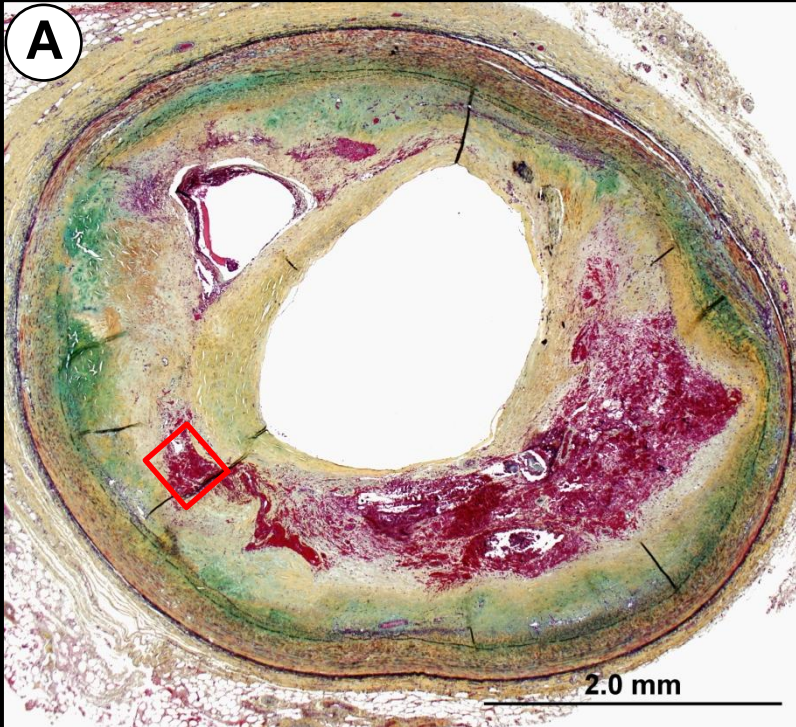
Frequency of Plaque Hemorrhage

rupture   erosion   Severe CAD (>75%)
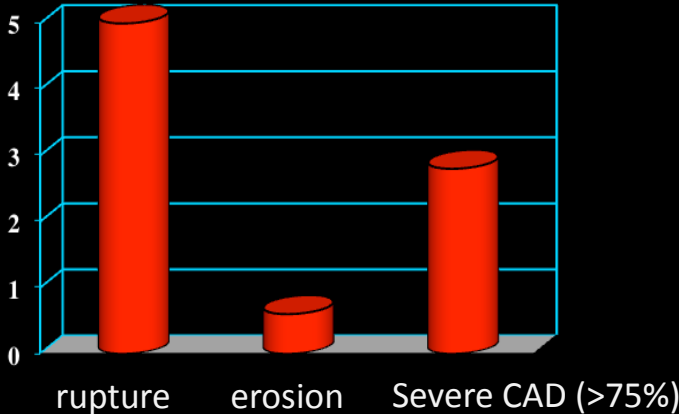
Morphometric Analysis of Hemorrhagic Events in Human

Hemorrhagic Pericarditis
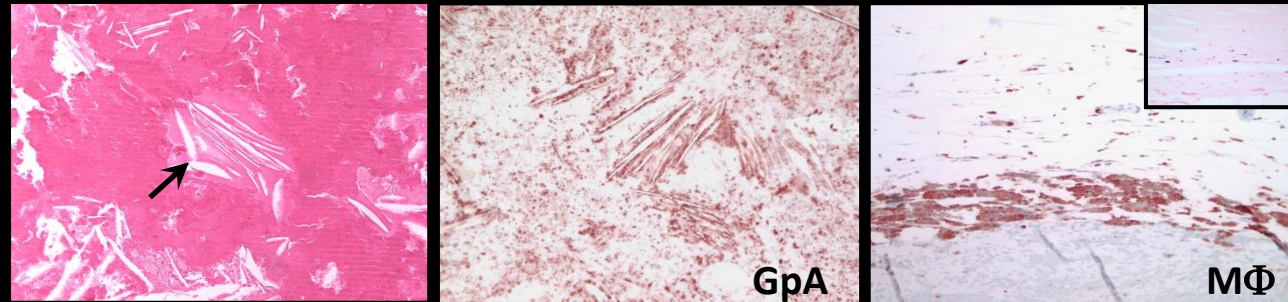
Vulnerable Plaque
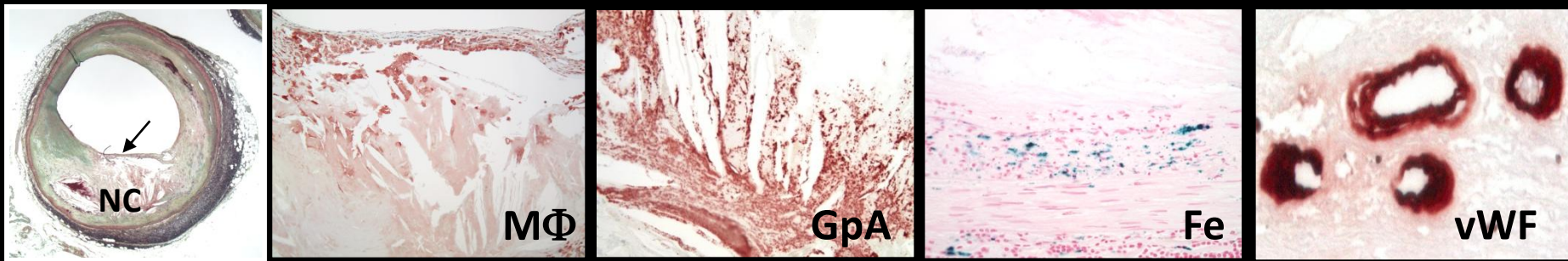
Plaque Type	GpA Score	Iron	Necrotic Core (mm²)	MΦ (mm²)
PIT *no* **core** (n=129)	0.09±0.04	0.07±0.05	0.0	0.002±0.001
FA *early* **core** (n=79)	0.23±0.07	0.17±0.08	0.06±0.02	0.018±0.004
FA *late* **core** (n=105)	*0.94±0.11	*0.41±0.09	*0.84±0.08	*0.059±0.007
TCFA (n=52)	*1.60±0.20	*1.24±0.24	*1.95±0.30	*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

TCFA with Intraplaque Hemorrhage

IVUS

Echo attenuation

OCT

Signal-poor

Histology

A

B

1.0 mm

Movat

Signal-rich

Fibrous cap thickness = 70 μm

A Necrotic core with hemorrhage

200 μm

50.0 μm

CD68 (macrophages)

Macrophages within thin-fibrous cap

200 μm

Signal-rich

Signal-poor

B Fibrous cap

Cholesterol cleft

Necrotic core with hemorrhage

CD68 (macrophages)

200 μm
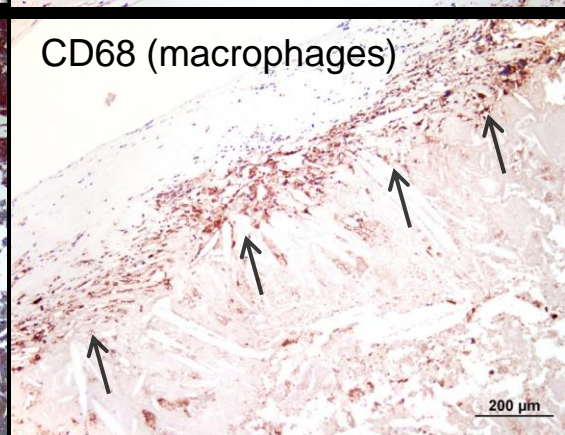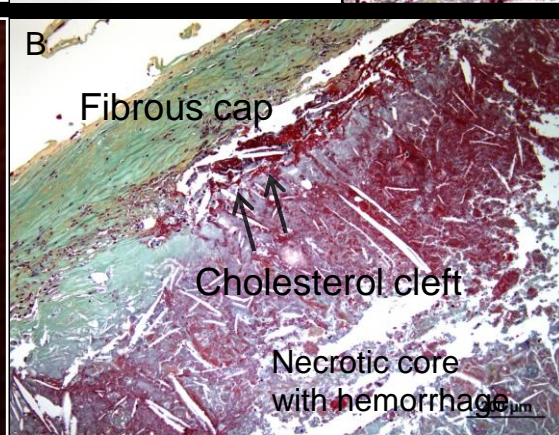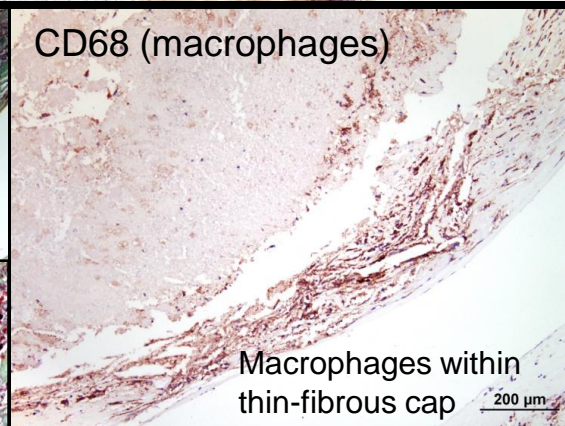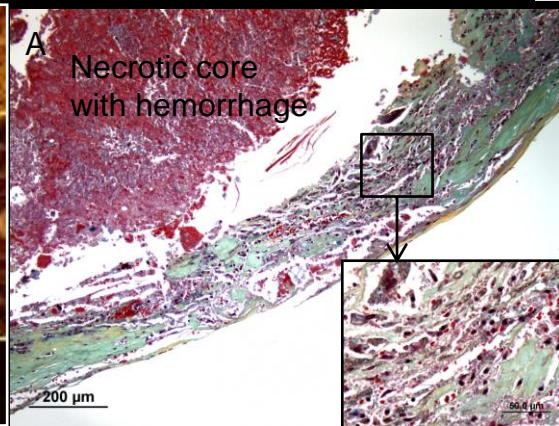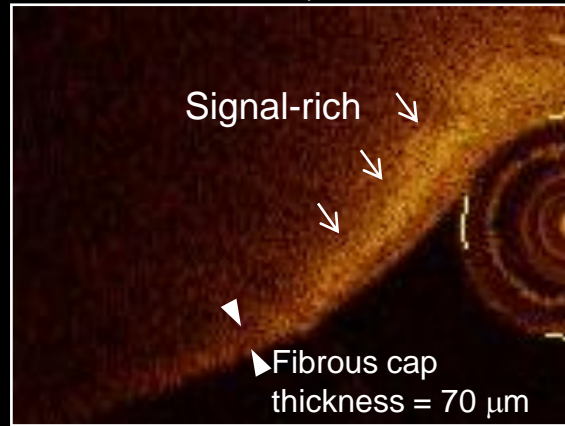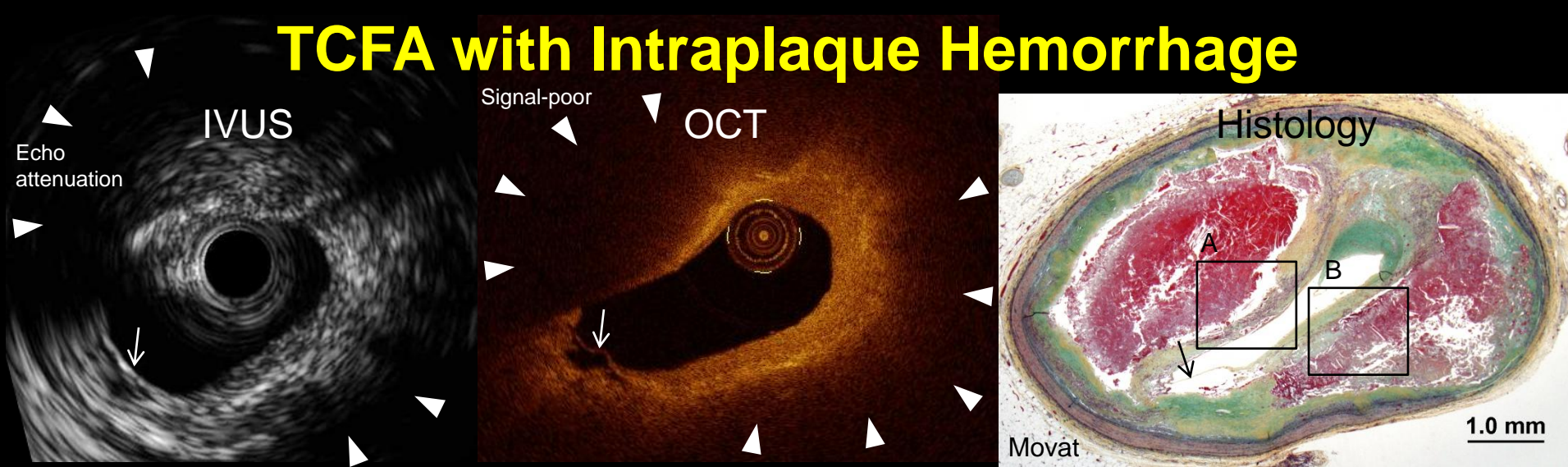
Distribution of Macrophage Sub-type

Human coronary plaque

Macrophage Diversity

Classically activated macrophage
+ Pro-inflammatory cytokines production
+ Antigen presentation & microbiological activity
+ Expression of MHC class II molecules

M1 Macrophage

IFN-γ, LPS

MHC class II

Pro-inflammatory cytokines
IL-6
TNF
IL-1

IL-10

$\uparrow$Mannose receptor

Monocyte

Hb:Hp

M (Hb)

Fe^{2+}

$\downarrow$Fe
$\downarrow$ROS

FPN

LXR ABCA1/ABC G1

$\uparrow$CD163

Free cholesterol/sterols

M2 Macrophage

IL-4, IL-13

MHC class II

Mannose Receptor Upreglation

Anti-inflammatory cytokines
IL-10
IL-1Ra

HDL

Activated PPARγ

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

Summary:
Progression of Vulnerable Plaque

➢Vulnerable plaques (TCFA) is a likely precursor lesions of rupture. Macrophage infiltration plays an important role in modification of plaque vulnerability.

➢Plaque erosion occurs 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 are 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.

➢Novel imaging technologies have progressed to detect VP but limitations remain due to lack of understanding of VP progression

Acknowledgments