Vulnerable Plaque Detection: What is New in 2018? Insight from Pathology

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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

Honorarium: Abbott Vascular, Lutonix, Terumo Corporation, and W.L. Gore.

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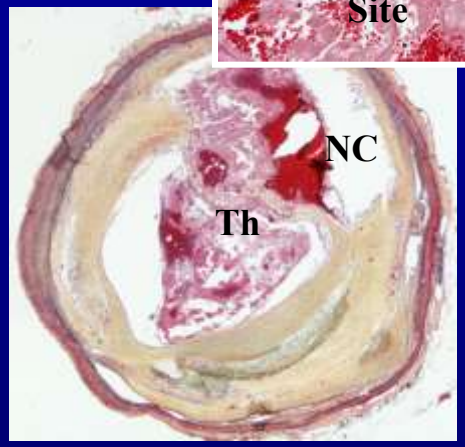
Owner of a healthcare company: No

Stockholder of a healthcare company: No

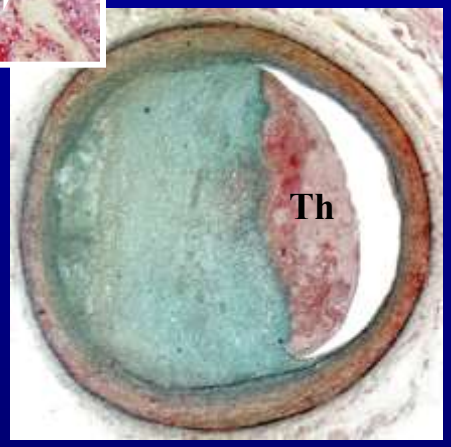
Pathology of Vulnerable Plaque

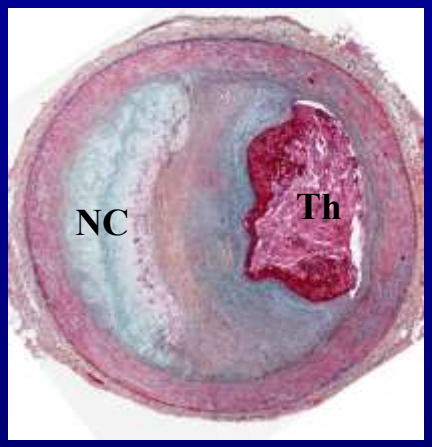
Causes of Coronary Thrombosis

Ruptur

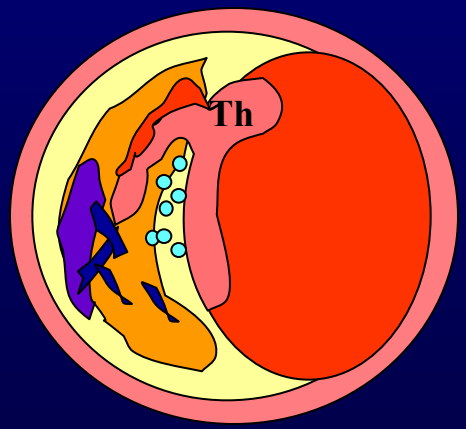


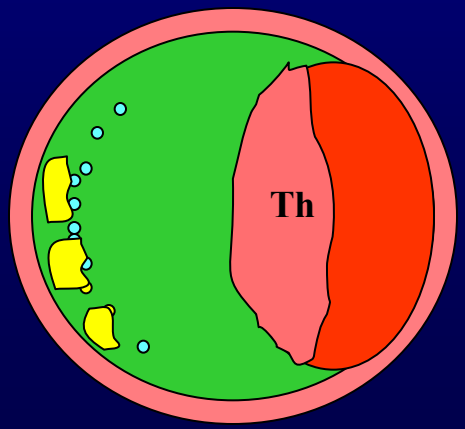
Erosion

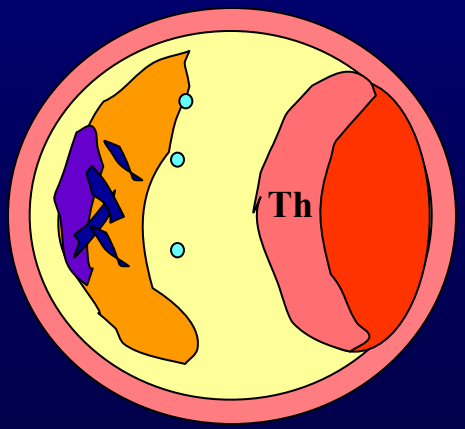


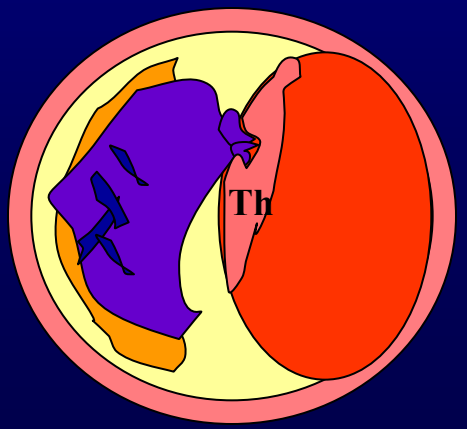


Calcified nodule









eVPath

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

Non-Progressive and Progressive Coronary Plaques

non-progressive

progressive

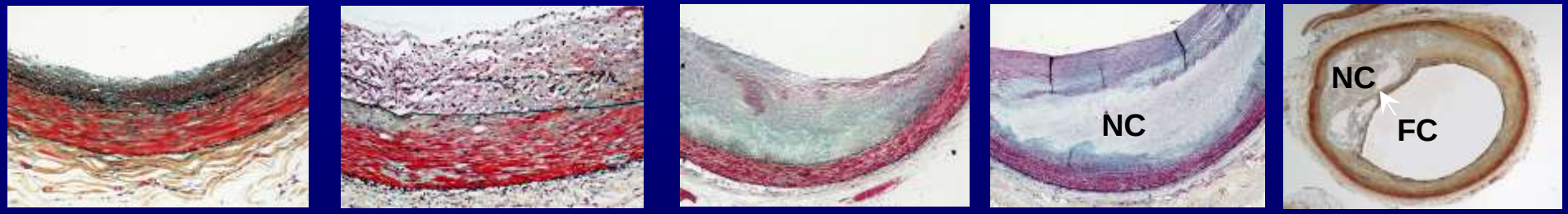
adaptive intimal thickening

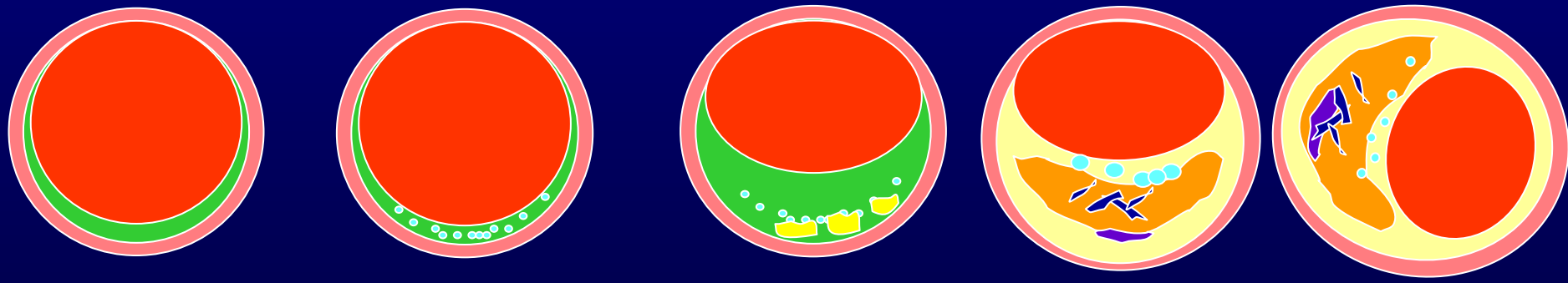
Intimal xanthoma

pathologic intimal thickening

fibroatheroma

thin-cap fibroatheroma

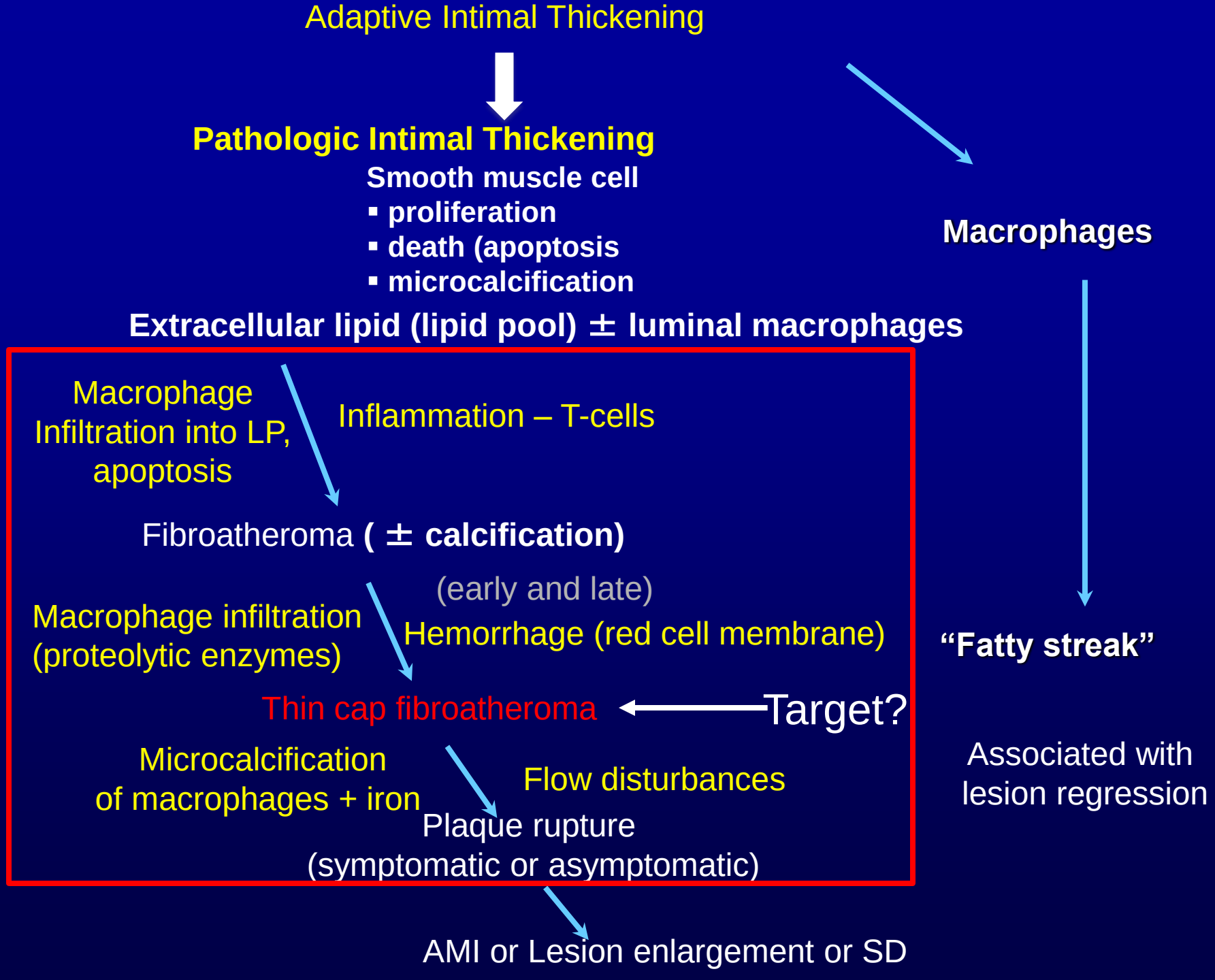




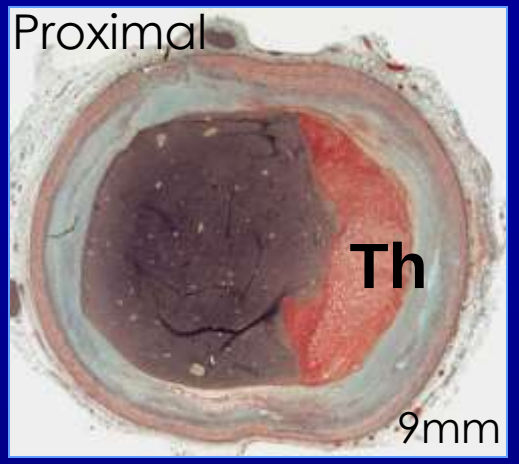
lipid pool

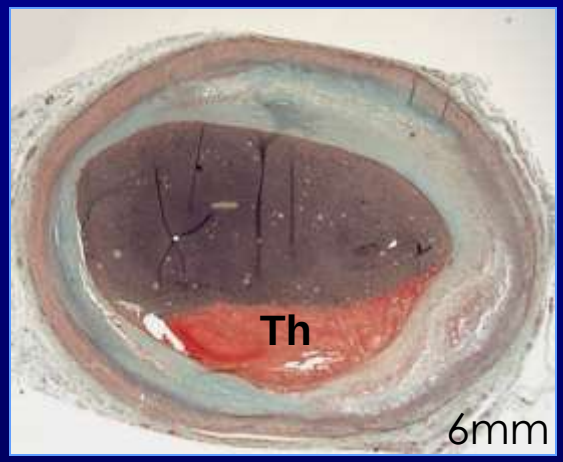
necrotic core

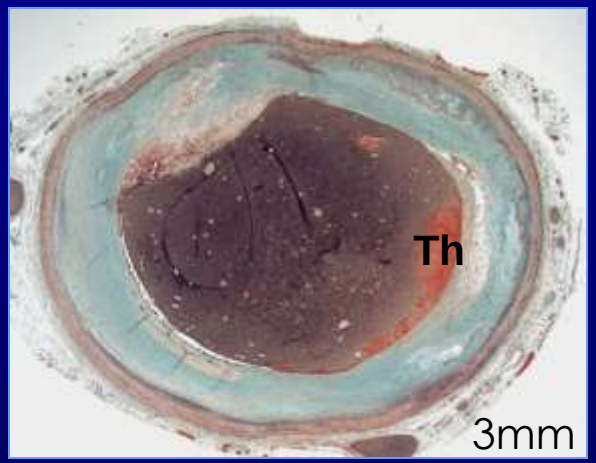
early → late necrosis

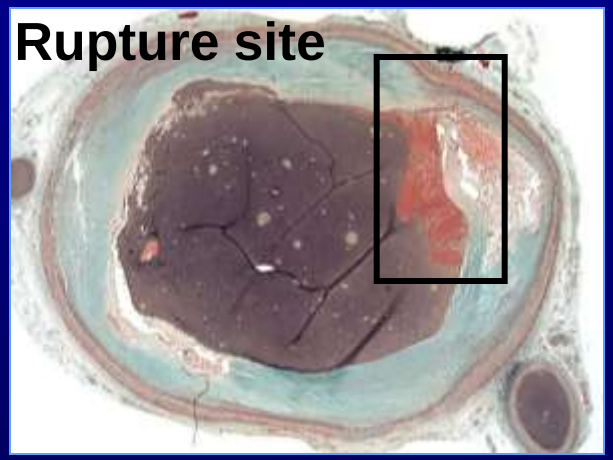

Adaptive Intimal Thickening
Pathologic Intimal Thickening
Smooth muscle cell
▪ proliferation
▪ death (apoptosis
▪ microcalcification
Extracellular lipid (lipid pool) ± luminal macrophages
Macrophages
Macrophage Infiltration into LP, apoptosis
Inflammation – T-cells
Fibroatheroma (± calcification)
(early and late)
Macrophage infiltration (proteolytic enzymes)
Hemorrhage (red cell membrane)
"Fatty streak"
Thin cap fibroatheroma
Target?
Microcalcification of macrophages + iron
Flow disturbances
Associated with lesion regression
Plaque rupture
(symptomatic or asymptomatic)
AMI or Lesion enlargement or SD

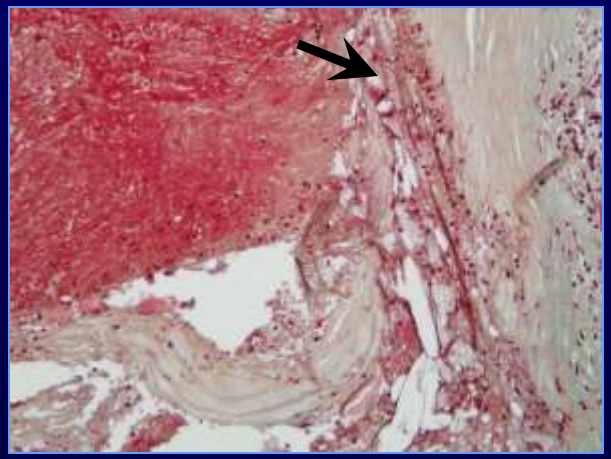
Plaque rupture with mild stenosis and non-occlusive thrombus: a mechanism by which plaques progress from an asymptomatic to plaque enlargement which may be symptom producing when severely narrowed

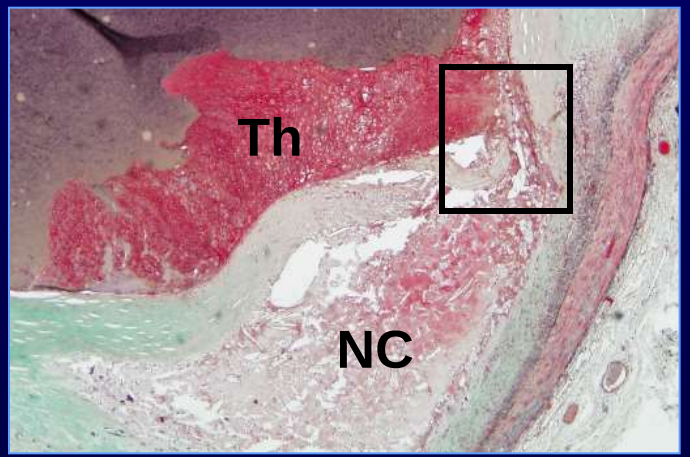






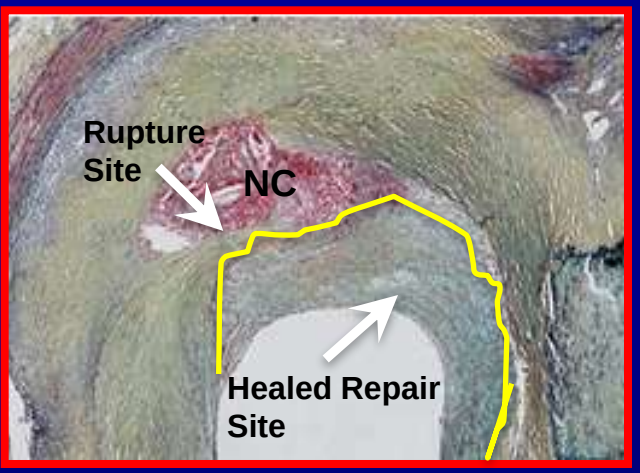


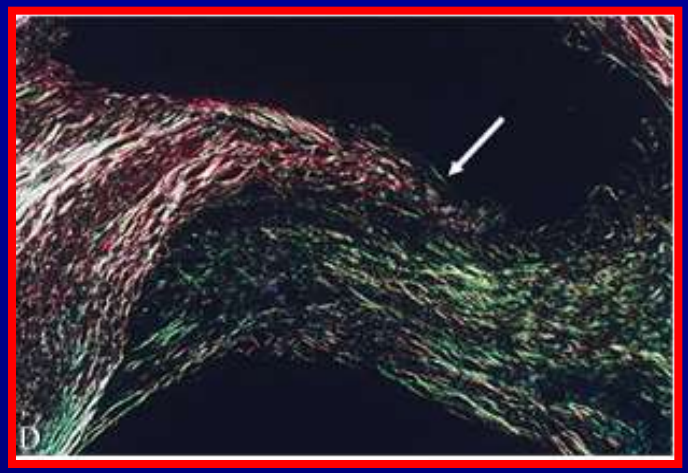




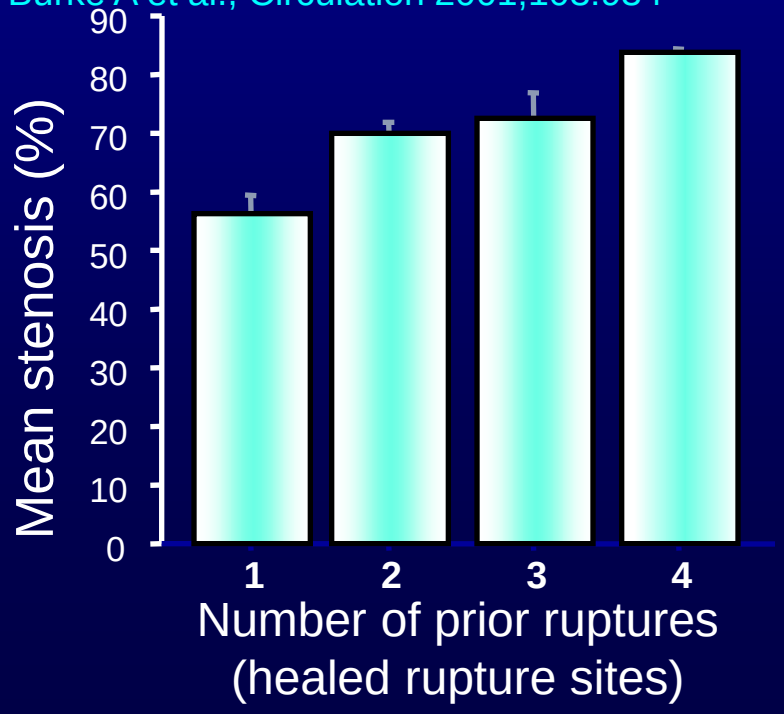
Healed Ruptures are responsible for Plaque Progression

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

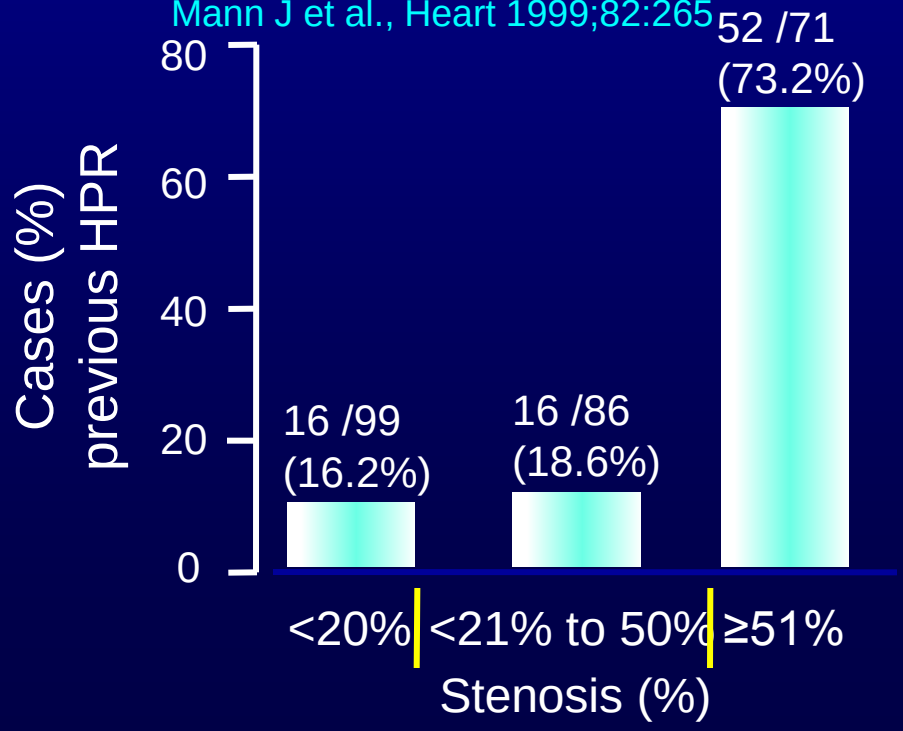




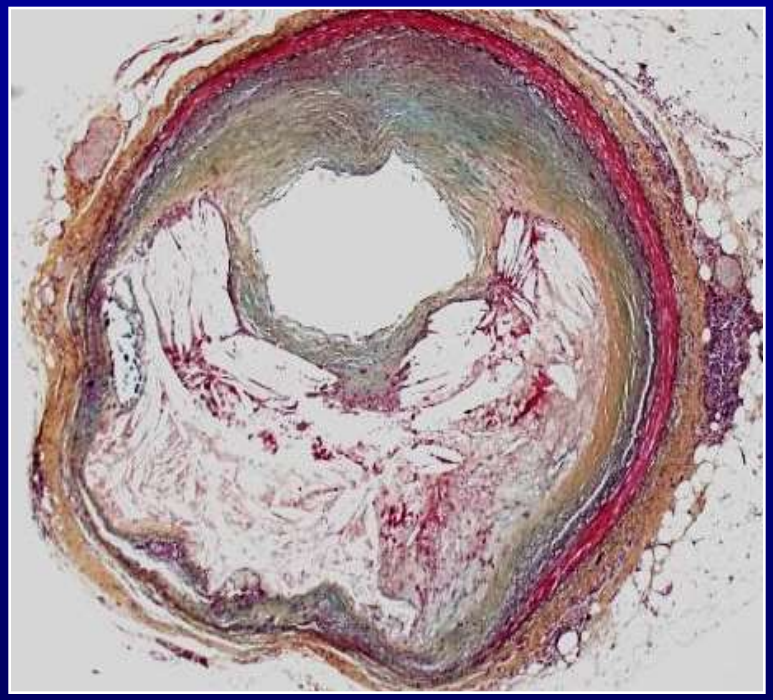
Burke A et al., Circulation 2001;103:934



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



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



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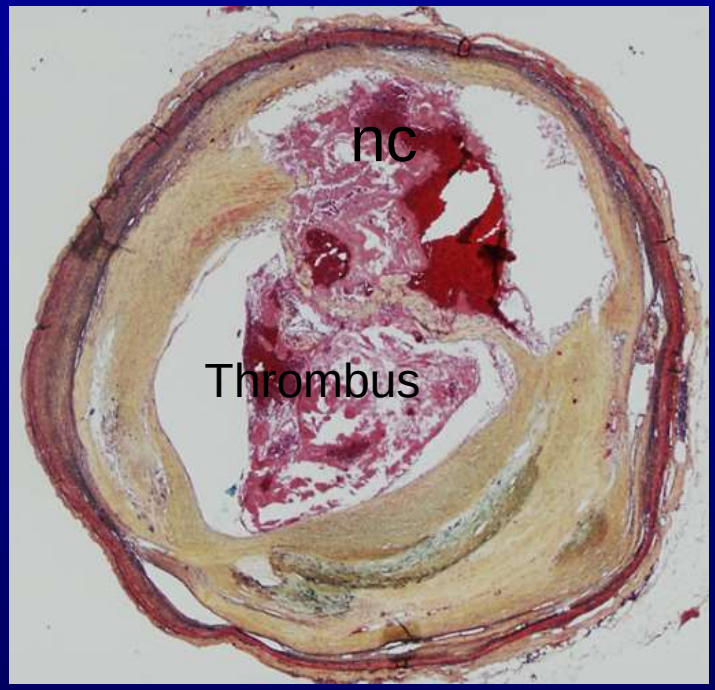
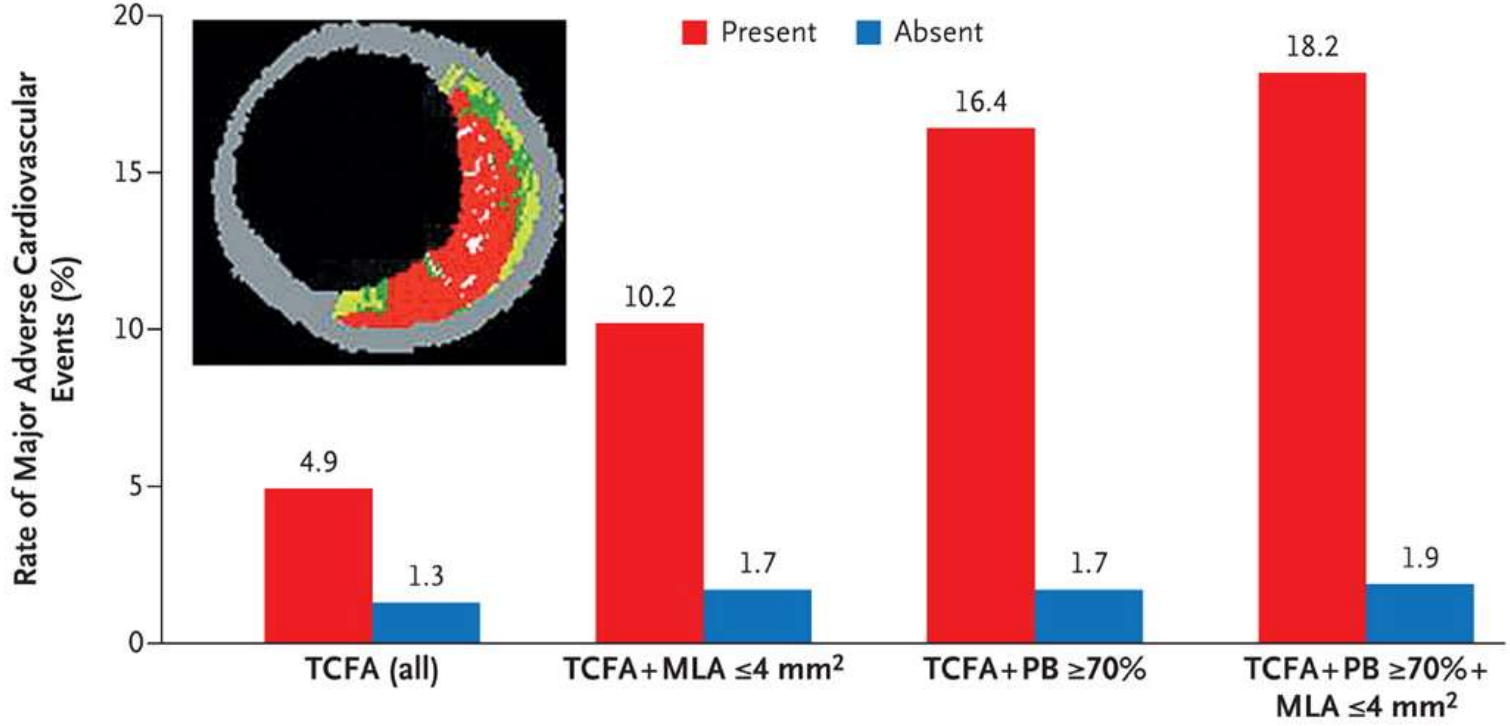


Thin cap fibroatheroma

- **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**

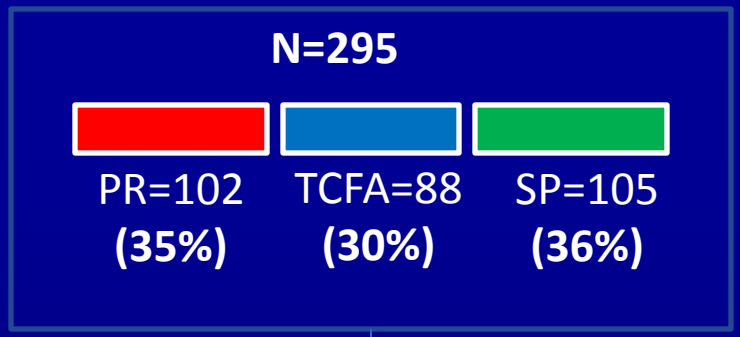


Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

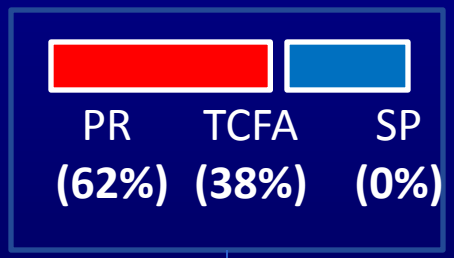
TCFA+PB>70%+MLA<4md conferred a hazard ratio of 11.05
yet 88.2 percent of patients with similar plaques did not have a MACE events
Most of these events were for angina not MI– and in the vast majority of so called high risk plaque there was no events at all!
Event rate in plaques without these features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

Partitioning Analysis By Morphological Parameters

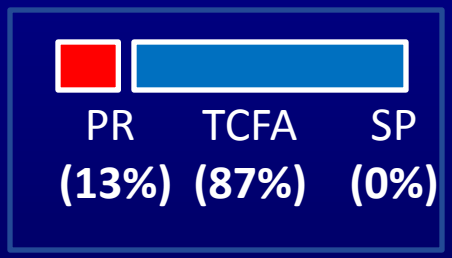
Include Cap Thickness



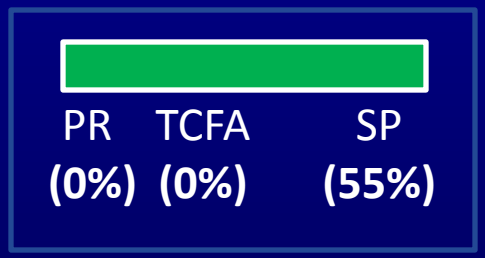
Cap Thickness<54µm



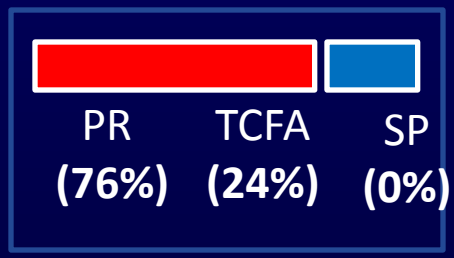
54≤Cap Thickness<84µm



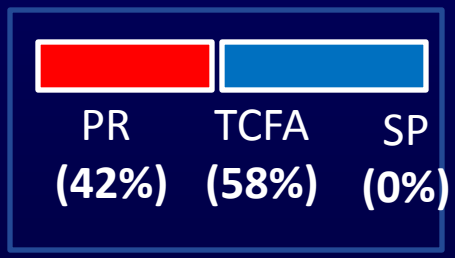
Cap Thickness≥84µm



%Stenosis≥74%



%Stenosis<74%



But this approach requires a technique with superior resolution such as OCT—Not useful for widespread screening purposes

What is the temporal relationship of TCFA to development of event?

Narula J. JACC. 2013

Summary: What Structural Features Predict Plaque Vulnerability

- Large necrotic core in combination with thin cap and excessive macrophage infiltration is the best predictor of future events
- Note there are many qualifications
- Large necrotic core – how to define it – area vs. volume – both are important
- Thin cap – how thin – length of the thin cap – circumference of thin cap or area of thin cap – all are important
- Macrophage infiltration of the thin cap – how many, how close, area and depth, etc.
- A lot of information is missing need better technology to be able to predict with at least 75 to 80% sensitivity and specificity
- We need an event which changes the trajectory of plaque progression

Presence of Intraplaque Hemorrhage Stimulates Progression of Carotid Atherosclerotic Plaques

A High-Resolution Magnetic Resonance Imaging Study

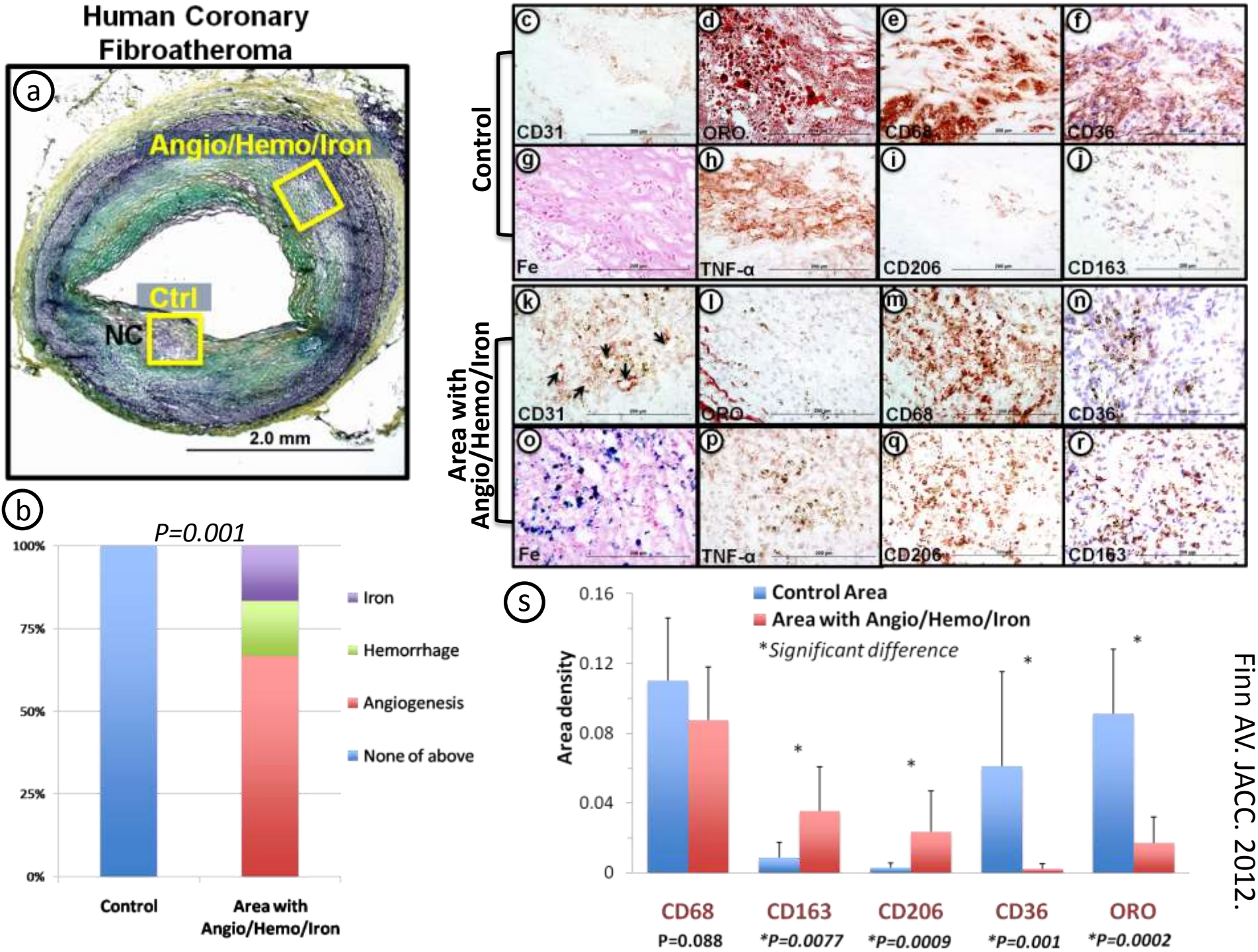
Norihide Takaya, MD, PhD; Chun Yuan, PhD; Baocheng Chu, MD, PhD; Tobias Saam, MD; Nayak L. Polissar, PhD; Gail P. Jarvik, MD, PhD; Carol Isaac, RVT; Judith McDonough, BS; Cynthia Natiello, RN; Randy Small, HT; Marina S. Ferguson, MT; Thomas S. Hatsukami, MD

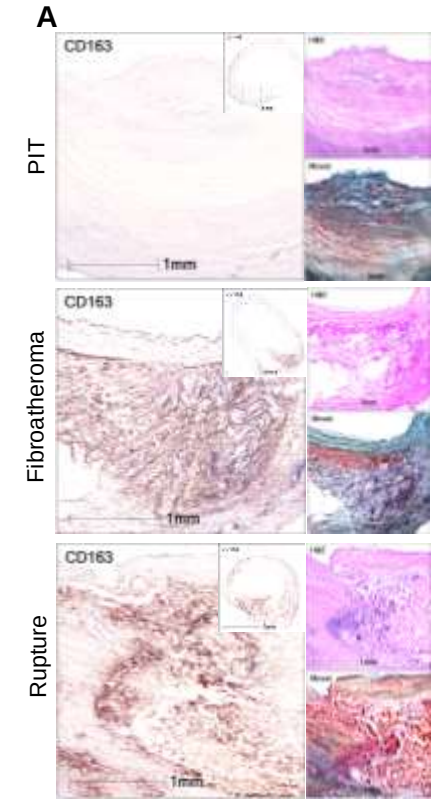
Background—Previous studies suggest that erythrocyte membranes from intraplaque hemorrhage into the necrotic core are a source of free cholesterol and may become a driving force in the progression of atherosclerosis. We have shown that MRI can accurately identify carotid intraplaque hemorrhage and precisely measure plaque volume. We tested the hypothesis that hemorrhage into carotid atheroma stimulates plaque progression.

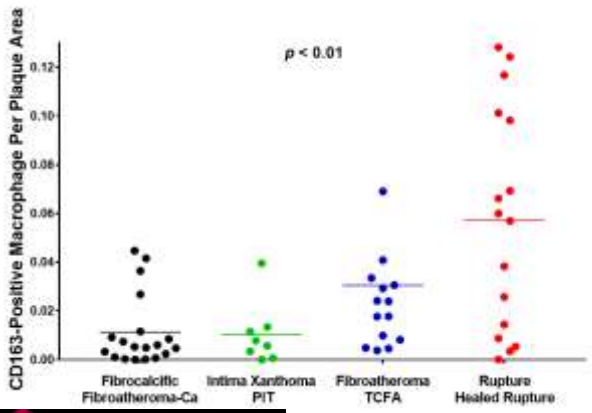
Methods and Results—Twenty-nine subjects (14 cases with intraplaque hemorrhage and 15 controls with comparably sized plaques without intraplaque hemorrhage at baseline) underwent serial carotid MRI examination with a multicontrast weighted protocol (T1, T2, proton density, and 3D time of flight) over a period of 18 months. The volumes of wall, lumen, lipid-rich necrotic core, calcification, and intraplaque hemorrhage were measured with a custom-designed image analysis tool. The percent change in wall volume (6.8% versus −0.15%; $P=0.009$) and lipid-rich necrotic core volume (28.4% versus −5.2%; $P=0.001$) was significantly higher in the hemorrhage group than in controls over the course of the study. Furthermore, those with intraplaque hemorrhage at baseline were much more likely to have new plaque hemorrhages at 18 months compared with controls (43% versus 0%; $P=0.006$).

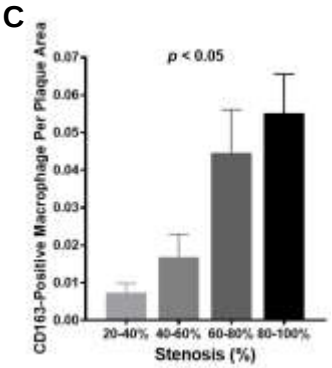
Conclusions—Hemorrhage into the carotid atherosclerotic plaque accelerated plaque progression in an 18-month period. Repeated bleeding into the plaque may produce a stimulus for the progression of atherosclerosis by increasing lipid core and plaque volume and creating new destabilizing factors. (***Circulation*. 2005;111:2768-2775.**)

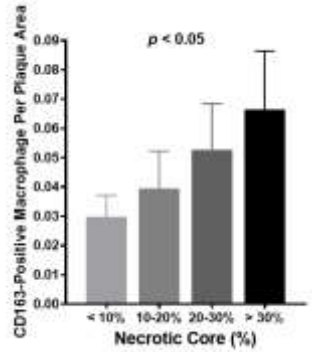
Key Words: magnetic resonance imaging ■ carotid arteries ■ hemorrhage ■ atherosclerosis ■ plaque

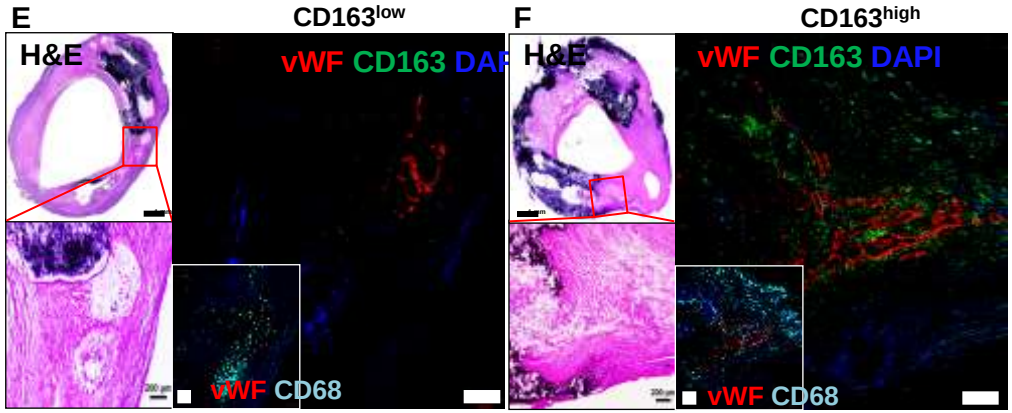

Human Coronary Fibroatheroma
a
Angio/Hemo/Iron
Ctrl
NC
2.0 mm
Control
Area with Angio/Hemo/Iron
c
CD31
d
ORO
e
CD68
f
CD36
g
Fe
h
TNF-α
i
CD206
j
CD163
k
CD31
l
ORO
m
CD68
n
CD36
o
Fe
p
TNF-α
q
CD206
r
CD163
b
P=0.001
100%
75%
50%
25%
0%
Iron
Hemorrhage
Angiogenesis
None of above
Control
Area with Angio/Hemo/Iron
s
Control Area
Area with Angio/Hemo/Iron
*Significant difference
Area density
0.16
0.12
0.08
0.04
0
CD68
P=0.088
CD163
*P=0.0077
CD206
*P=0.0009
CD36
*P=0.001
ORO
*P=0.0002
Finn AV. JACC. 2012.

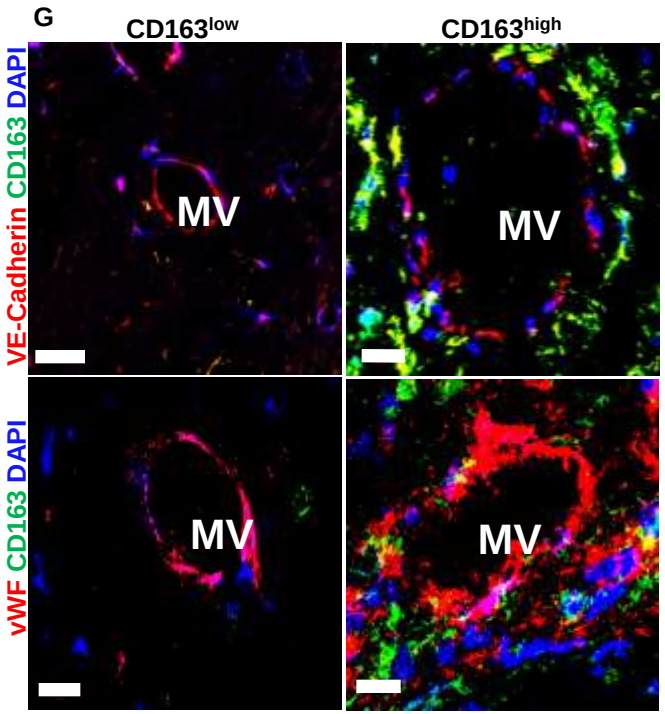


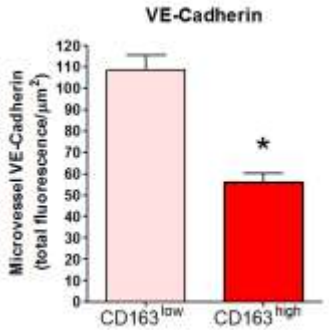


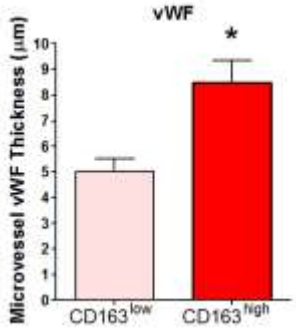






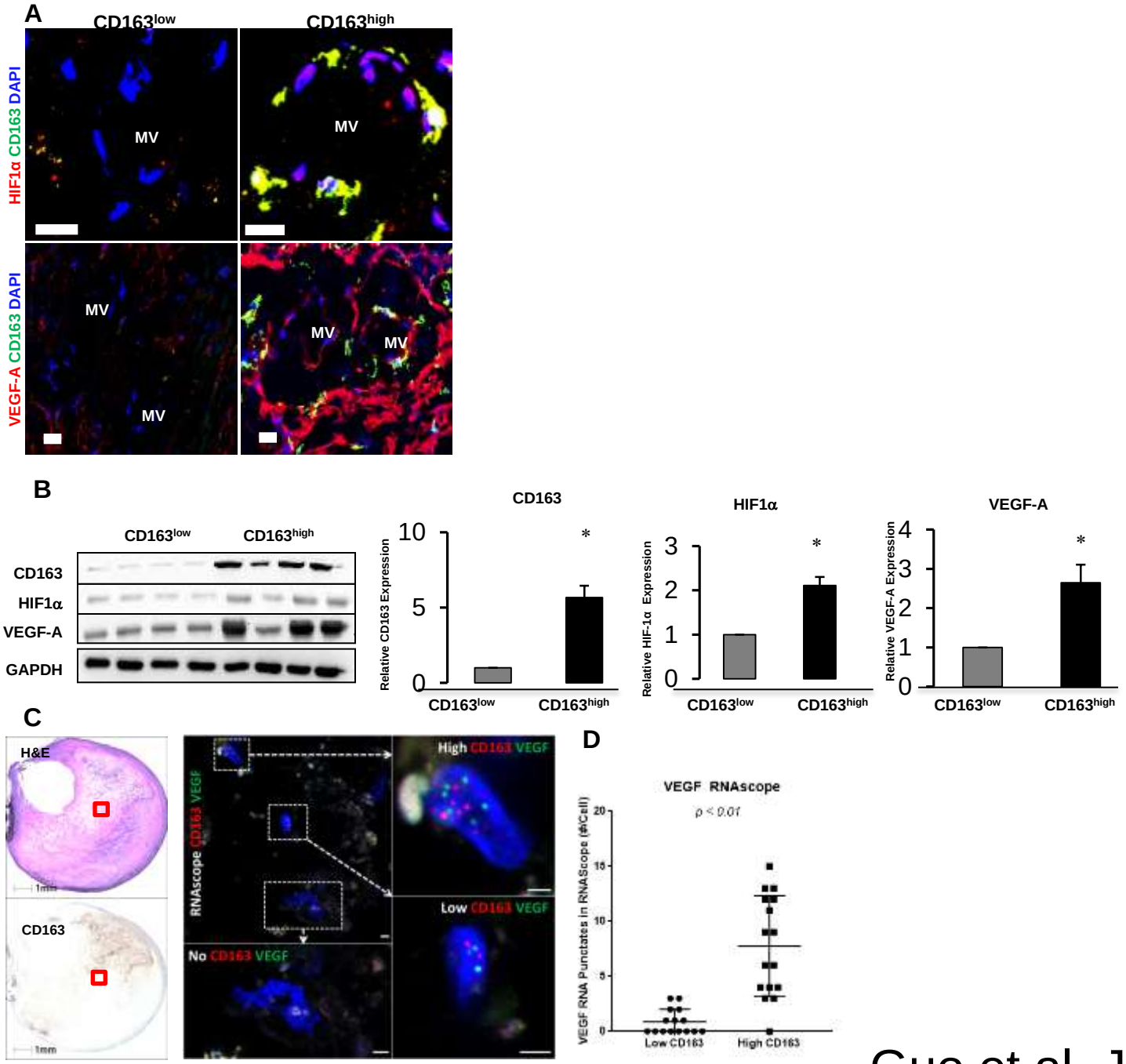




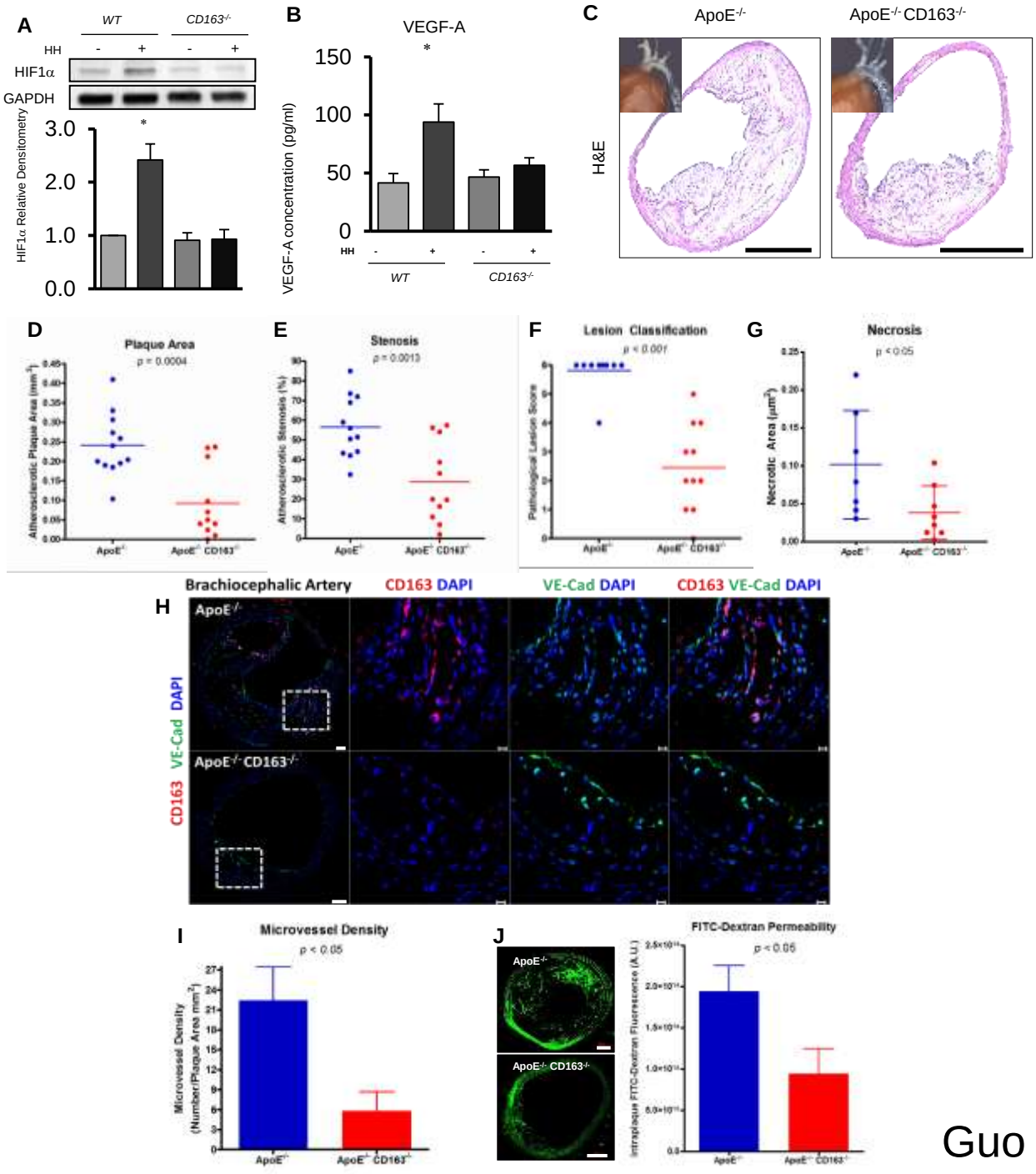


vPath

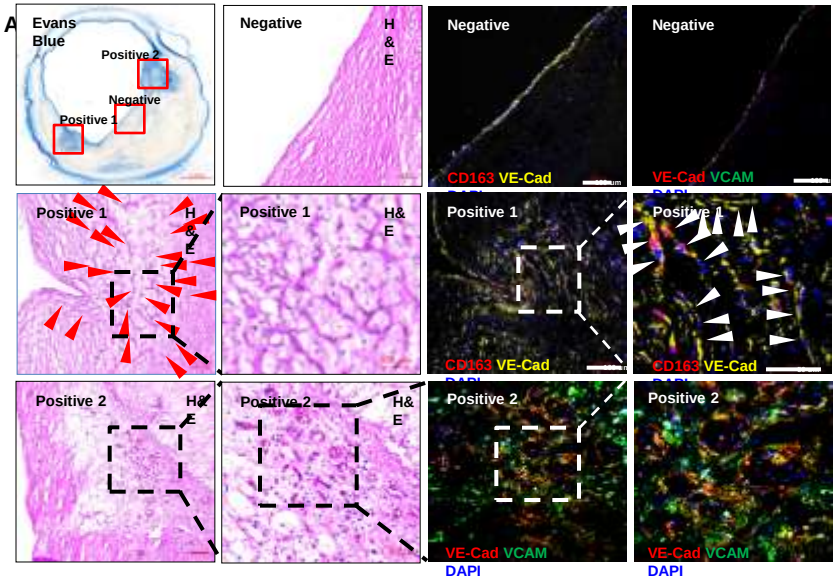
Guo et al. JCI 2018

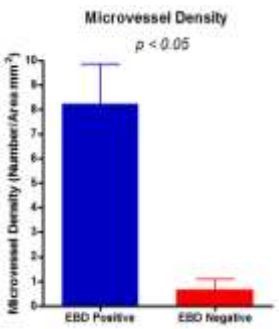


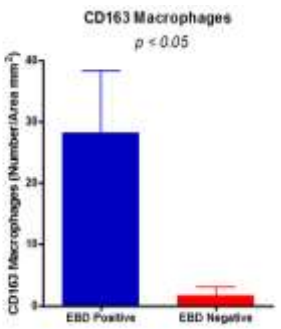
Guo et al. JCI 2018

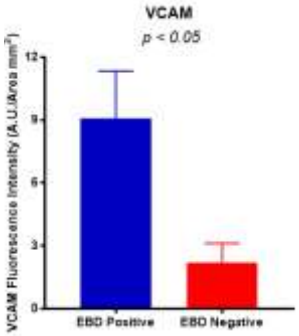


Guo et al. JCI 2018



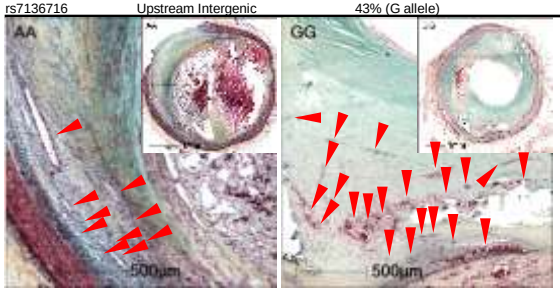






E

SNP Number	SNP Type	Minor allele frequency in total (n=346 patients)	Homozygous Minor Allele in Rupture (n=51 patients)	Homozygous Minor Allele in non-Rupture (n=295 patients)	P-value
rs7136716	Upstream Intergenic	43% (G allele)	14 (27.5%)	46 (15.6%)	0.046



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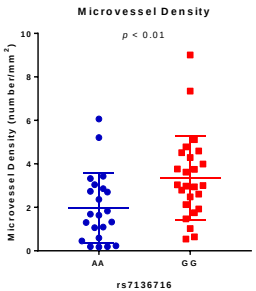

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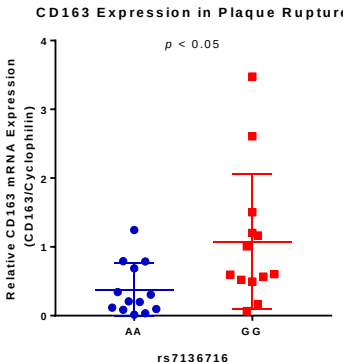

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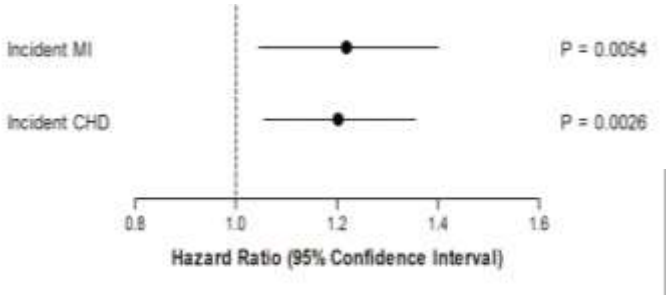

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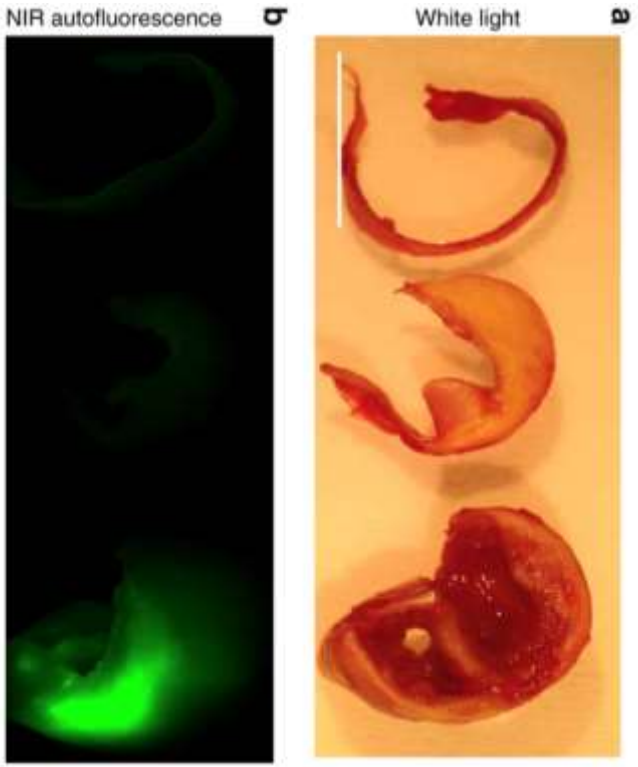

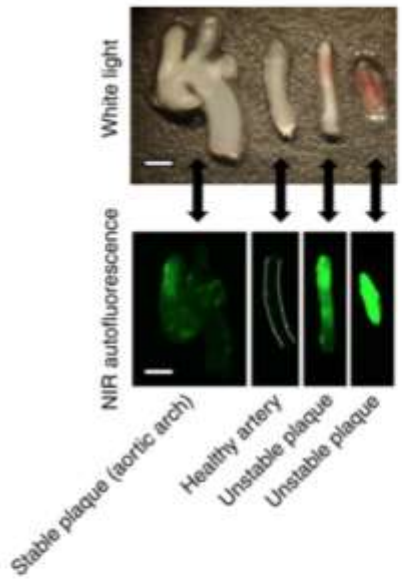

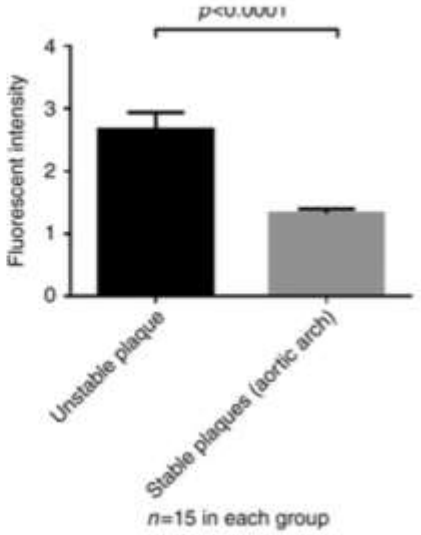

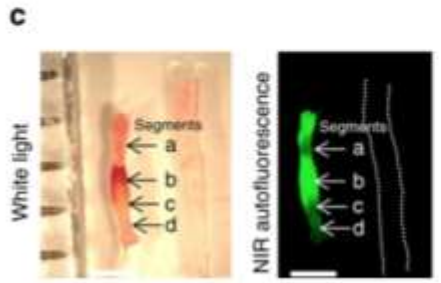

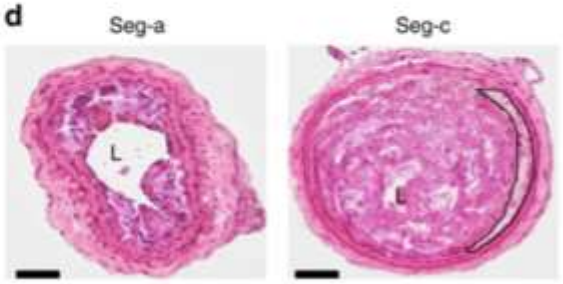

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VP Detection

- Relying on morphometric characteristics for VP alone will not provide enough information to target vulnerable plaque
- We need to focus on identifying critical events which fundamentally alter the natural history of plaque
- IPH is very likely the best of these
- NIRF imaging appears to hold promise for the identification of IPH

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