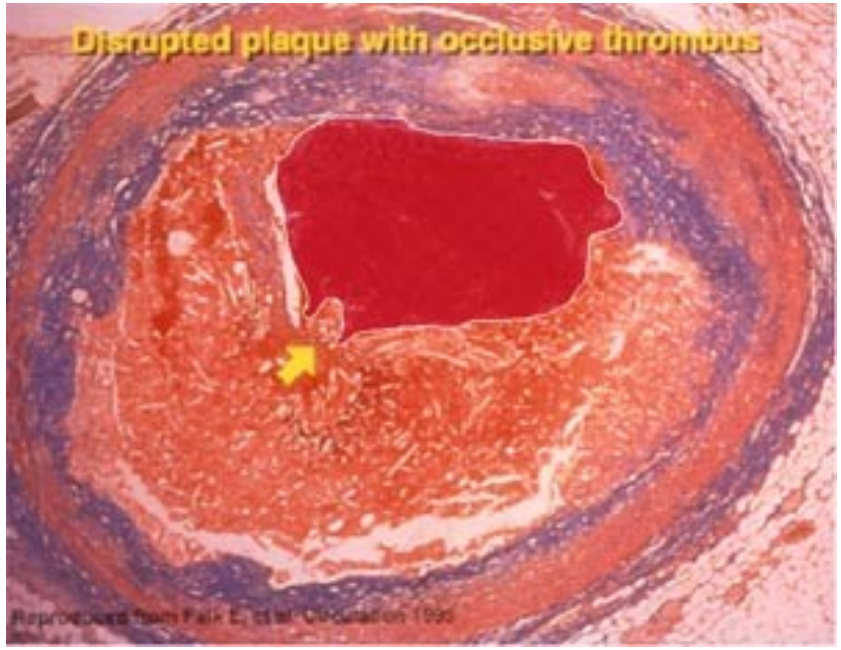
ACS pathophysiology: an Update



חיים דנברג
המרכז הרפואי הדסה
ירושלים


VULNERABLE PLAQUE
VULNERABLE PATIENT
VULNERABLE BLOOD
VULNERABLE MYOCARDIUM

Thrombus Formation and ACS

Plaque Disruption/Fissure/Erosion

Thrombus Formation

Old Terminology:

UA | NQMI | STE-MI

New Terminology:

Non-ST-Segment Elevation Acute Coronary Syndrome (ACS) ⟷ ST-Segment Elevation Acute Coronary Syndrome (ACS)

Atherothrombosis and Acute Coronary Symdromes: Terminology

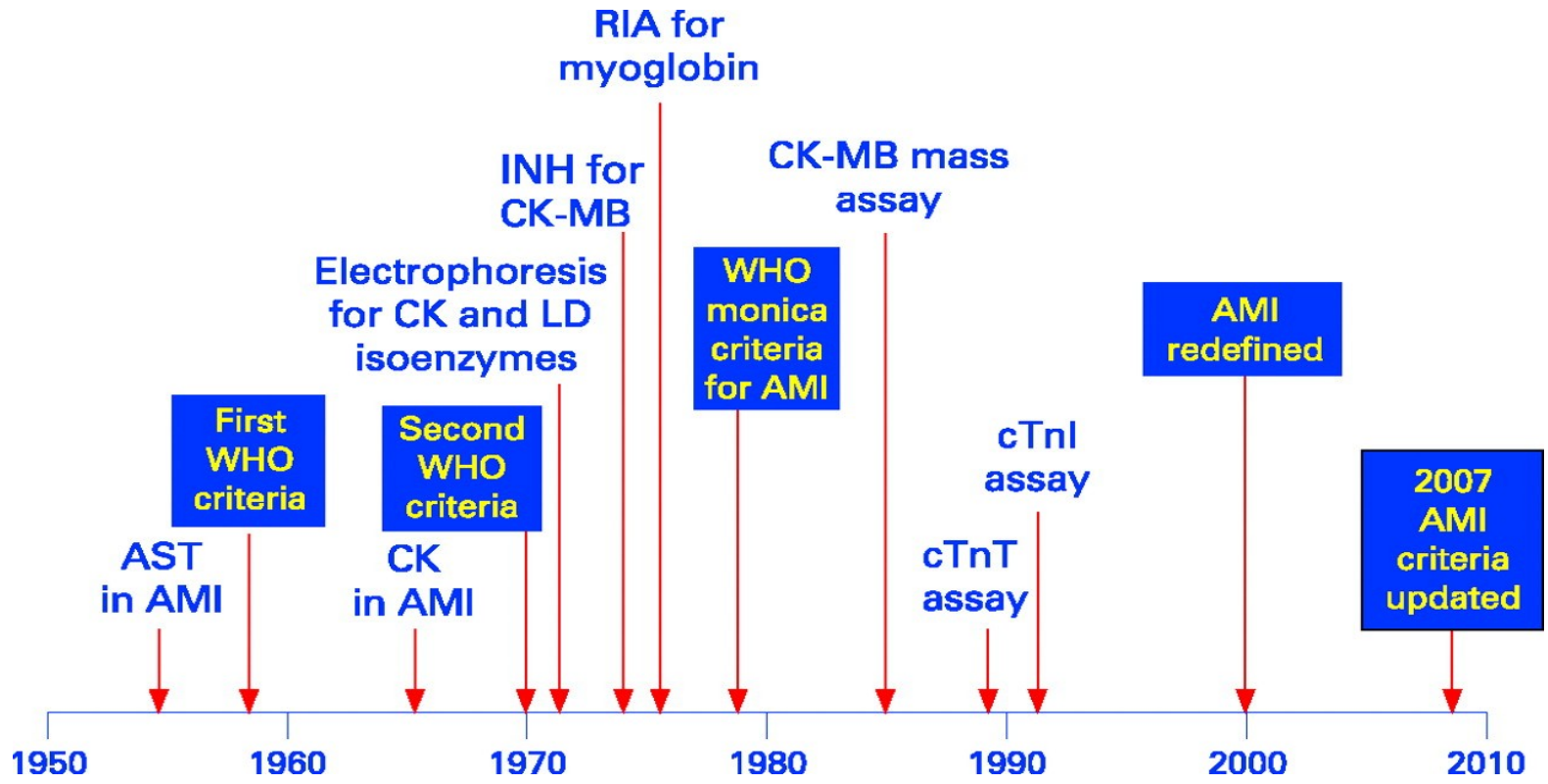
Culprit lesion	A lesion in a coronary artery considered, on the basis of angiographic, autopsy, or other findings, to be responsible for the clinical event. In unstable angina, myocardial infarction, and sudden coronary death, the culprit lesion is often a plaque complicated by thrombosis extending into the lumen.
Eroded plaque	A plaque with loss and/or dysfunction of the lumenal endothelial cells leading to thrombosis. There is usually no additional defect or gap in the plaque, which is often rich in smooth muscle cells and proteoglycans.
High-risk, vulnerable, and thrombosis-prone plaque	These terms can be used as synonyms to describe a plaque that is at increased risk of thrombosis and rapid stenosis progression.
Inflamed thin-cap fibroatheroma	An inflamed plaque with a thin cap covering a lipid-rich, necrotic core. An inflamed thin-cap fibroatheroma is suspected to be a high-risk/vulnerable plaque.
Plaque with a calcified nodule	A heavily calcified plaque with the loss and/or dysfunction of endothelial cells over a calcified nodule, resulting in loss of fibrous cap, that makes the plaque at high-risk/vulnerable. This is the least common of the three types of suspected high-risk/vulnerable plaques.
Ruptured plaque	A plaque with deep injury with a real defect or gap in the fibrous cap that had separated its lipid-rich atheromatous core from the flowing blood, thereby exposing the thrombogenic core of the plaque. This is the most common cause of thrombosis.
Thrombosed plaque	A plaque with an overlying thrombus extending into the lumen of the vessel. The thrombus may be occlusive or non-occlusive.
Vulnerable patient	A patient at high risk (vulnerable, prone) for experiencing a cardiovascular ischemic event due to a high atherosclerotic burden, high-risk vulnerable plaques, and/or thrombogenic blood.

Adapted with permission from Schaar JA, et al. Eur Heart J 2004;25:1077–82.

New (universal) MI definition

- Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2: MI secondary to ischemia due to oxygen demand:supply imbalance (coronary artery spasm, embolism, anemia, arrhythmias, hypertension, or hypotension)
- Type 3: Sudden unexpected cardiac death accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
- Type 4a: MI associated with PCI
- Type 4b: MI associated with stent thrombosis (definite)
- Type 5: Myocardial infarction associated with CABG

History of biomarkers and the definition of acute myocardial infarction (AMI).



Alpert, J. S et al. Heart 2008;94:1335-1341

Elevations of troponin in the absence of overt IHD

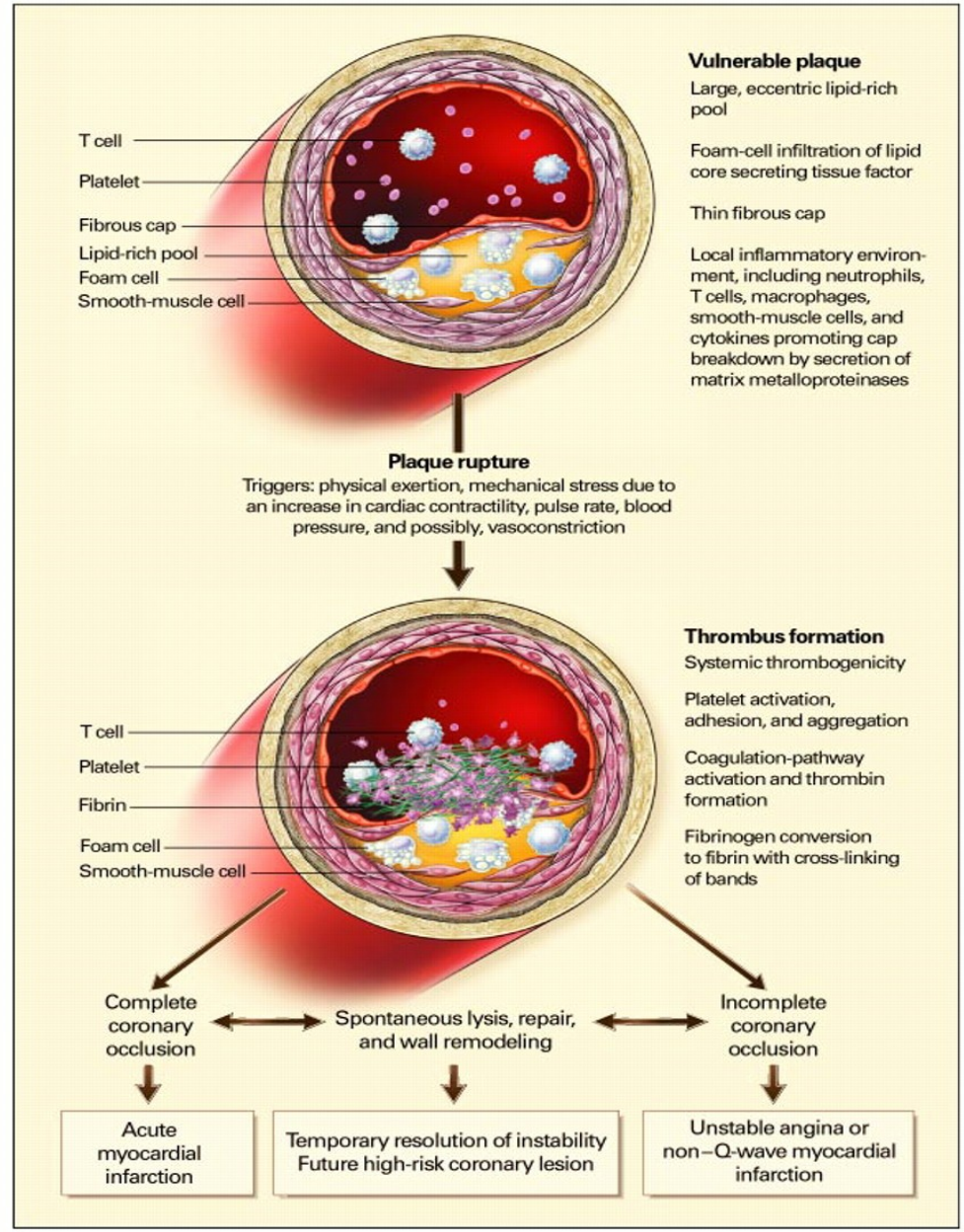
Table 2 Elevations of troponin in the absence of overt ischemic heart disease

Cardiac contusion, or other trauma including surgery, ablation, pacing, etc.
Congestive heart failure—acute and chronic
Aortic dissection
Aortic valve disease
Hypertrophic cardiomyopathy
Tachy- or bradyarrhythmias, or heart block
Apical ballooning syndrome
Rhabdomyolysis with cardiac injury
Pulmonary embolism, severe pulmonary hypertension
Renal failure
Acute neurological disease, including stroke or subarachnoid haemorrhage
Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, and scleroderma
Inflammatory diseases, e.g. myocarditis or myocardial extension of endo-/pericarditis
Drug toxicity or toxins
Critically ill patients, especially with respiratory failure or sepsis
Burns, especially if affecting >30% of body surface area
Extreme exertion

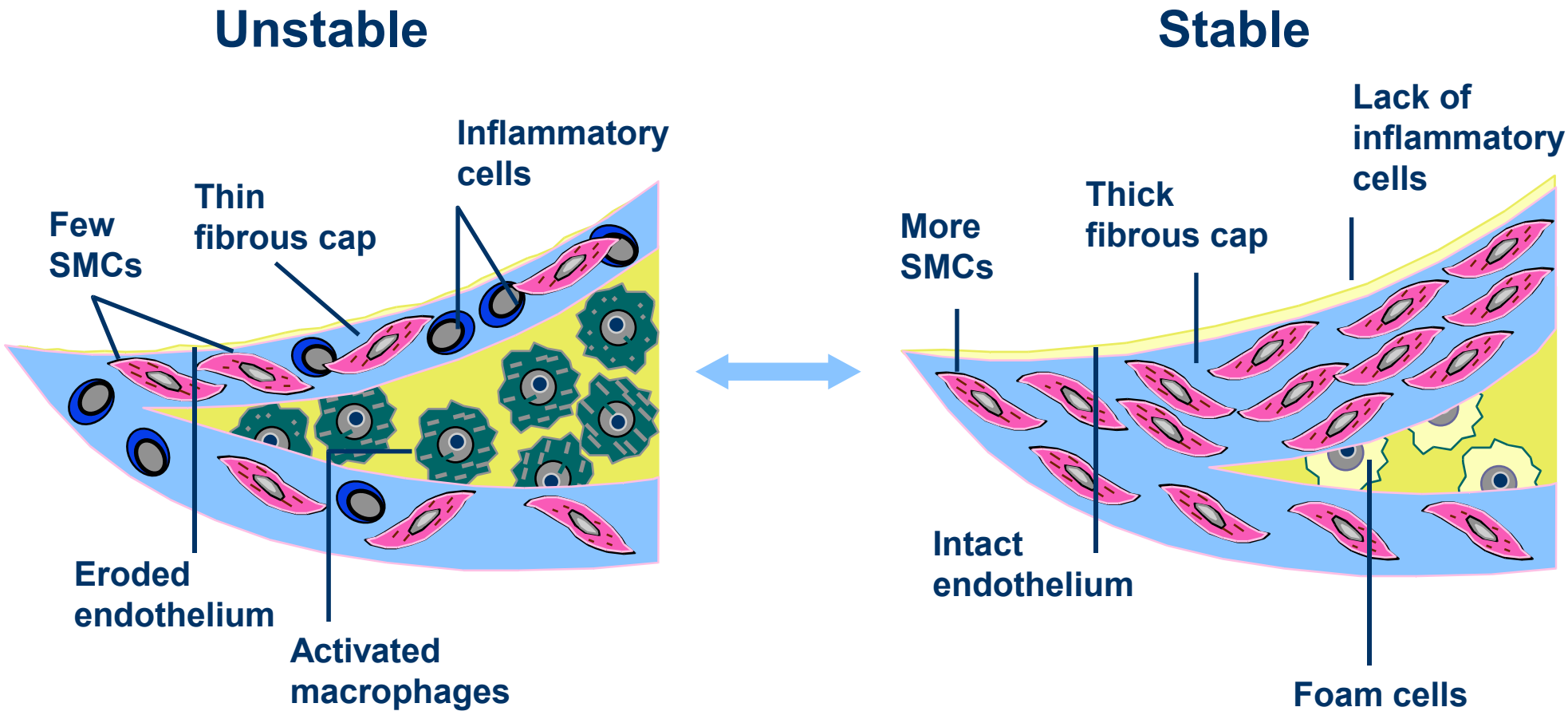
Modified from Jaffe *et al.*,[4] and French and White.[5]

Thygesen, K. et al. Circulation 2007

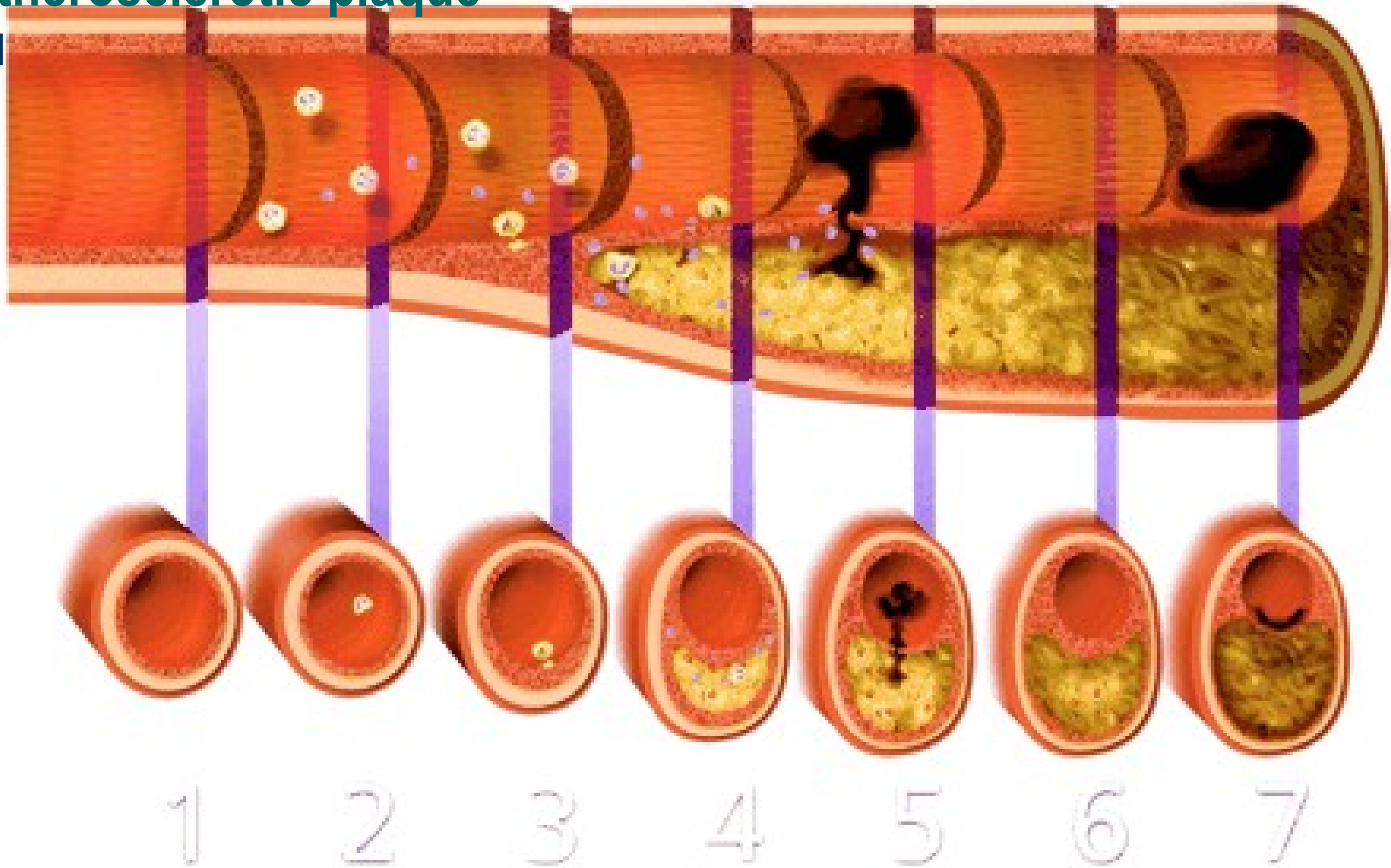
Stable and Unstable Plaques



Characteristics of Unstable and Stable Plaque



Initiation, progression, and complication of human coronary atherosclerotic plaque

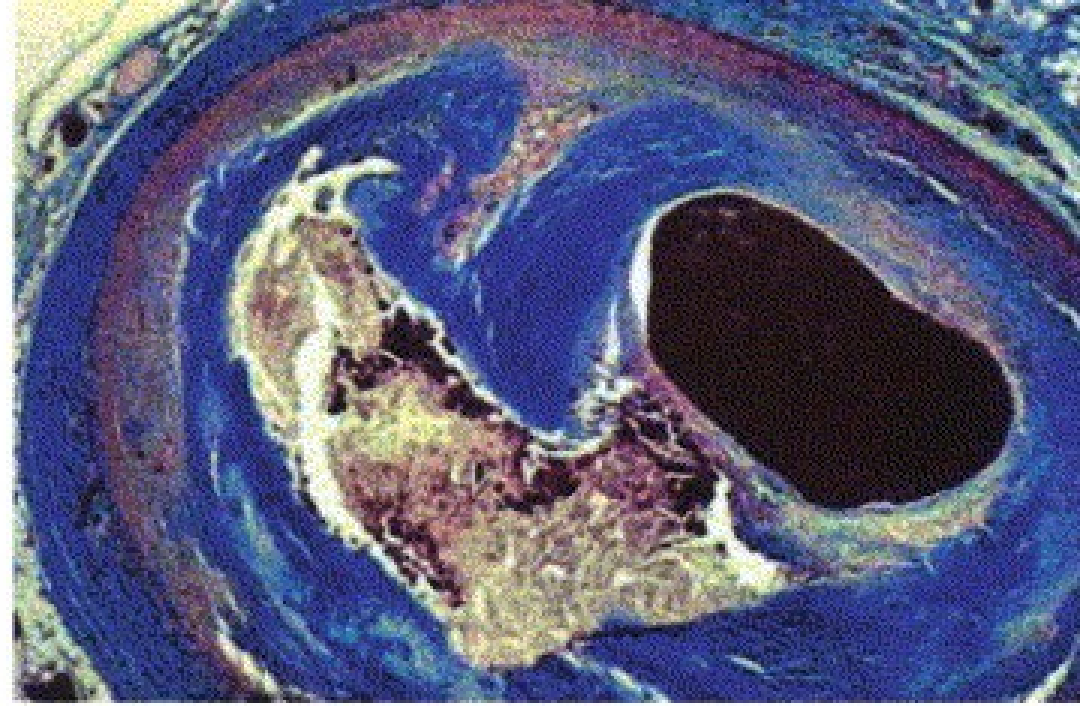


Vulnerable plaque

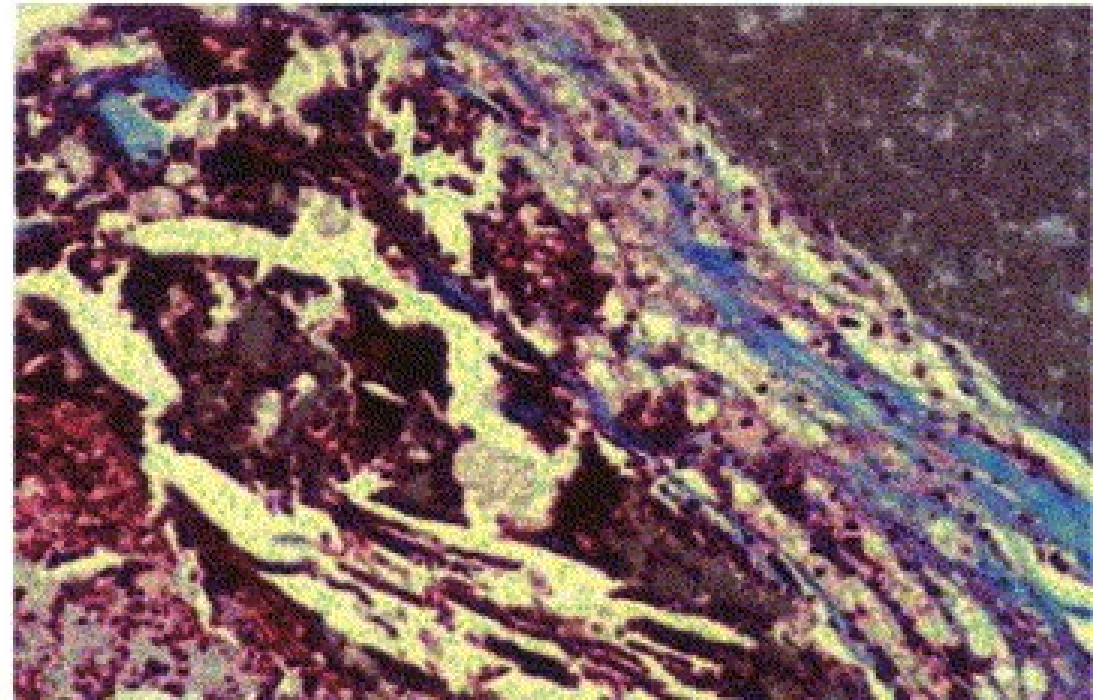
A plaque with:

1) fibrous cap <65 μm thick

2) infiltrate of macrophages (>25 per high-magnification [0.3-mm diameter] field)



a



b

Human atheroma that rupture (vulnerable plaques) share certain common characteristics:

1. Lipid-rich central core (40% of its volume), with an abundant amount of lipid-laden macrophage foam cells derived from blood monocytes.
2. Thin, friable fibrous caps. (cap thickness < 60 micron)
3. Inflammation in the fibrous cap
4. Blood vessels from the vasa-vasorum penetrating the plaque
5. Fractures in the internal elastic lamina

Libby P. *Circulation* 1995;91(11):2844-50.

Pasterkamp G, *Atherosclerosis* 2000;150(2):245-53.

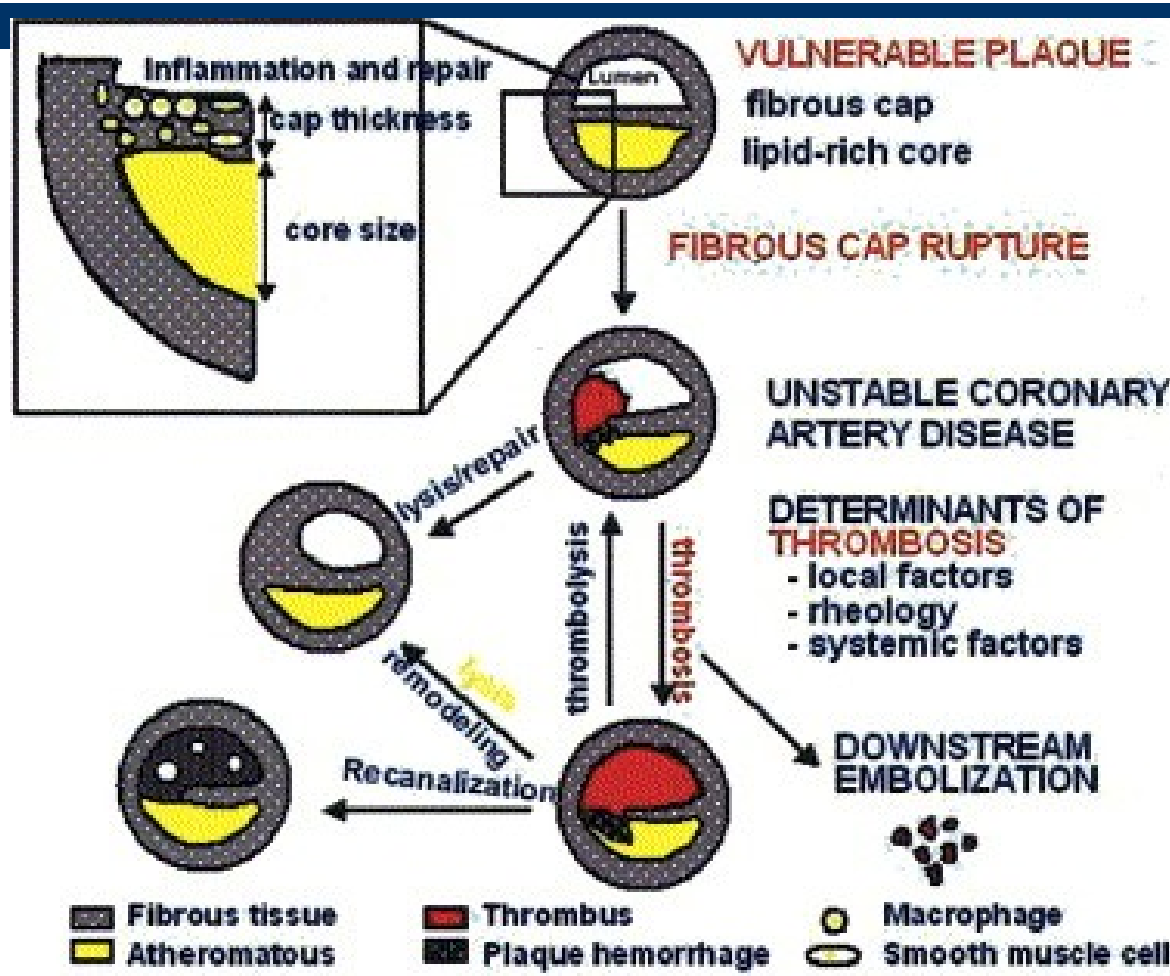
Kinlay S, *J Cardiovasc Pharmacol* 1998;32(Suppl 3):S62-6.

Sukhova GK, *Circulation* 1999;99(19):2503-9.

Pasterkamp G, *ATVB* 1999;19(1):54-8.

Ricquier D, *J Intern Med* 1999;245(6):637-42.

Plaque rupture



Plaque

Morphology/Structure

- Plaque cap thickness
- Plaque lipid core size
- Plaque stenosis (luminal narrowing)
- Remodeling (expansive vs constrictive remodeling)
- Color (yellow, glistening yellow, red, etc)
- Collagen content versus lipid content, mechanical stability (stiffness and elasticity)
- Calcification burden and pattern (nodule vs scattered, superficial vs deep, etc)
- Shear stress (flow pattern throughout the coronary artery)

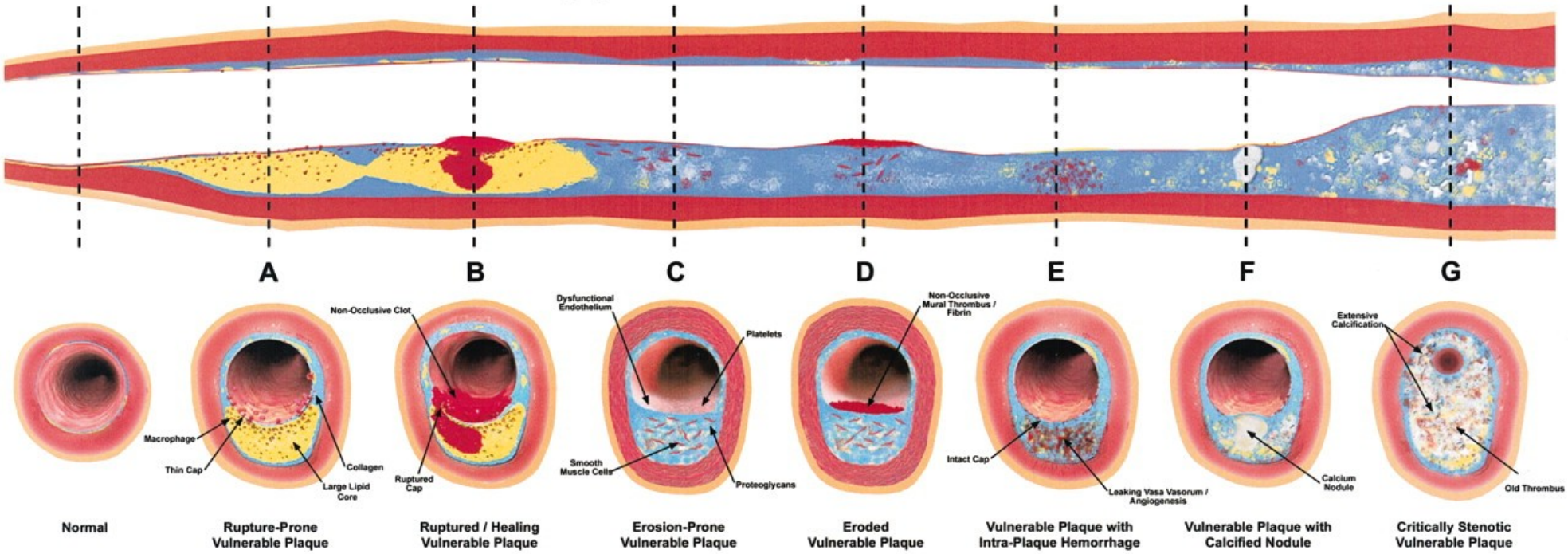
Activity/Function

- Plaque inflammation (macrophage density, rate of monocyte infiltration and density of activated T cell)
- Endothelial denudation or dysfunction (local NO production, anti-/procoagulation properties of the endothelium)
- Plaque oxidative stress
- Superficial platelet aggregation and fibrin deposition (residual mural thrombus)
- Rate of apoptosis (apoptosis protein markers, coronary microsatellite, etc)
- Angiogenesis, leaking vasa vasorum, and intraplaque hemorrhage
- Matrix-digesting enzyme activity in the cap (MMPs 2, 3, 9, etc)
- Certain microbial antigens (eg, HSP60, *C. pneumoniae*)

Pan-Arterial

- Transcoronary gradient of serum markers of vulnerability
- Total coronary calcium burden
- Total coronary vasoreactivity (endothelial function)
- Total arterial burden of plaque including peripheral (eg, carotid IMT)

Different Types of Vulnerable Plaque



Atherothrombotic lesion types

I lesions, consisting of macrophage-derived foam cells that contain lipid droplets

II lesions, consisting of both macrophages and smooth-muscle cells and mild extracellular lipid deposits

III lesions, consisting of smooth-muscle cells surrounded by extracellular connective tissue, fibrils, and lipid deposits

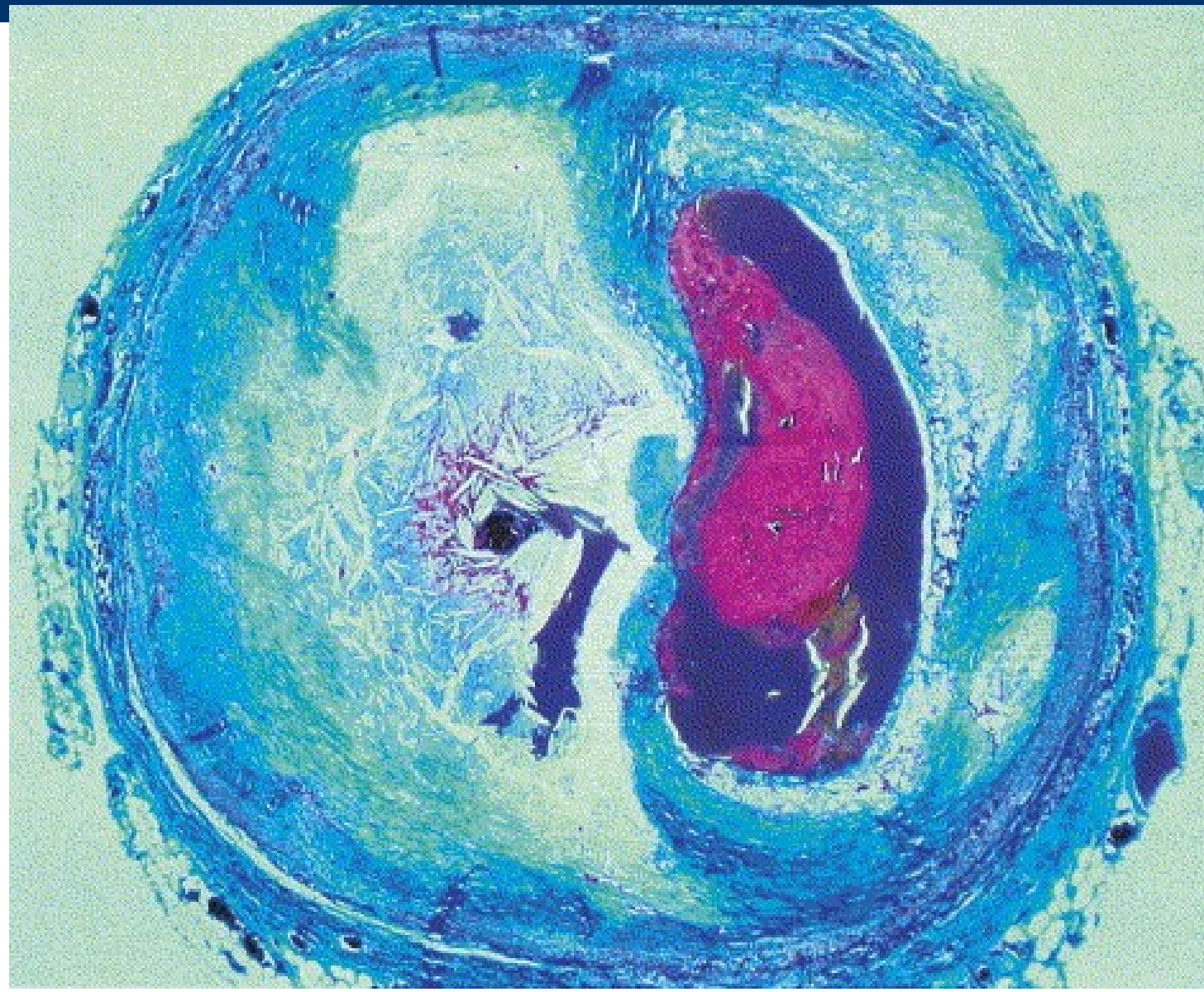
IV lesions, consisting of confluent cellular lesions with a great deal of extracellular lipid intermixed with normal intima, which may predominate as an outer layer or cap

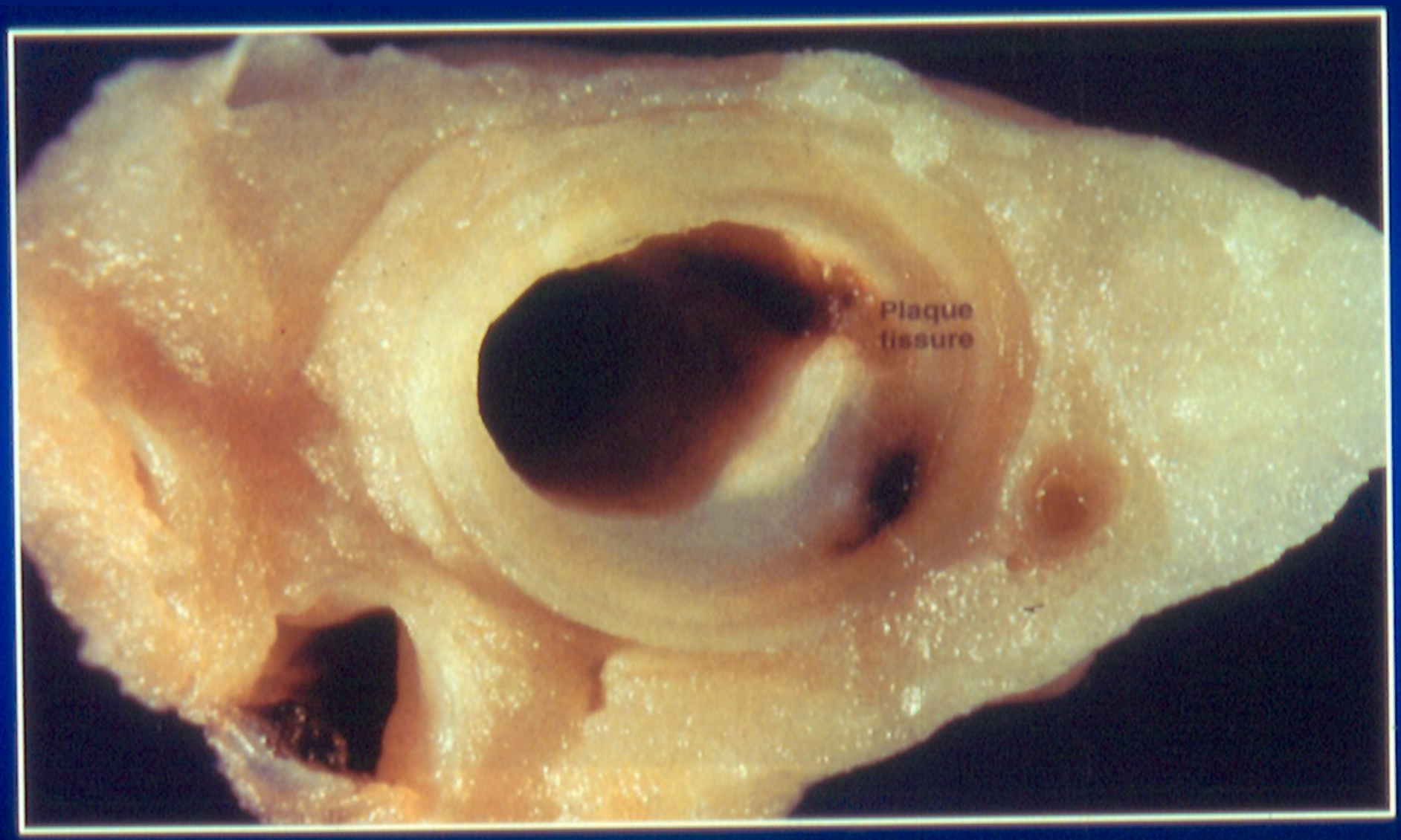
Va lesions, possessing an extracellular lipid core covered by an acquired fibrous cap

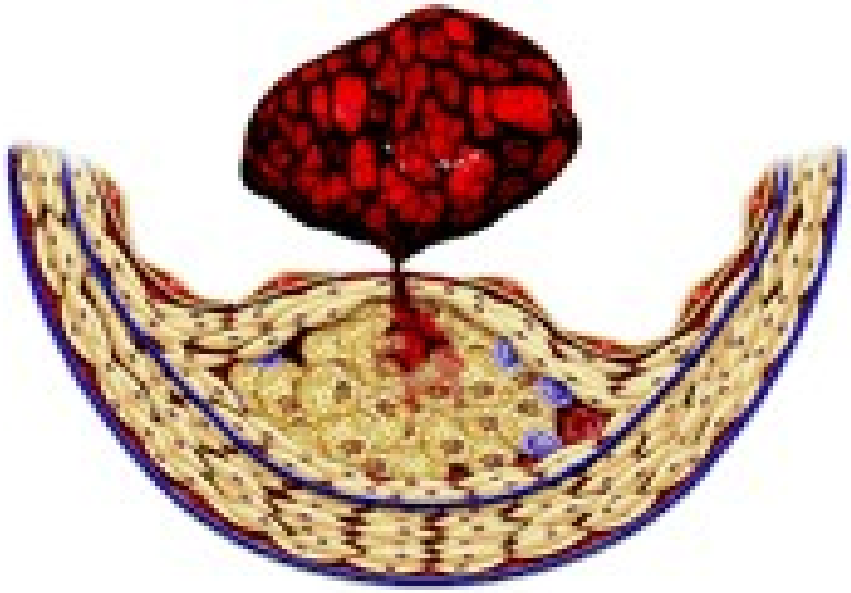
VI lesions, originating from ruptured (type IV or Va) or eroded lesions, and leading to mural, non-obstructive thrombosis

Vb (calcific) or Vc (fibrotic) lesions that may cause angina

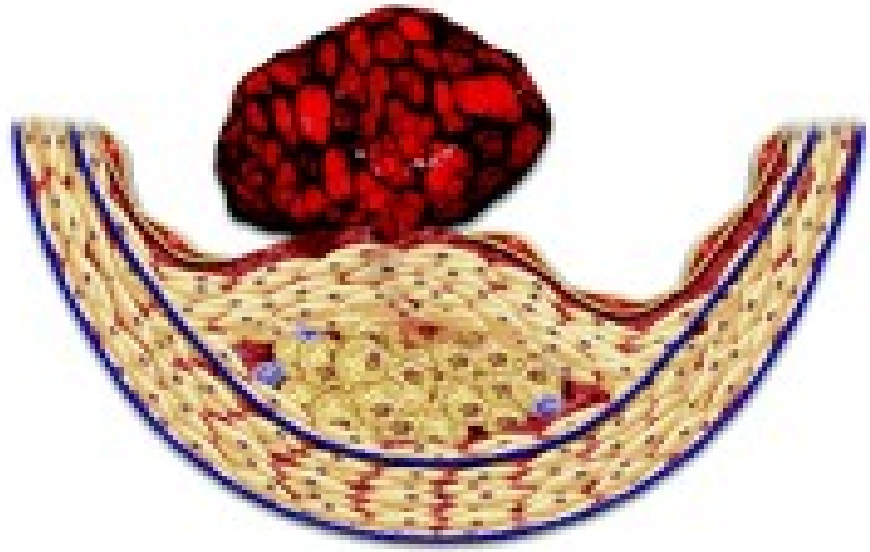
Ruptured Plaque



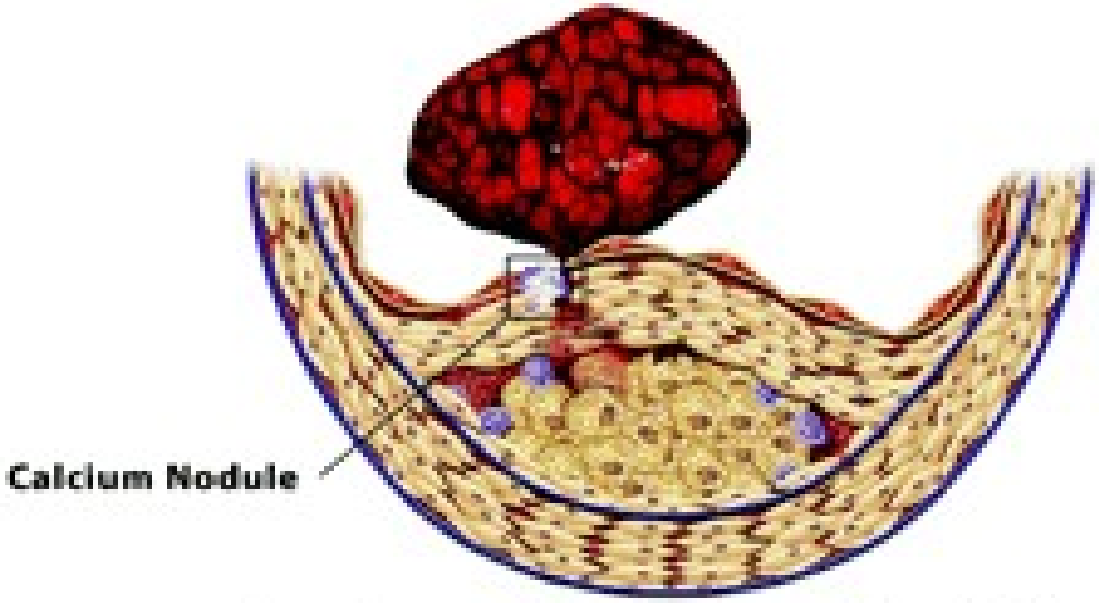

Plaque
fissure



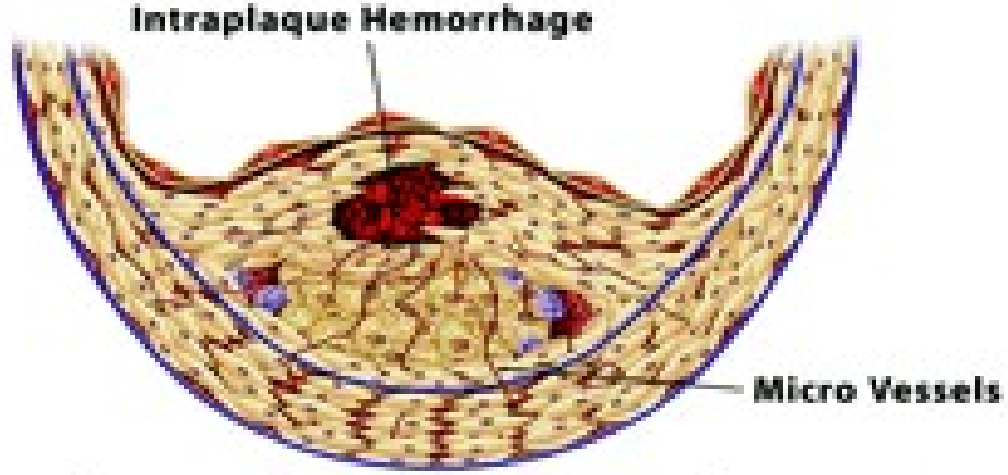
Rupture of Fibrous Cap



Superficial Erosion



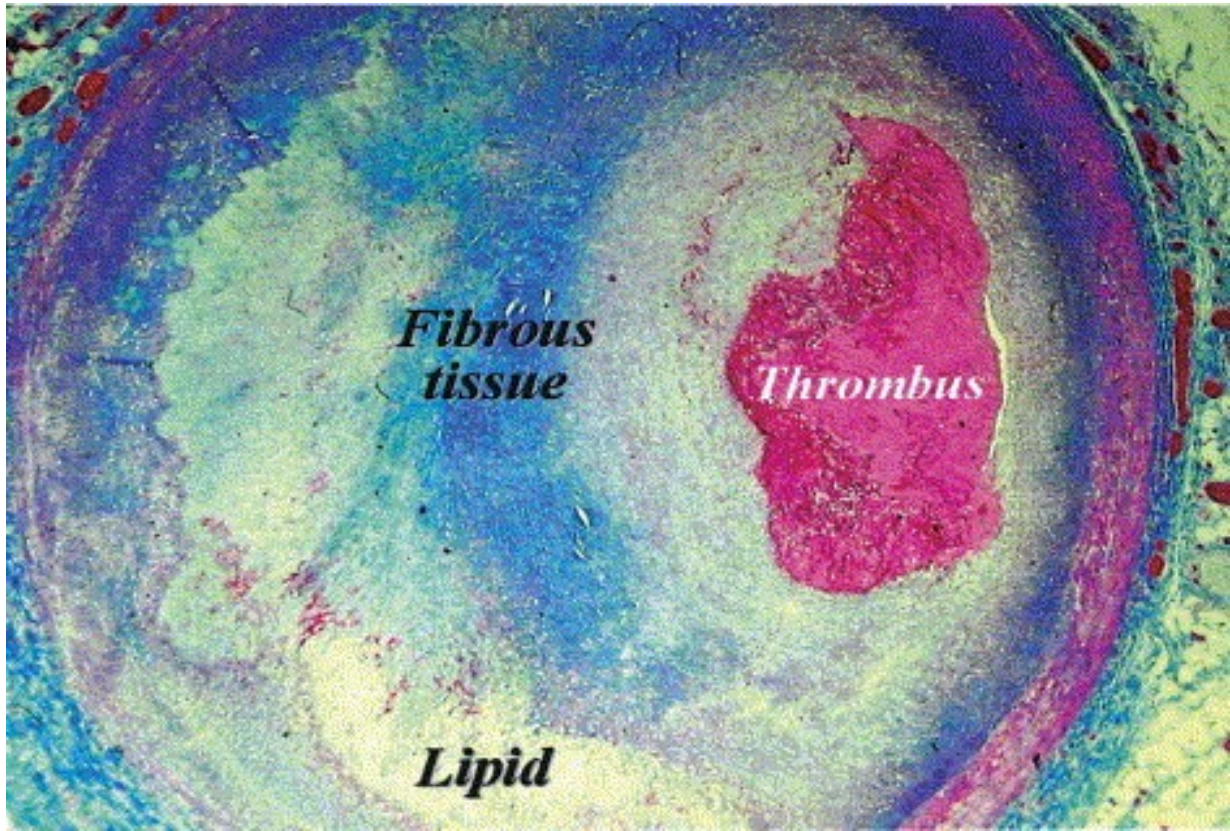
Erosion of Calcium Nodule



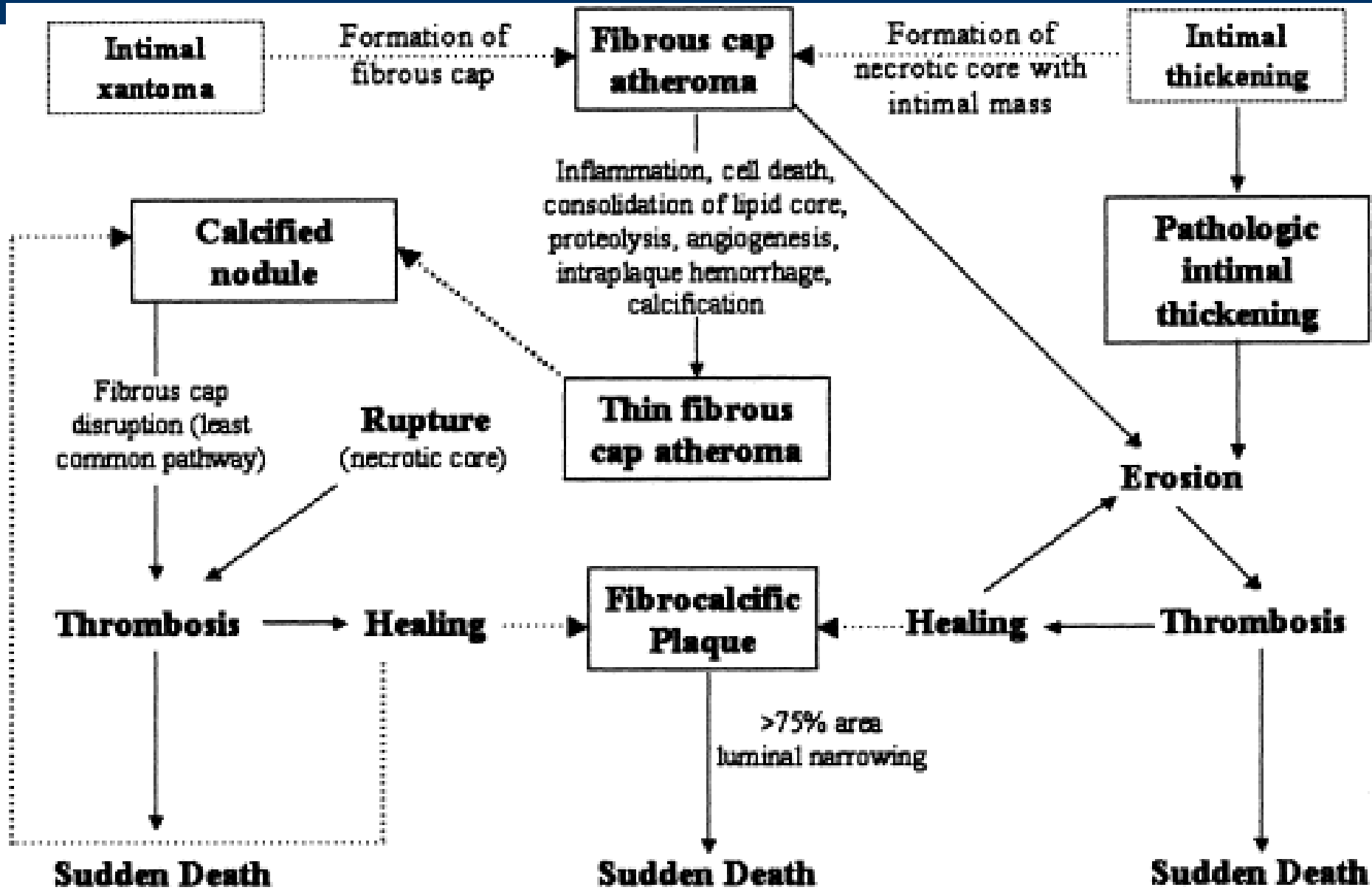
Intraplaque Hemorrhage

Plaque Erosion

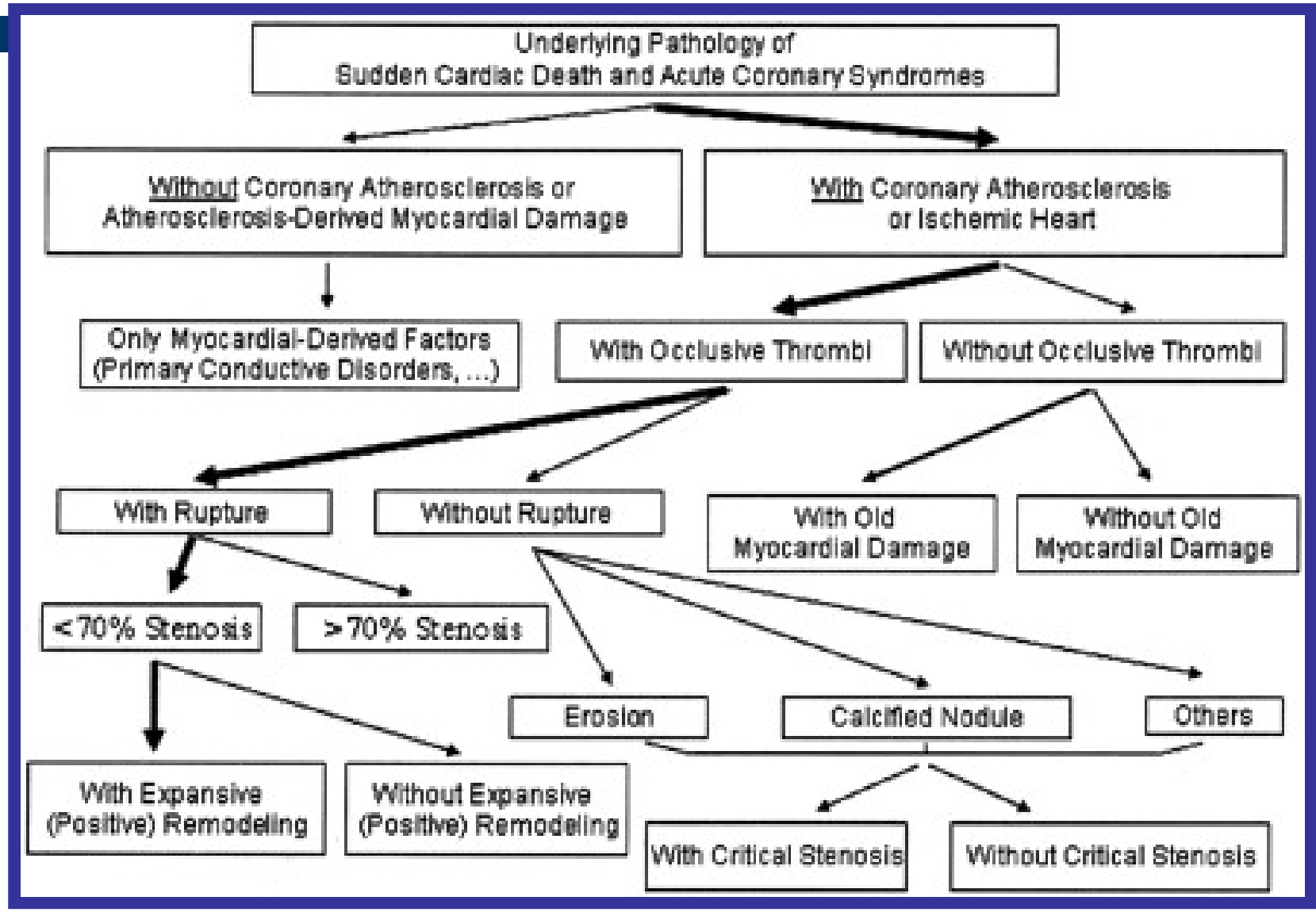
- 30% to 40% of coronary thrombosis occurs at sites at which plaque rupture cannot be identified
- of 50 consecutive cases of sudden cardiac death attributable to coronary thrombosis, in which 22 had superficial erosion of a proteoglycan-smooth muscle cell–rich plaque (Farb. Et al).

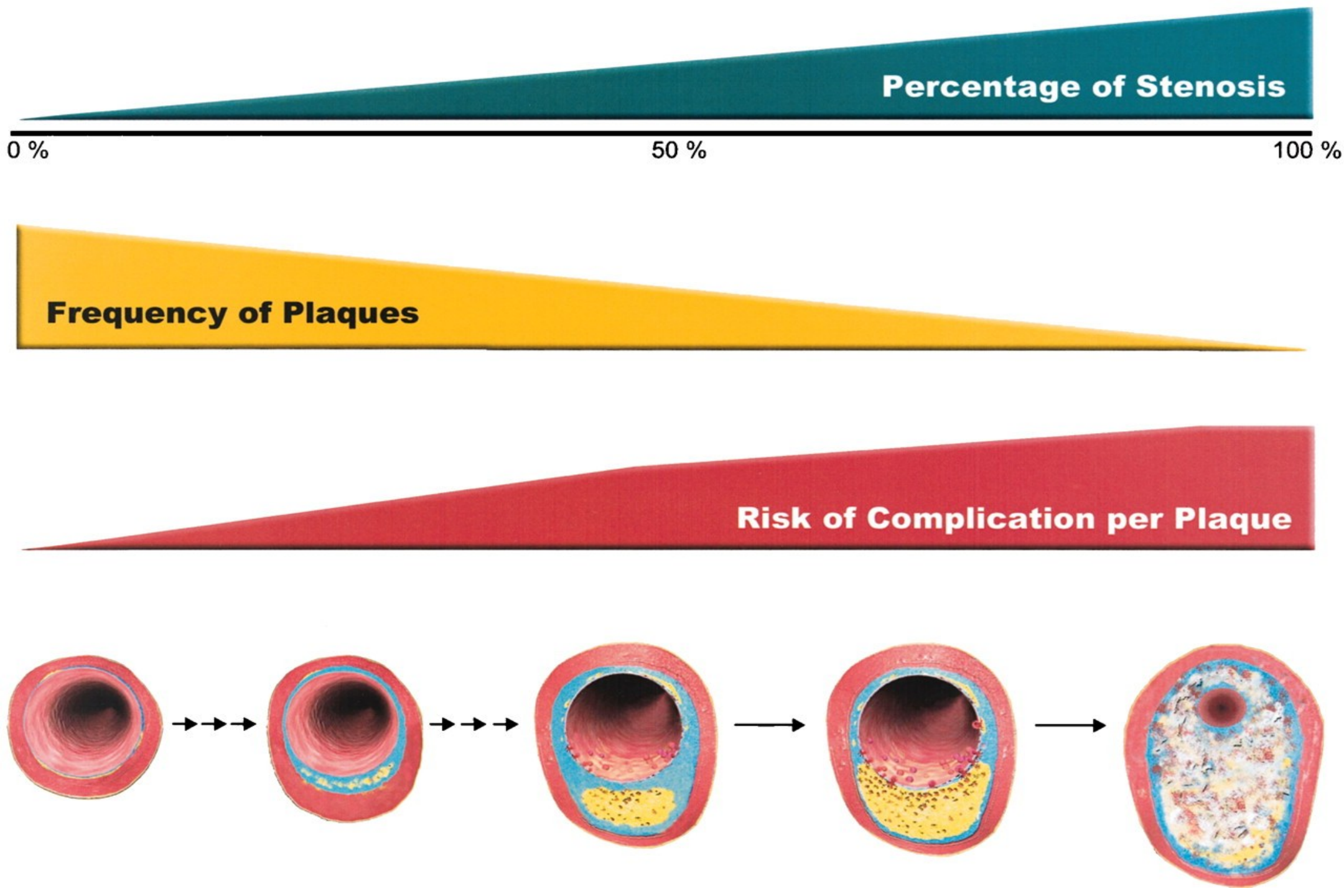


Atherothrombotic lesion classification: Virmani

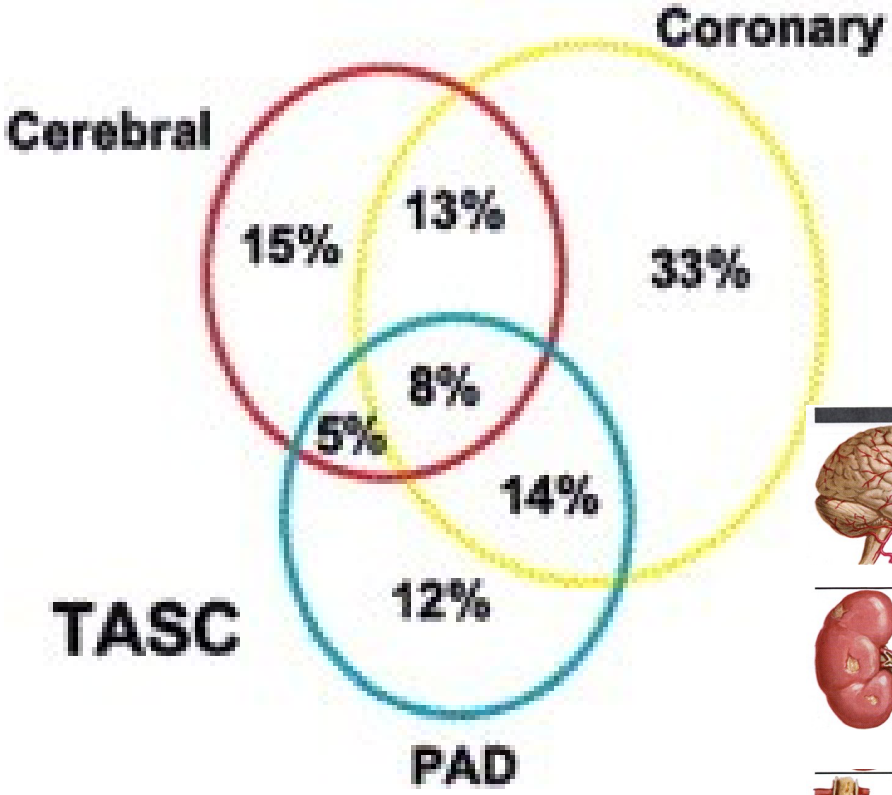


Pathology of Acute Coronary Syndrome

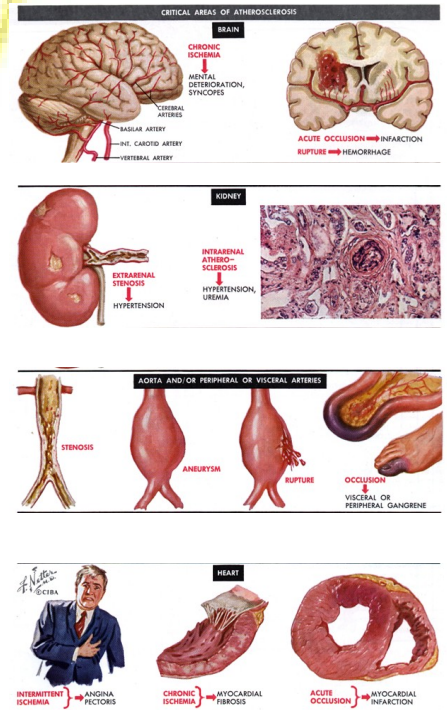


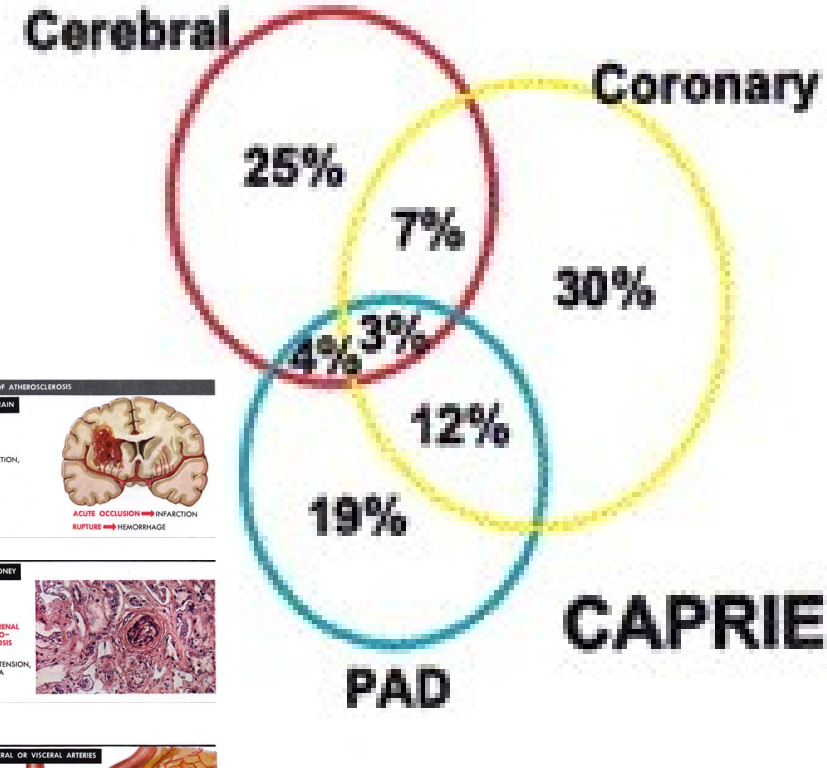

Percentage of Stenosis
0 %
50 %
100 %
Frequency of Plaques
Risk of Complication per Plaque

Atherothrombosis: a systemic disease



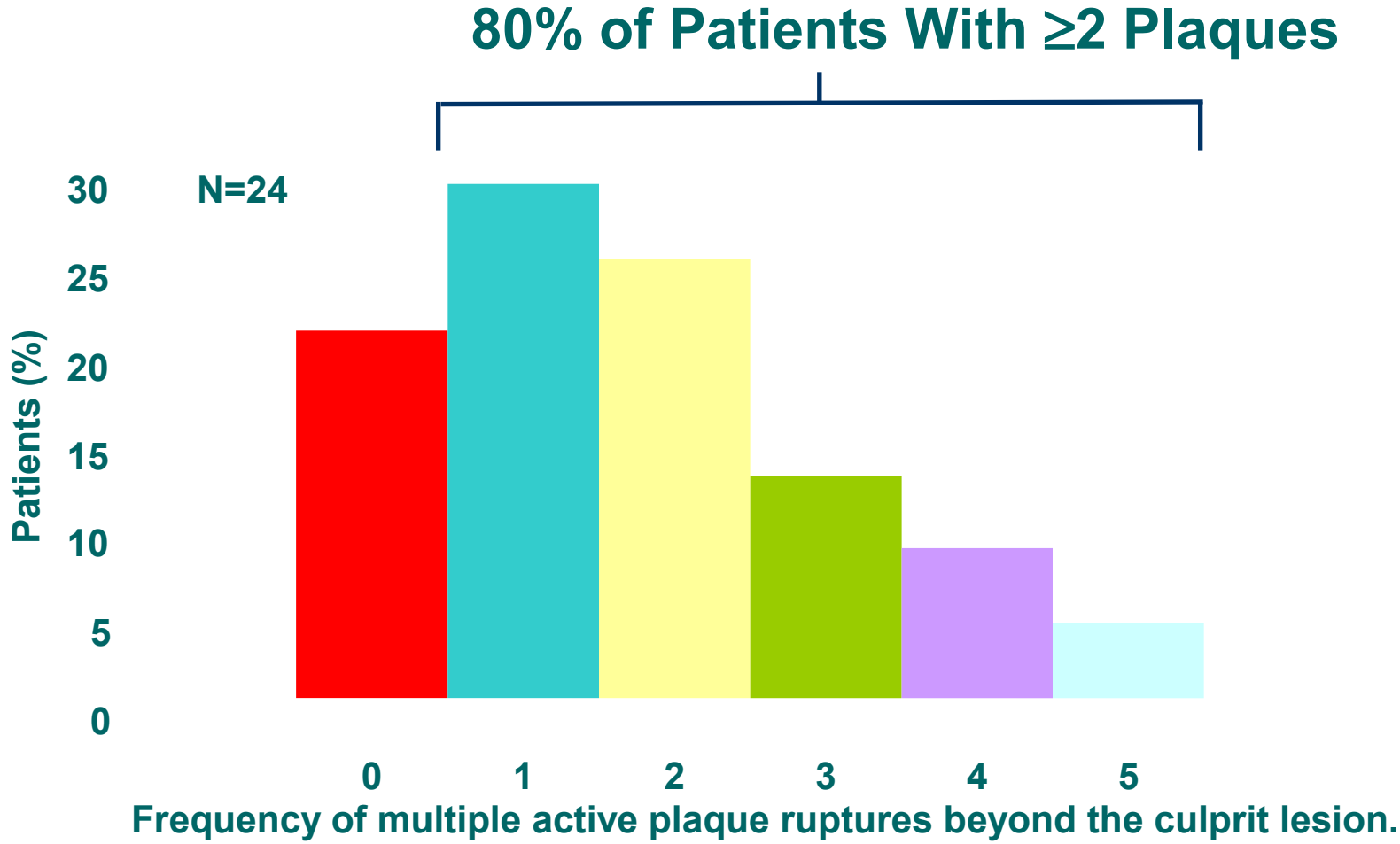
~2,000





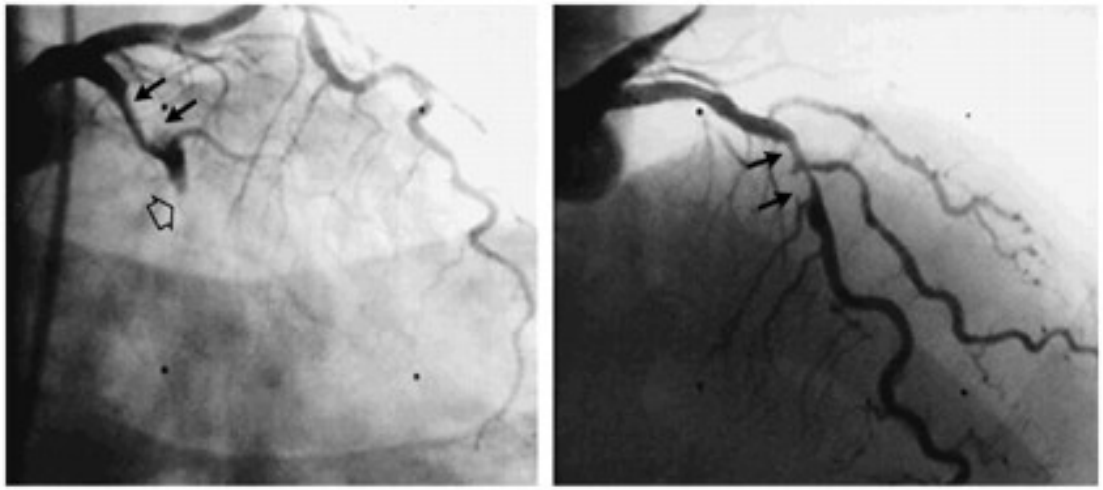
~20,000

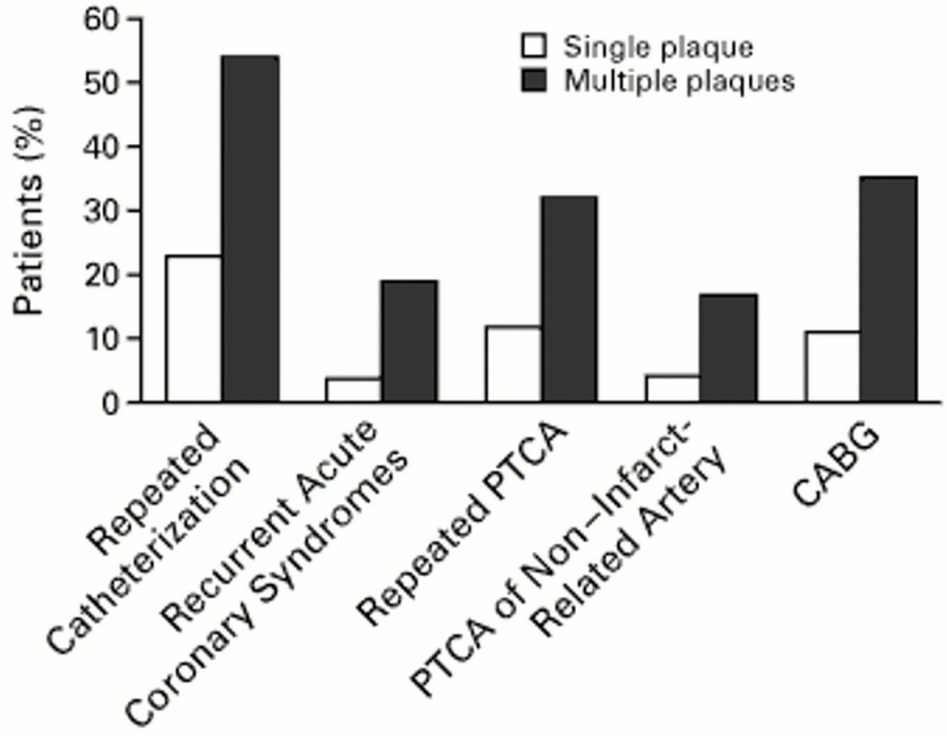
ACS a Systemic Disease:
Frequency of Multiple "Active" Plaques



Adapted from Rioufol G, et al. *Circulation.* 2002;106:804-808.

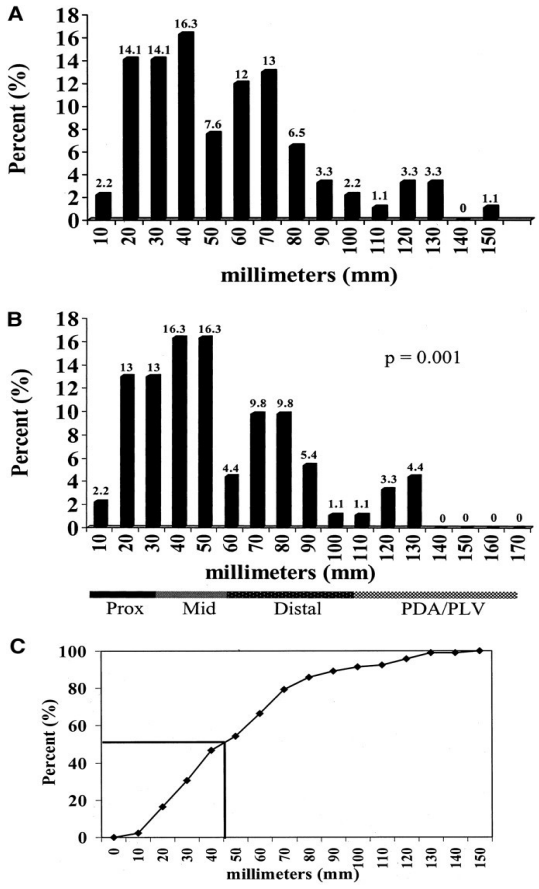
Multiple Complex Coronary Plaques in Patients with AMI



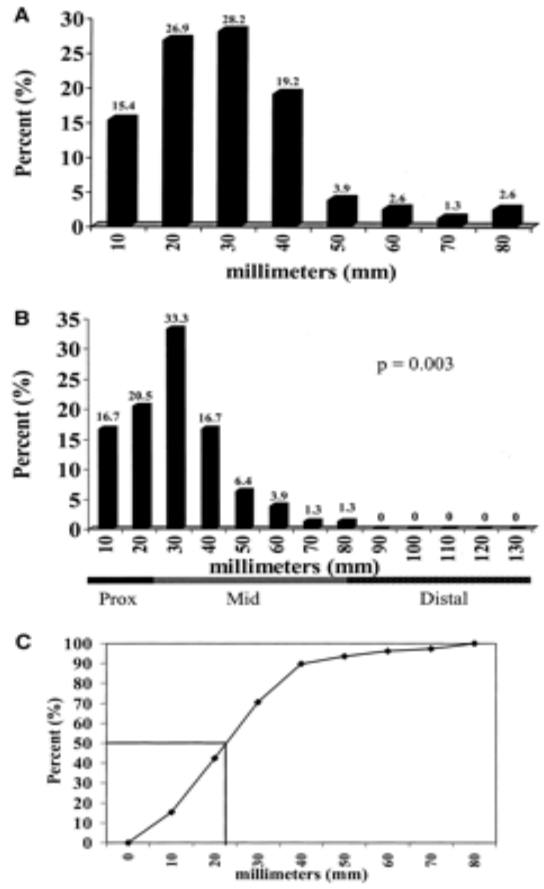


Goldstein et al. NEJM 2000

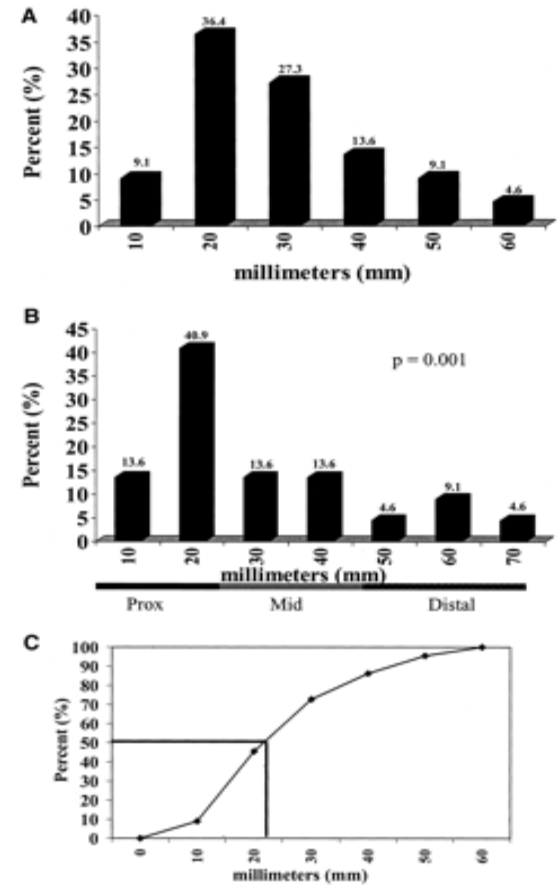
Coronary Artery Spatial Distribution of Acute Myocardial Infarction Occlusions



RCA

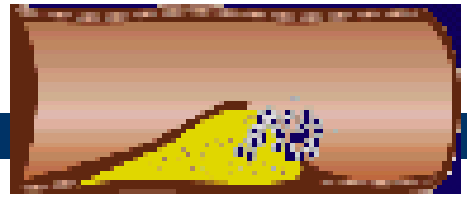


LAD

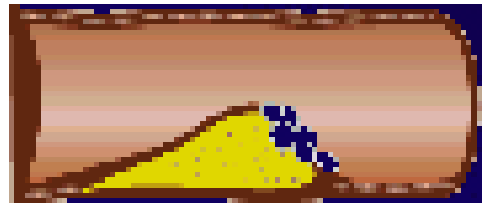


LCx

Pathogenesis of Acute Coronary Syndromes: the integral role of platelets



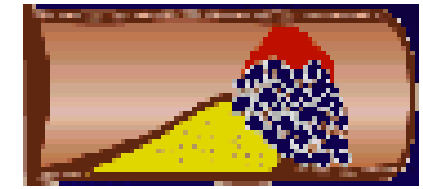
Plaque
Fissure or
Rupture



Platelet
Adhesion

Platelet
Activation

Platelet
Aggregation

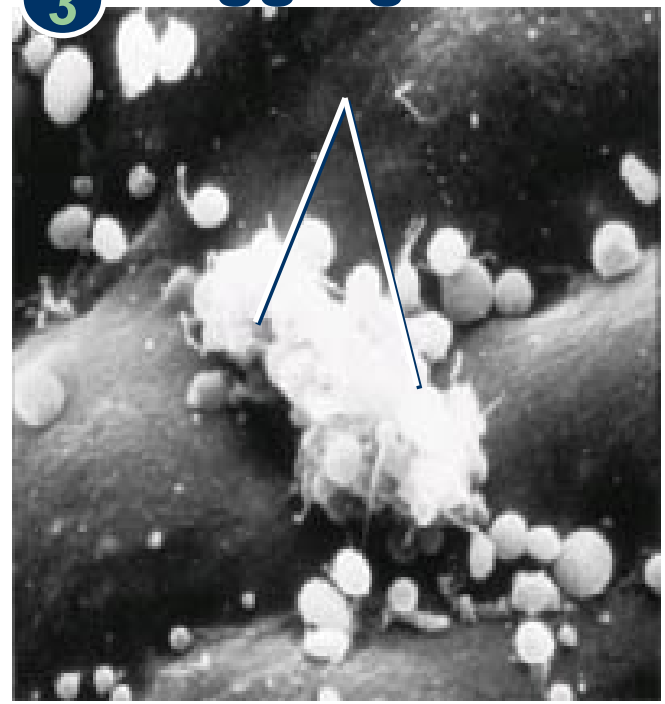


Thrombotic
Occlusion

The Role of Platelets in Atherothrombosis

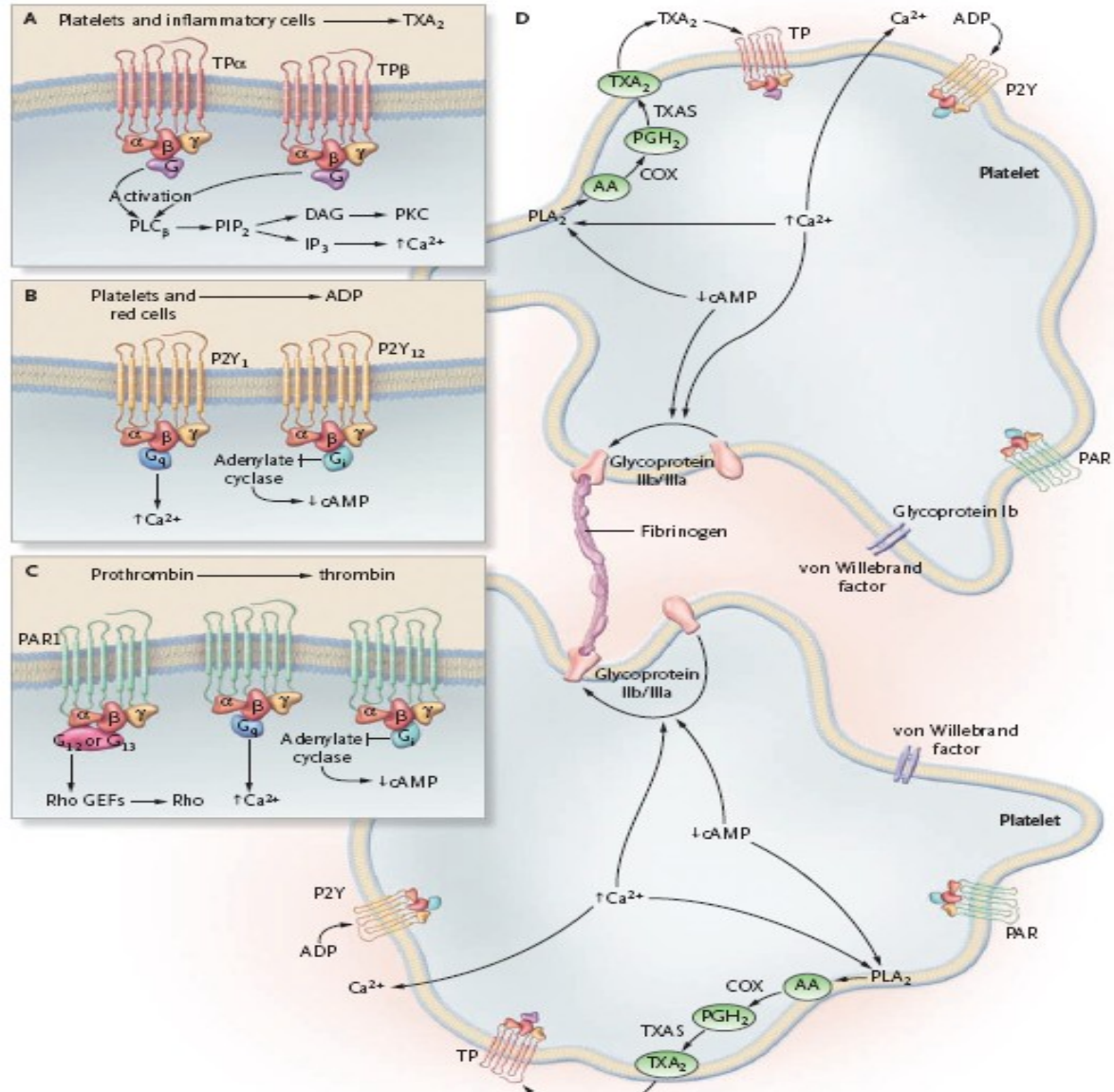
1 Adhesion

3 Aggregation

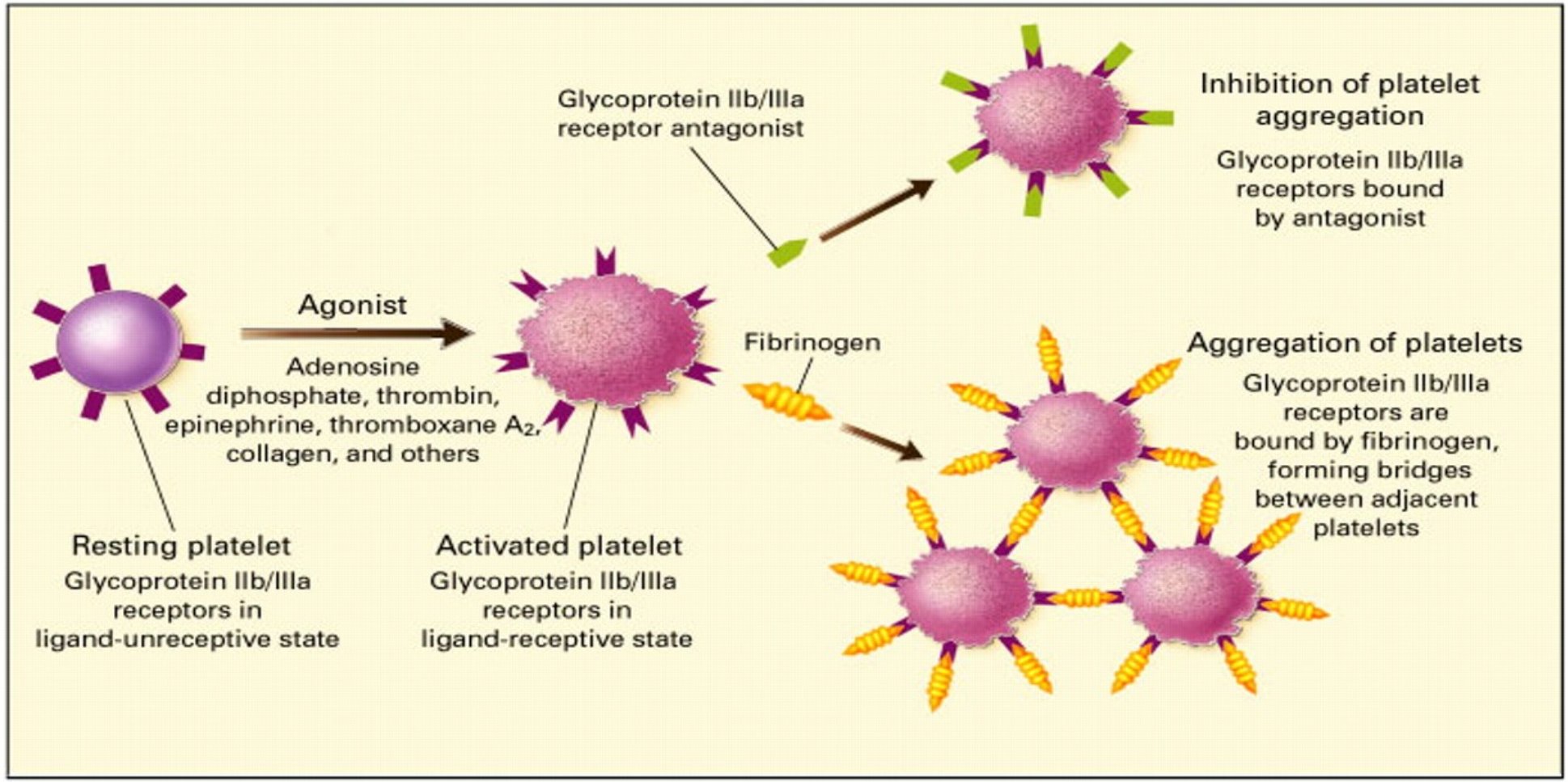


2 Activation

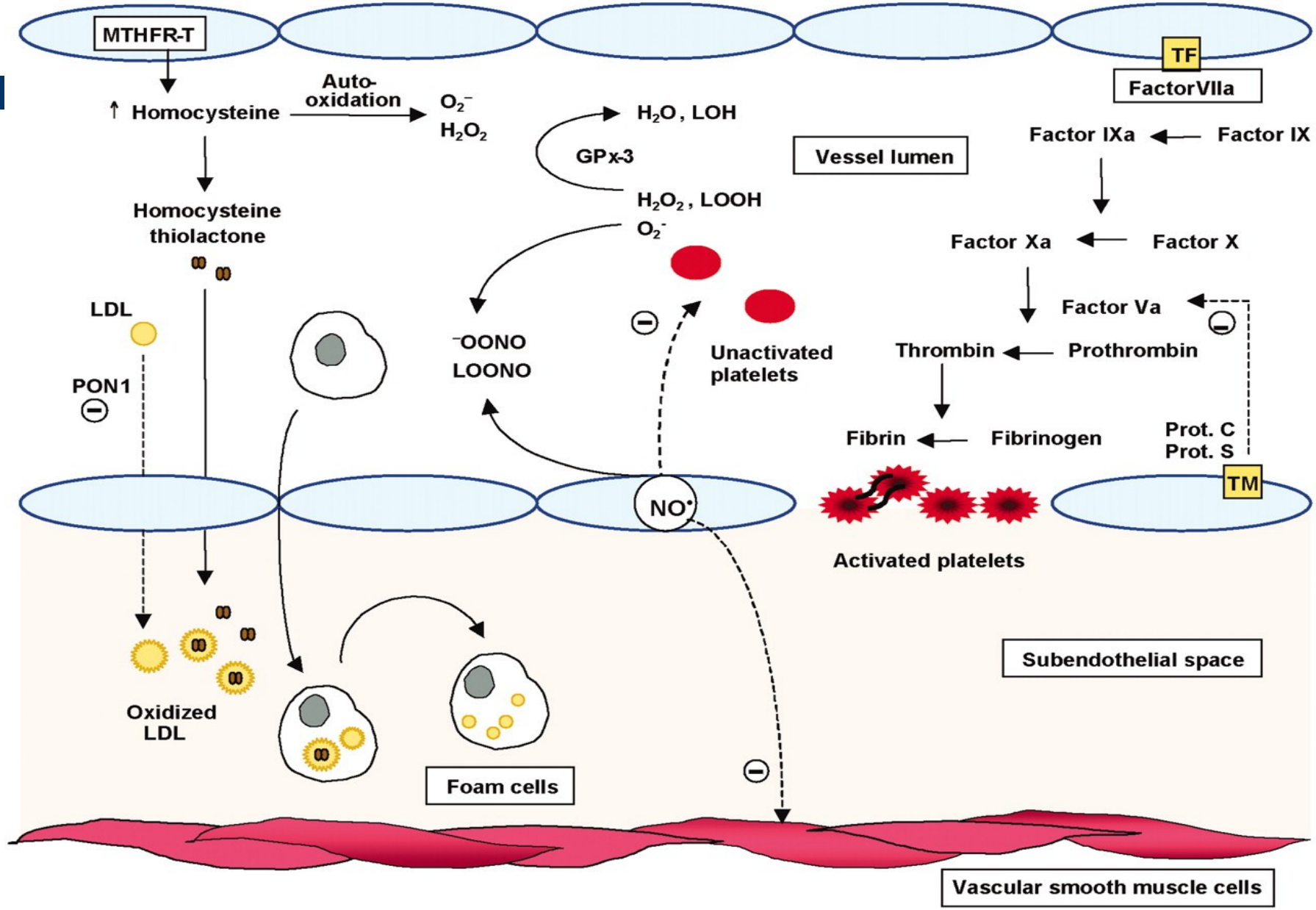
Agonists, receptor and effector systems in platelet activation



Platelet Inhibition With GP IIb/IIIa Inhibitors

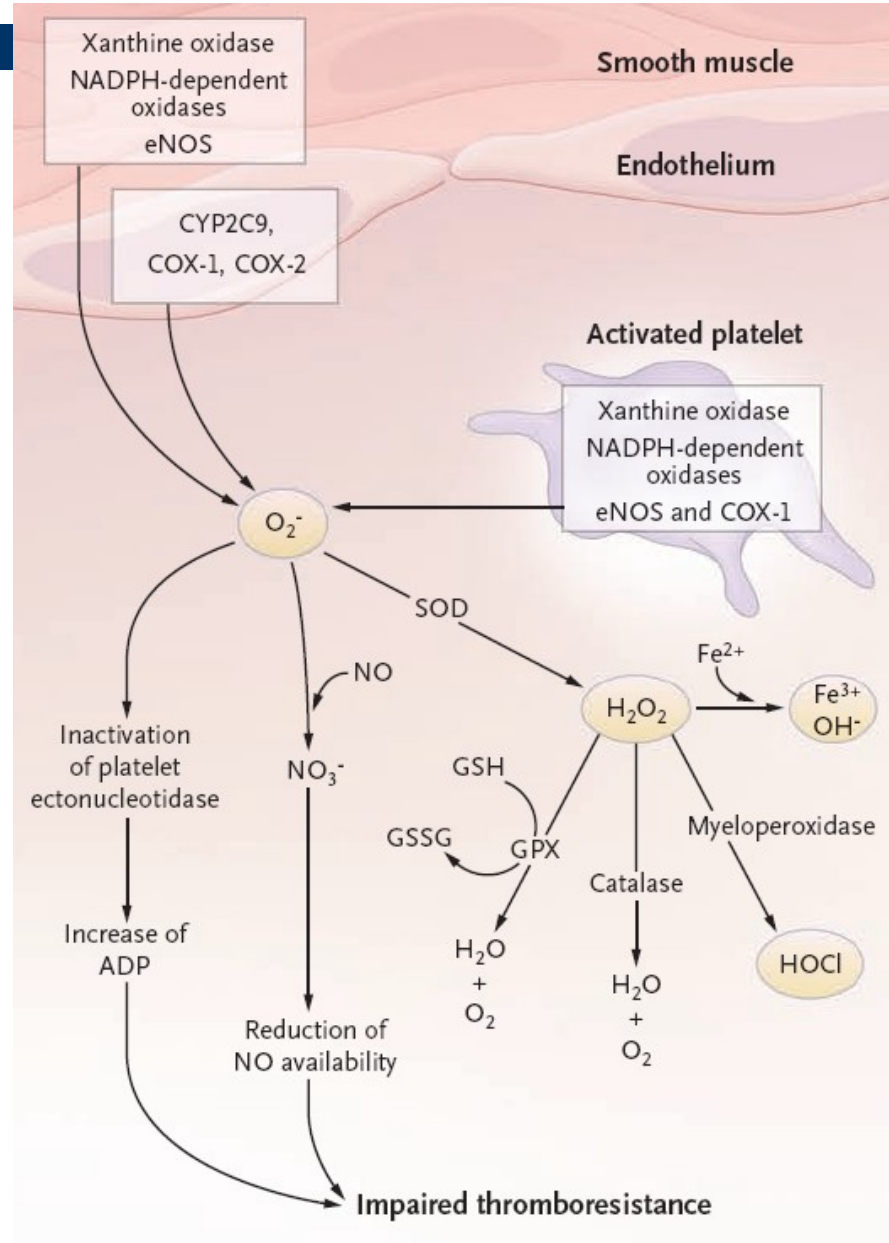


Vascular hemostatic and antioxidant defense mechanisms

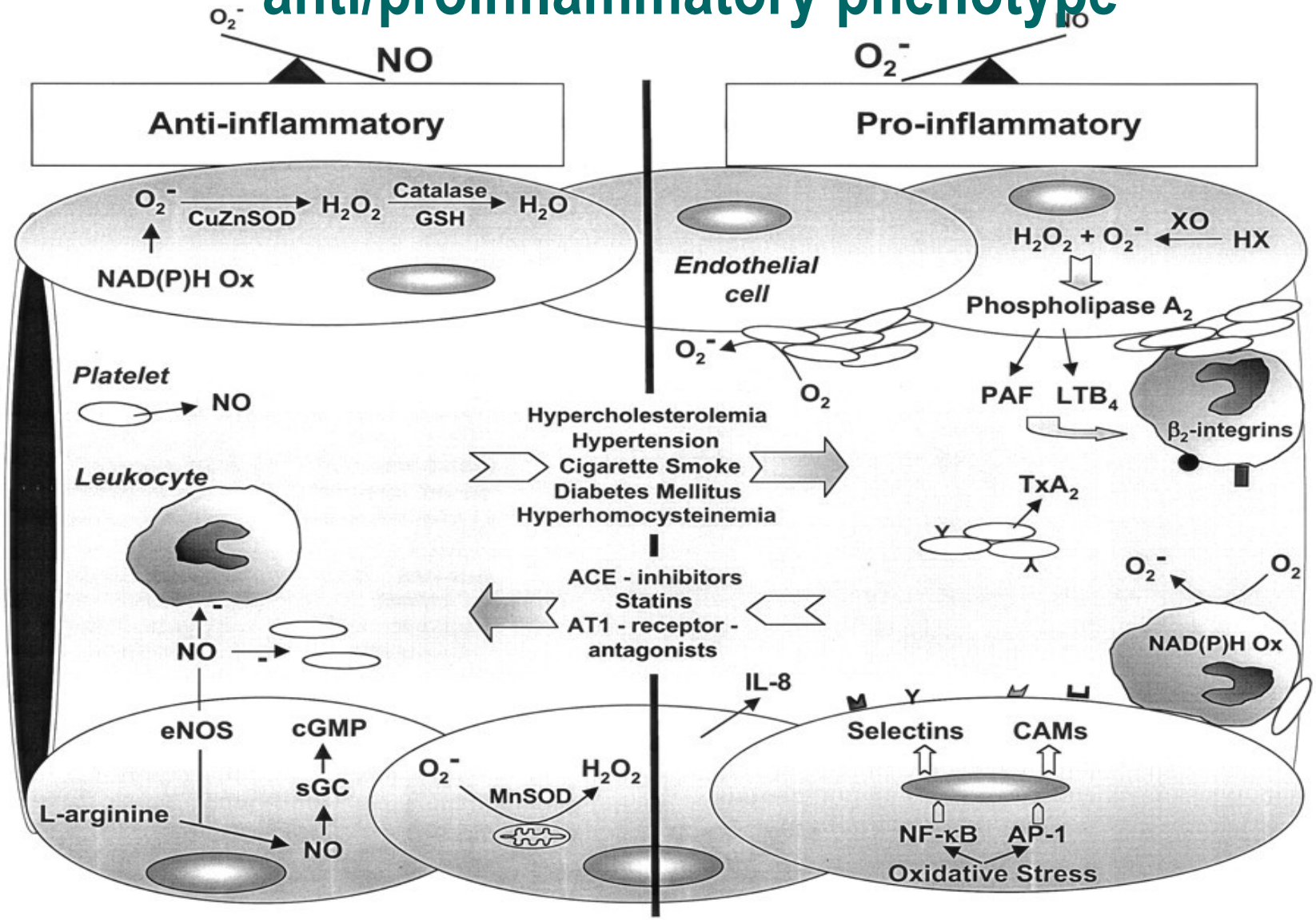


Voetsch, B. et al. Arterioscler Thromb Vasc Biol 2004;24:216-229

ROS in platelet activation

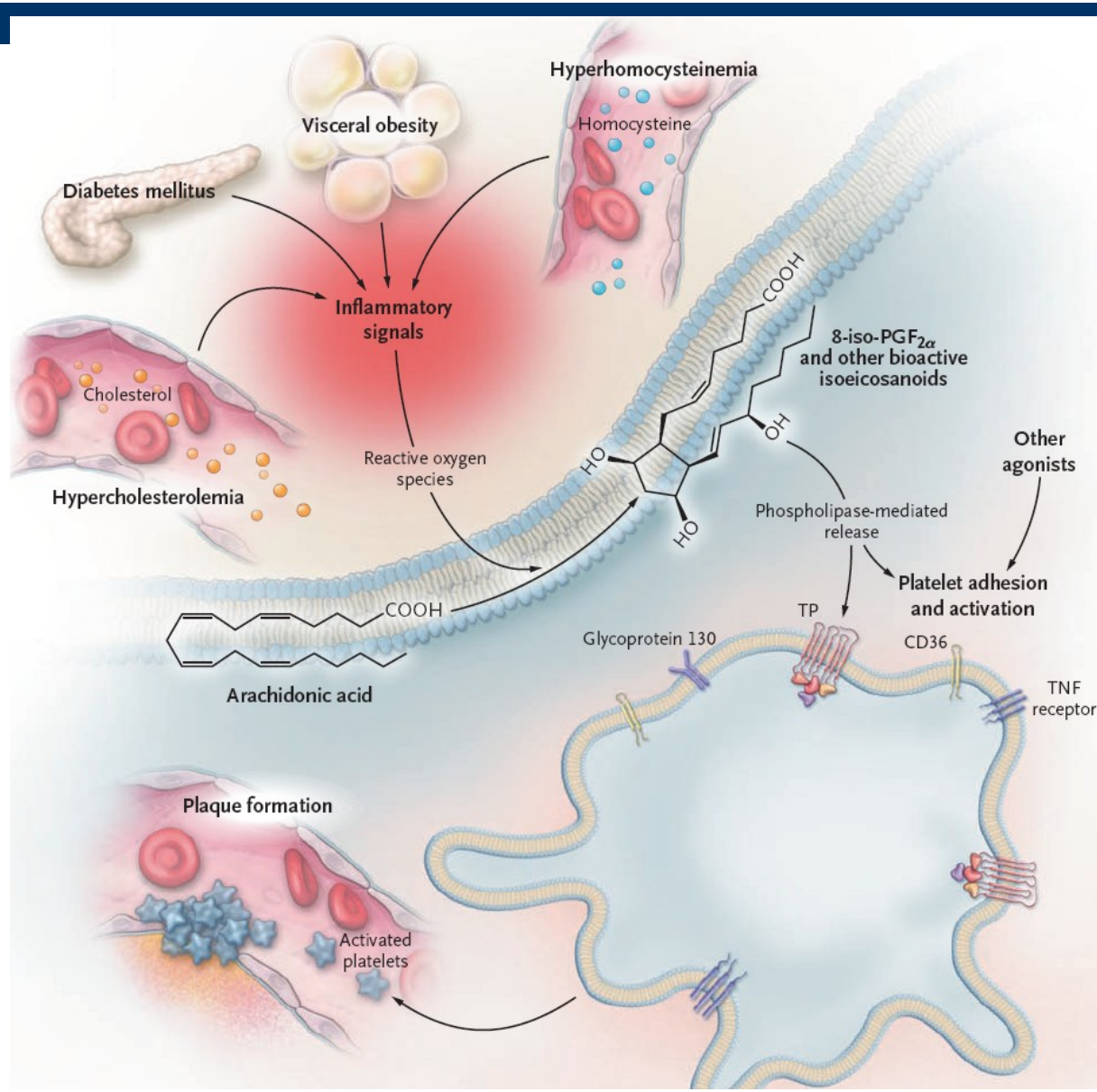


Superoxide-NO balance affects the vascular anti/proinflammatory phenotype

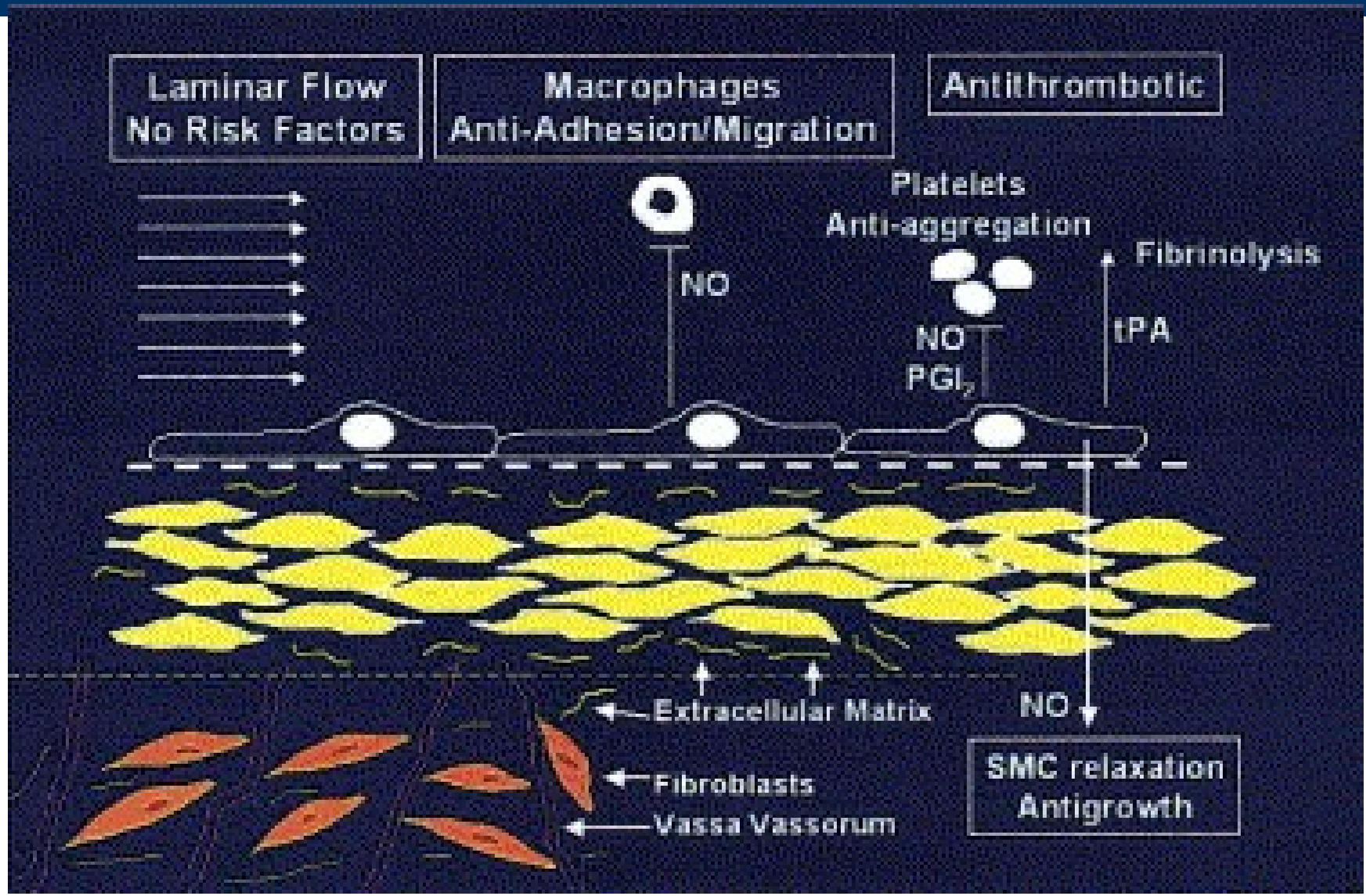


Granger, D. N. et al. Hypertension 2004;43:924-931

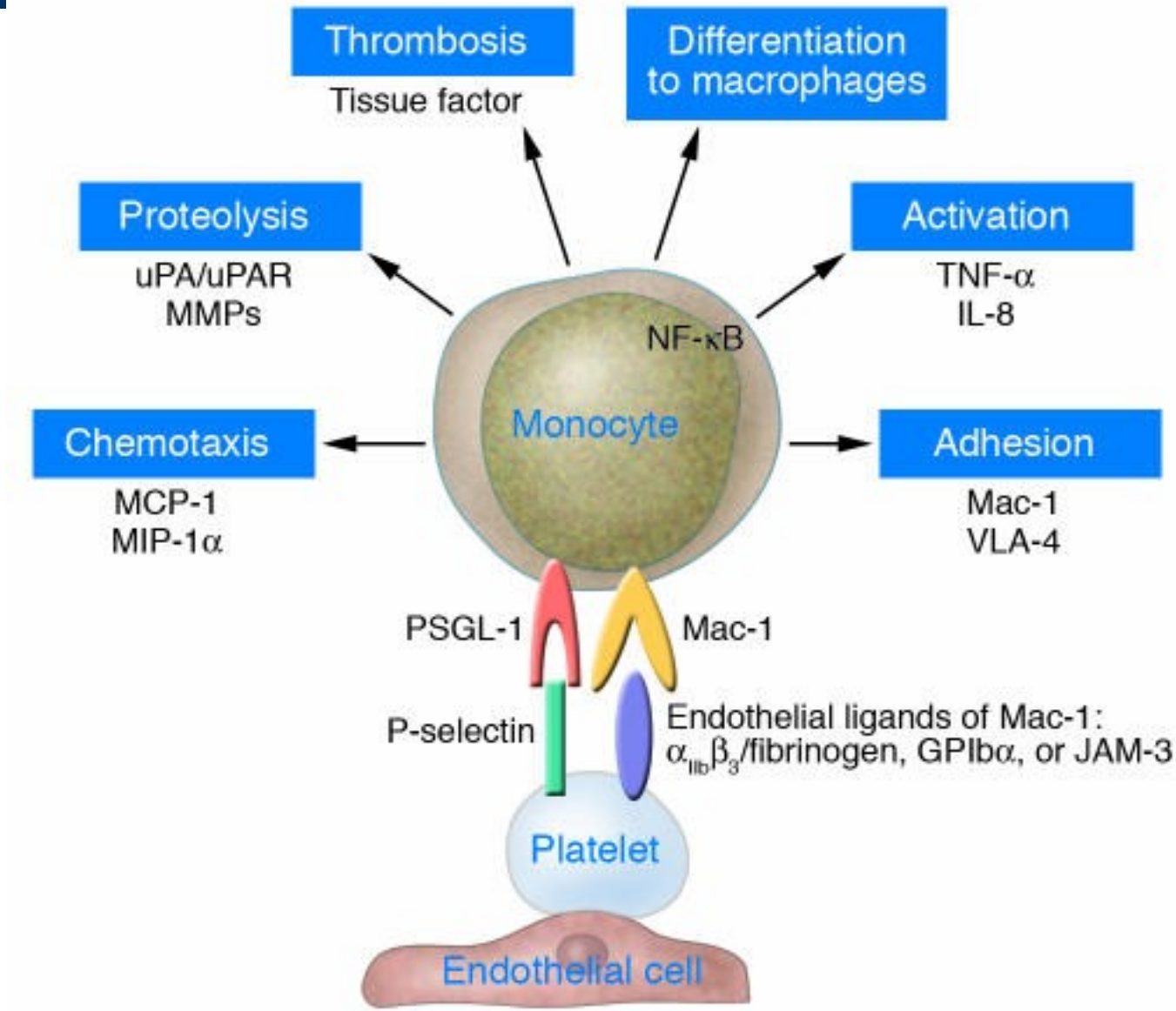
Isoprostanes: between inflammation and thrombosis



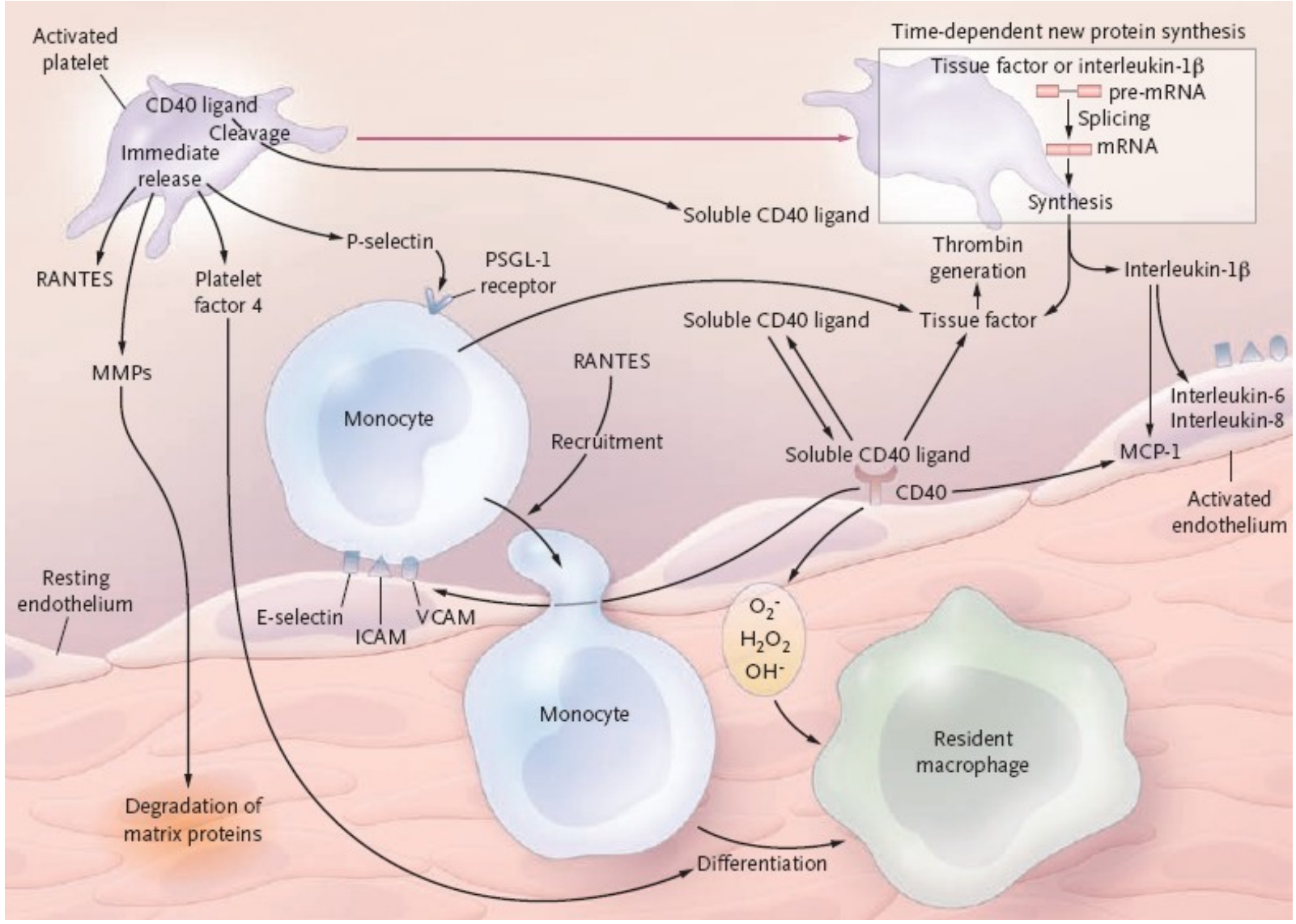
Endothelial Dysfunction



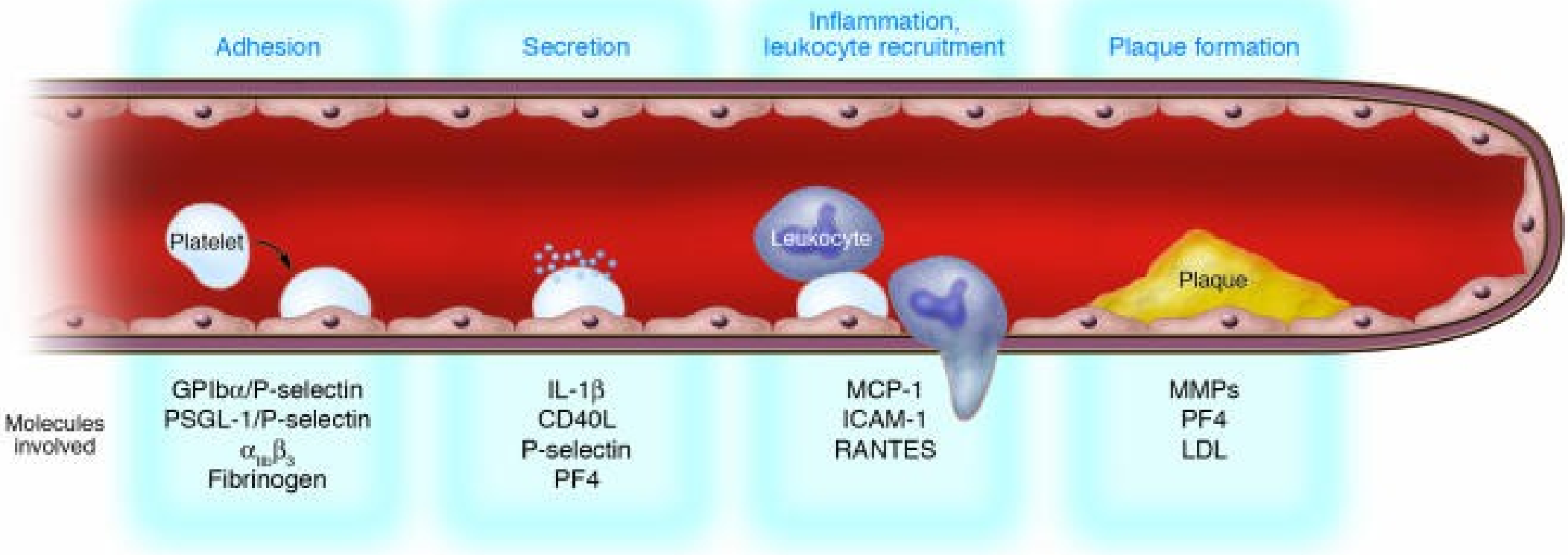
Platelets and inflammation



Platelet-derived mediators of the inflammatory response

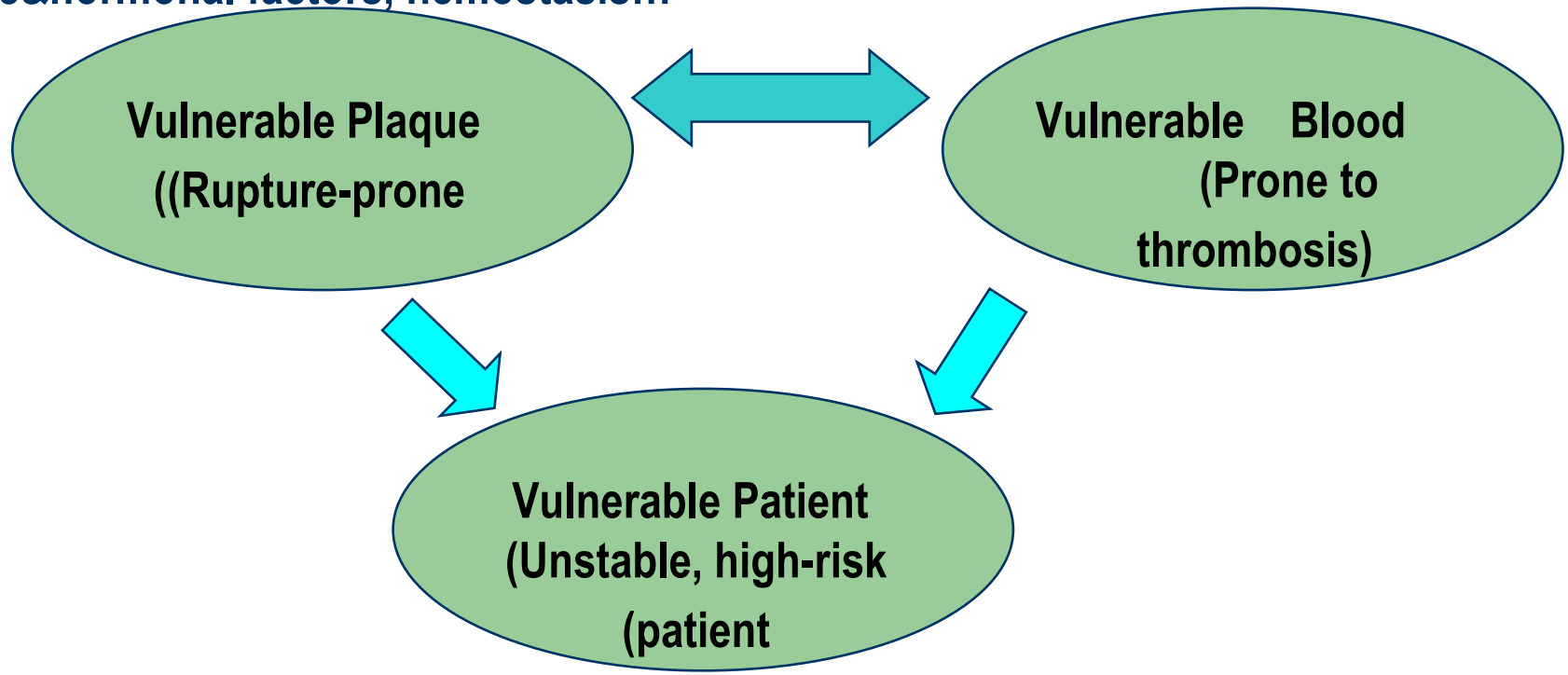


Platelets in atherogenesis



The Virchow Triad of Thrombogenicity

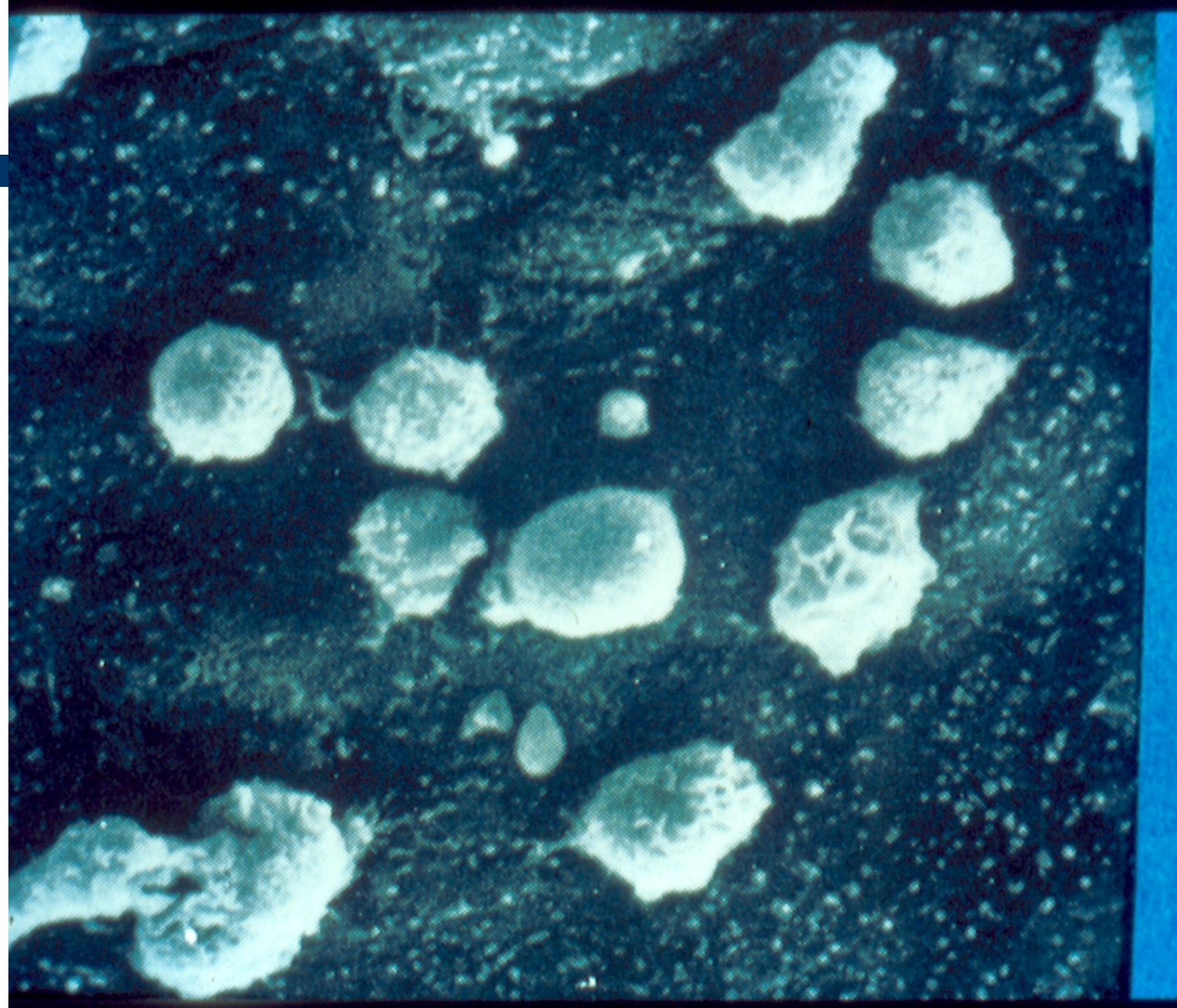
- Local vessel wall substrates
  - Plaque components, inflammation, post-injury..
- Rheology
  - Shear stress, vasoconstrictor, bifurcation, post-intervention…
- Systemic factors of circulating blood
  - Metabolic&hormonal factors, hemostasis…

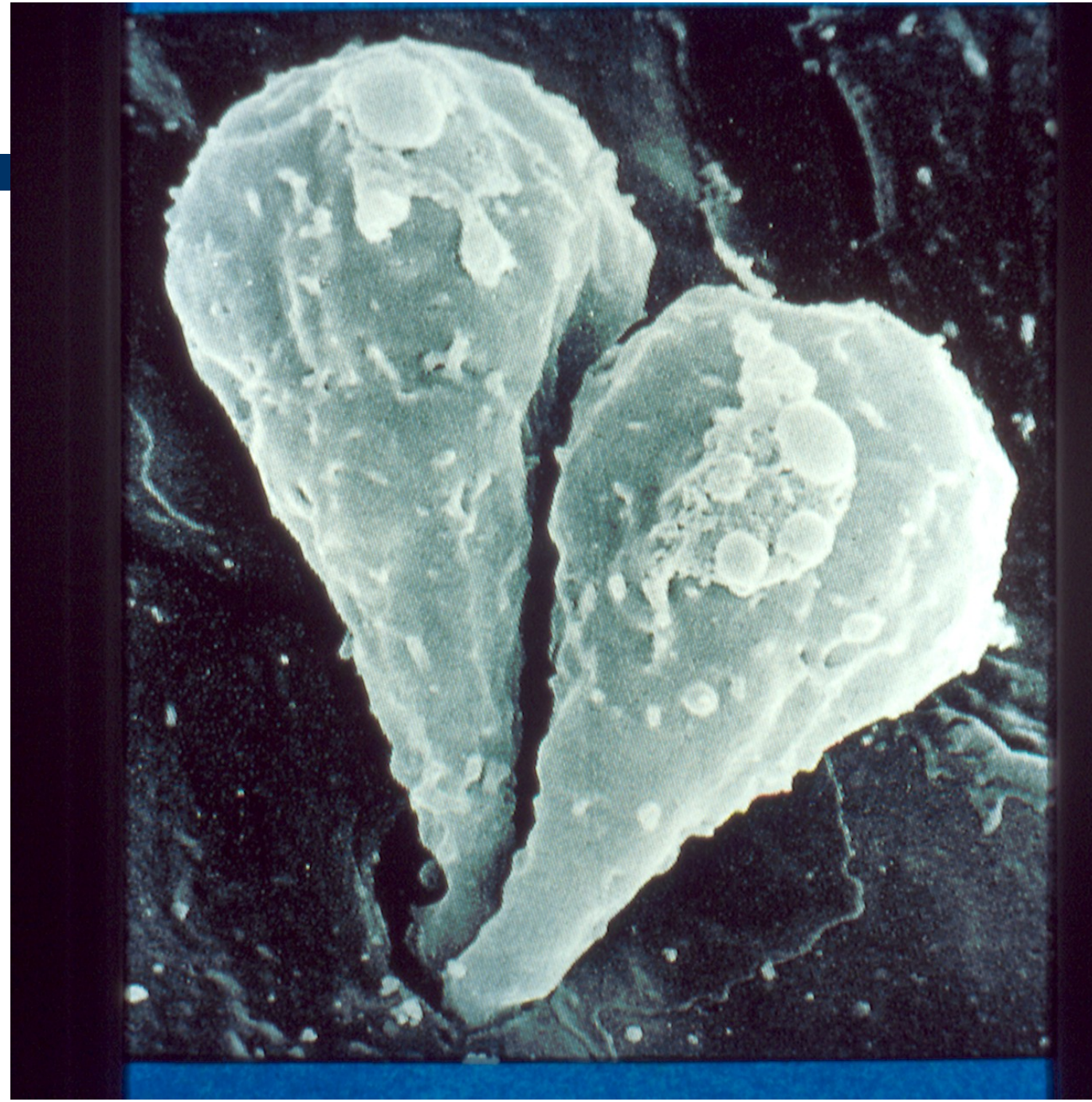


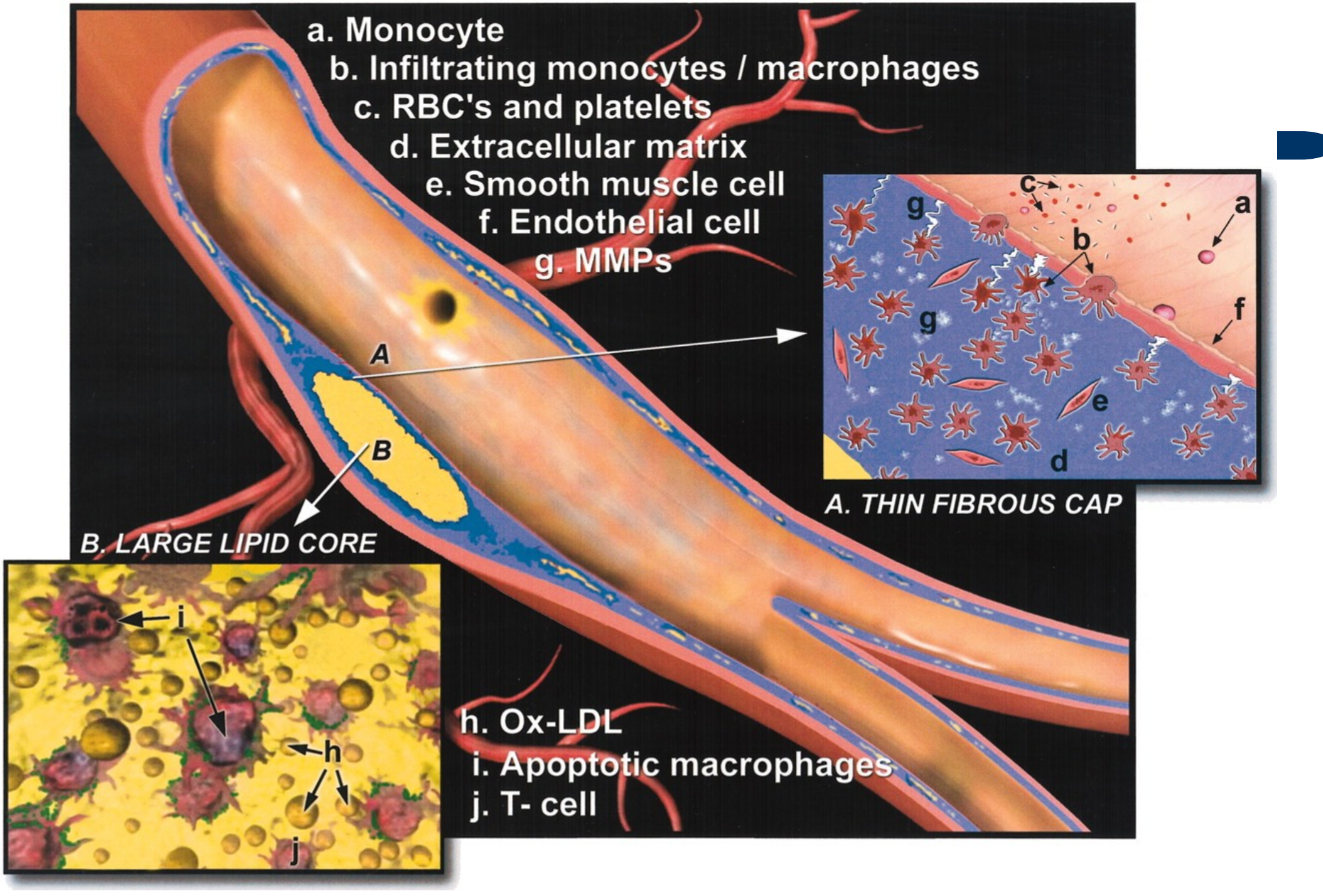
Innate immunity in atherothrombosis

- Scavenger receptors SR-A and CD-36 / oxLDL uptake, NFkB activation
- Toll like receptors (TLR4)

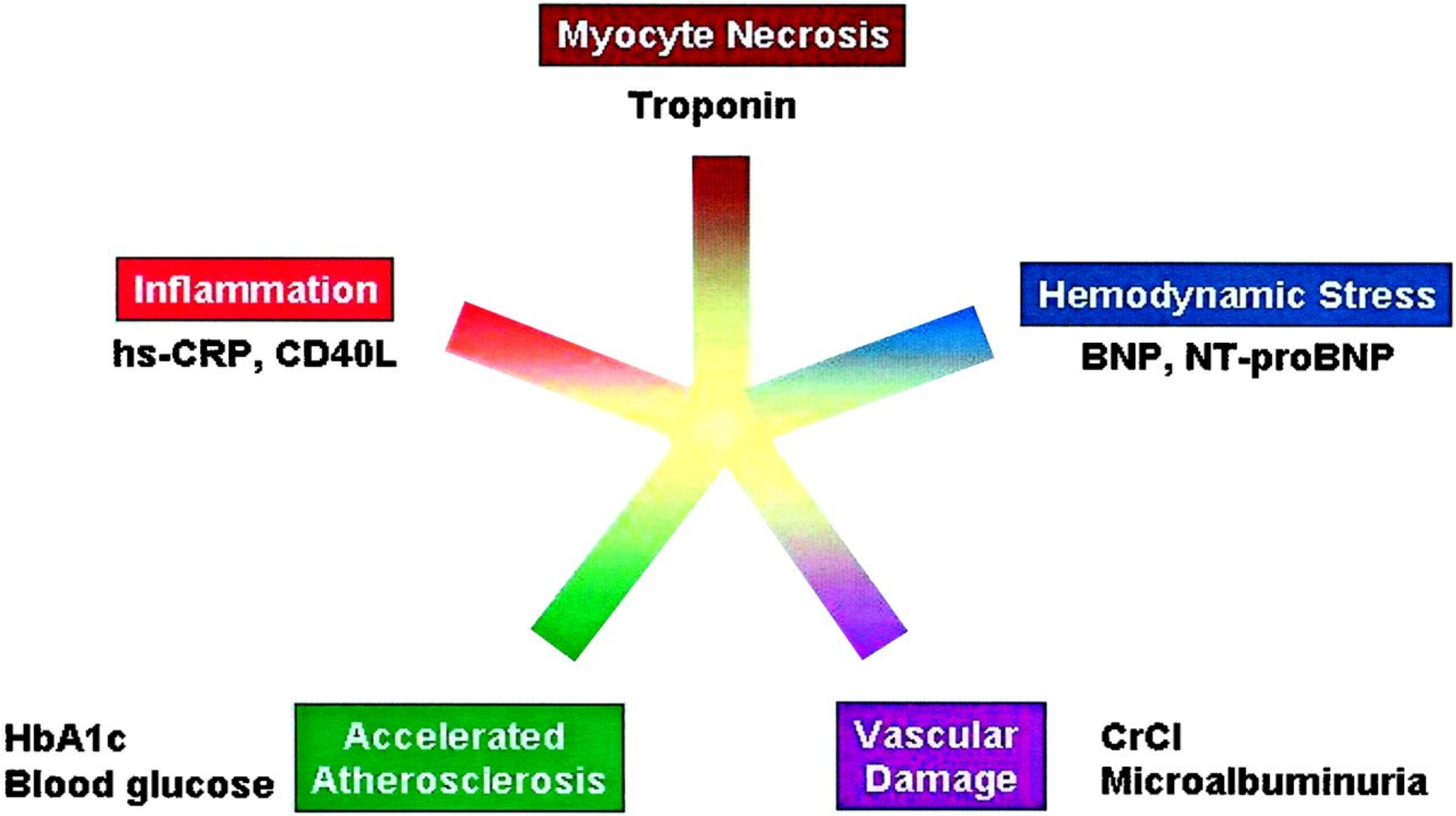
Adaptive Immunity





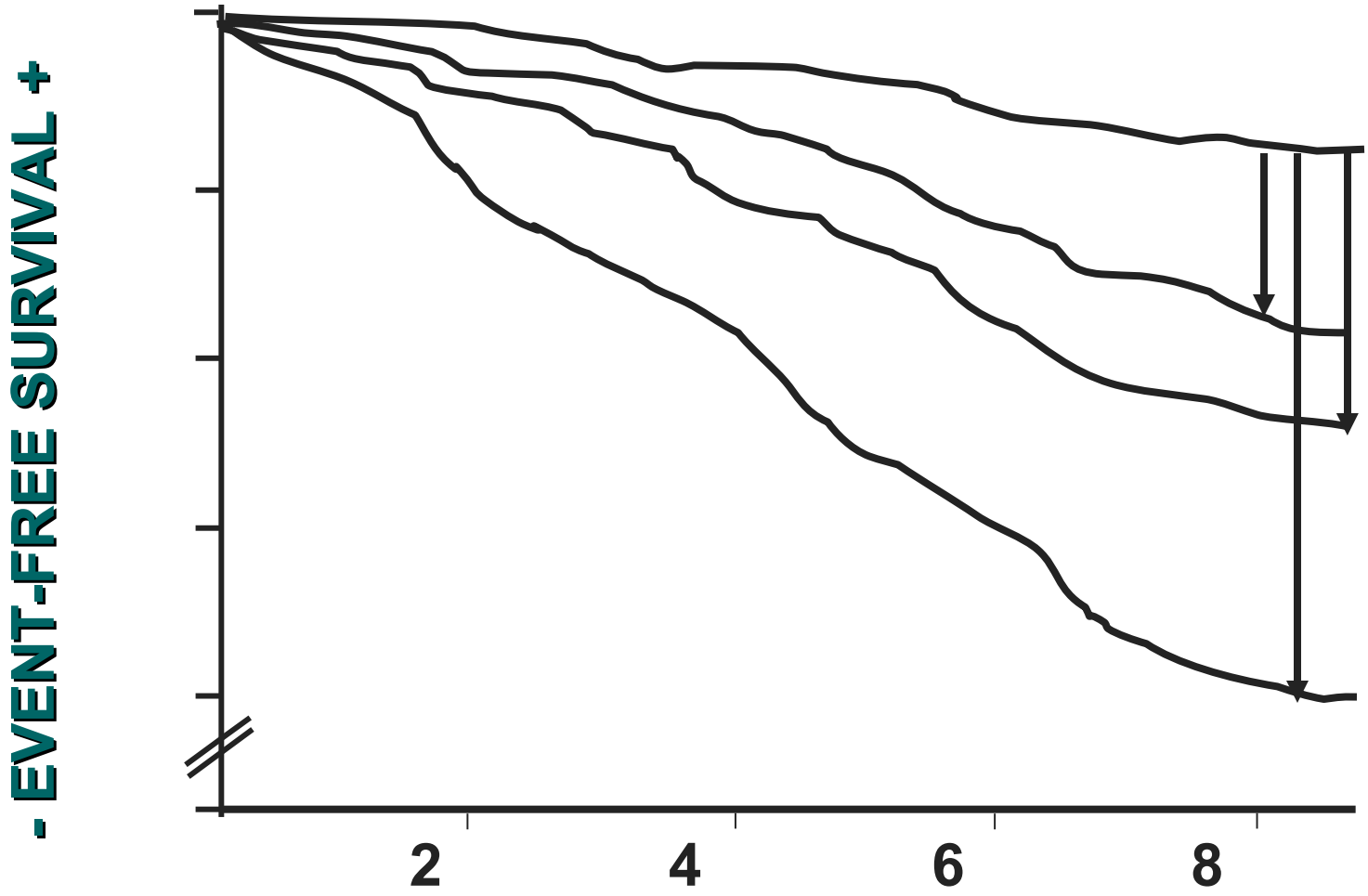

a. Monocyte
b. Infiltrating monocytes / macrophages
c. RBC's and platelets
d. Extracellular matrix
e. Smooth muscle cell
f. Endothelial cell
g. MMPs
A
B
A. THIN FIBROUS CAP
B. LARGE LIPID CORE
h. Ox-LDL
i. Apoptotic macrophages
j. T- cell

Biomarkers in Atherothrombosis: Implications for Prognosis and Therapy



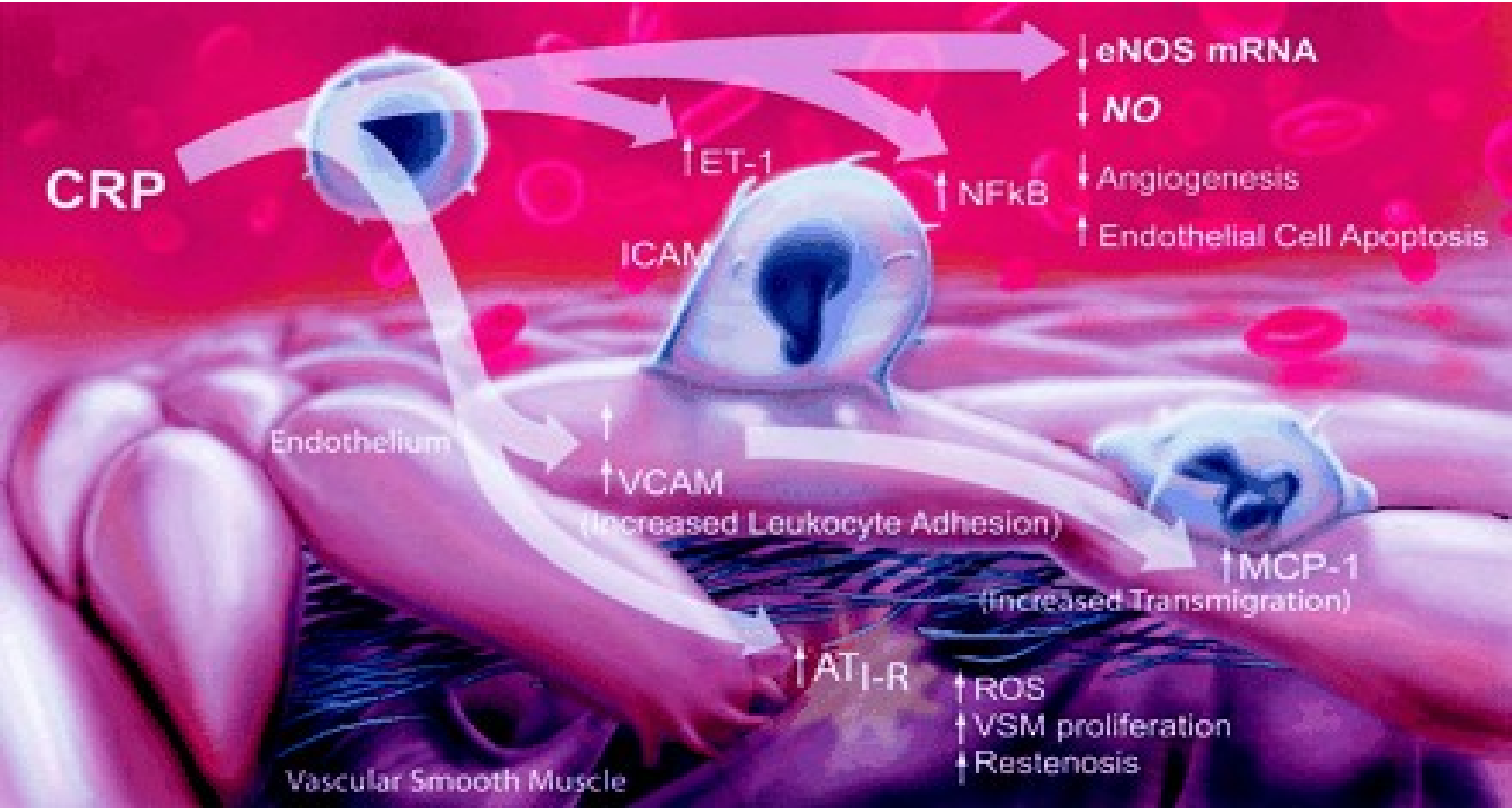
Morrow DA, Braunwald E: *Circulation* 2003;108:250

CRP and LDL: additive predictive value

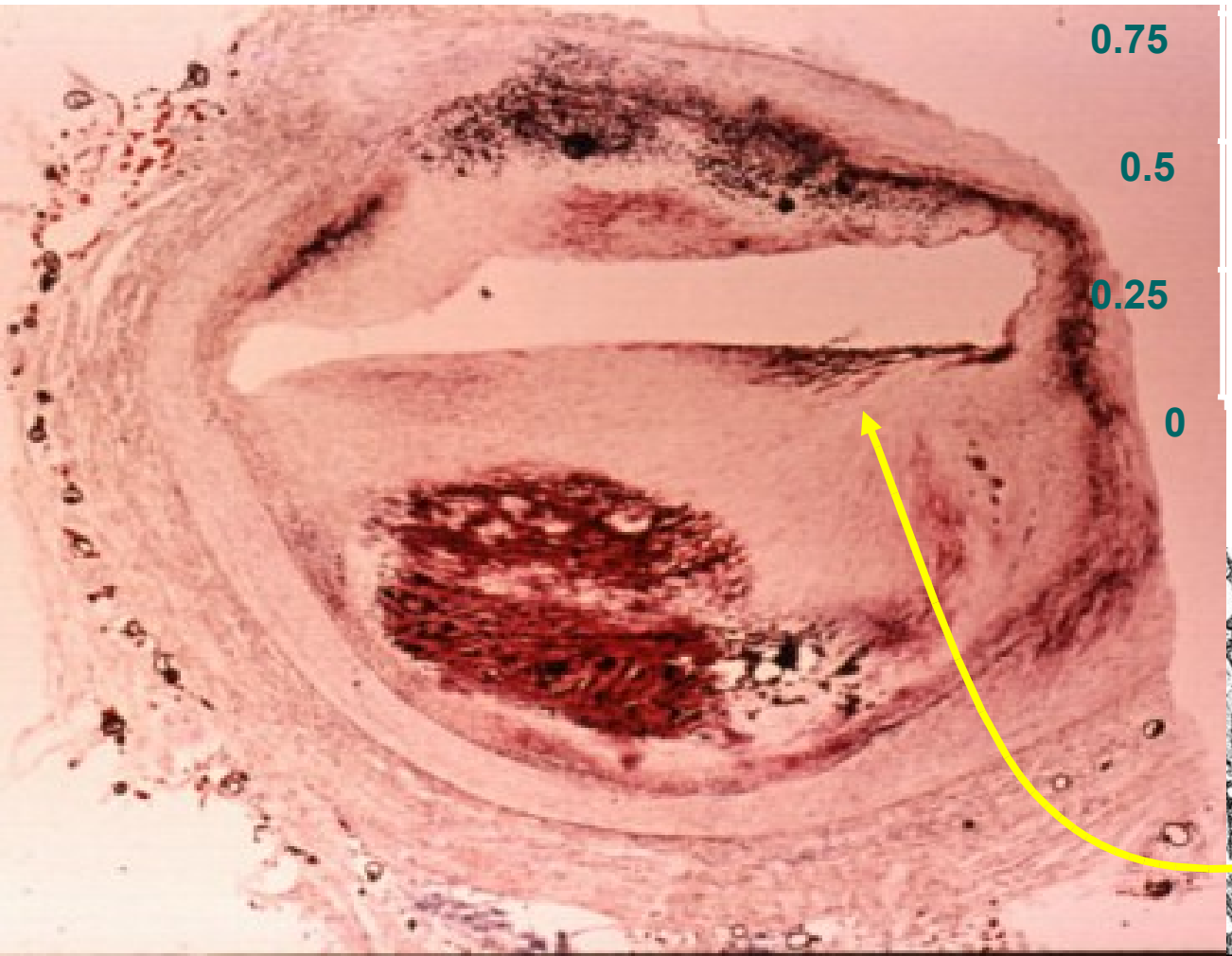


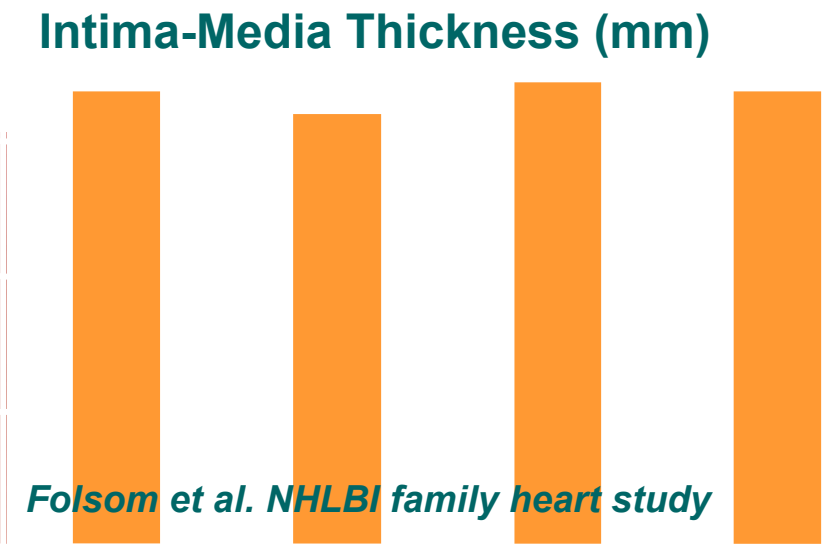
Ridker et al.

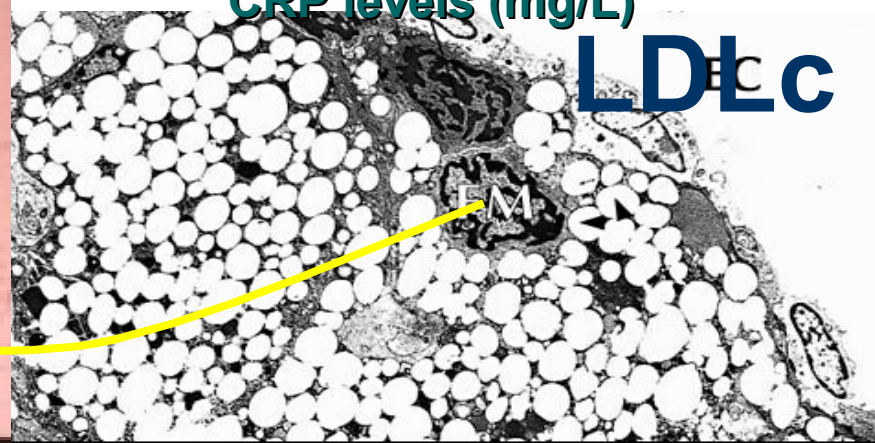
CRP, inflammation, and endothelial activation



LDL, CRP and BURDEN OF ASVD







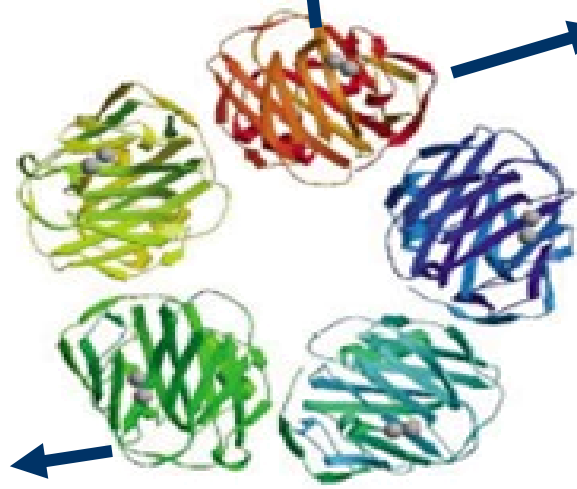
Pro-atherogenic and pro-inflammatory effects of CRP (*in vitro* studies):

Enhances uptake of oxidized LDL by macrophages

Activates complement

Increases platelet adhesion to endothelial cells under physiological flow conditions

Induces TF expression in macrophages



Produced locally in atherosclerotic lesion

Decreases eNOS mRNA and NO

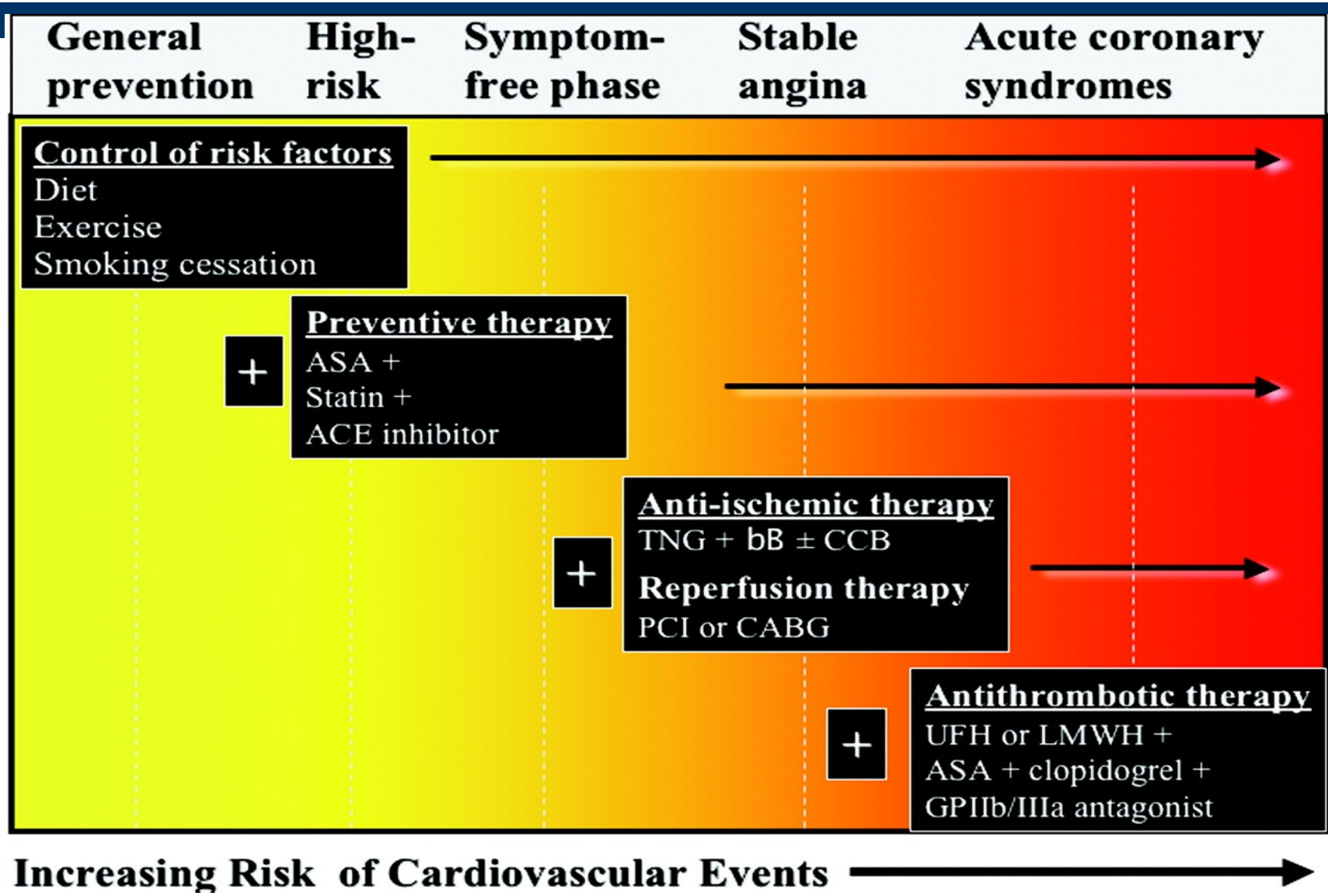
Induces secretion of IL6, IL8,MMP2 & MMP9

Contributes to the migration of SMC

Induces monocyte chemoattractant chemokine 1 (MCP-1) production facilitating leukocyte adhesion

Activates endothelial cells to produce adhesion molecules: ICAM1, VCAM1 and E selectin

Matching therapy with pathophysiology



Libby, P. et al. Circulation 2005;111:3481-3488

בהצלחה, אל תעבדו קשה מדי!

שאלה 1:

מי מהבאים אינו משפעל טסיות?

2) **פרוסטציקלין**

3) **קולגן**

4) **תרומבוקסן**

5) **תרומבין**

6) **אדנוזין די-פוספאט**

שאלה 2:

מה נקשר לחלבון GP2b3a ומקשר בין טסיות?

1. **תרומבין**
2. **ADP**
3. **קולגן**
4. **פיברינוגן**
5. **תרומבוקסאן**

שאלה 3:

מבין הבאים, מי איננו תורם לתהליך הדלקתי-טרשתי בדופן העורק ולחוסר יציבות (Vulnerability) הרובד הטרשתי?

2. Vascular cell adhesion molecule-1
3. Monocyte chemoattractant protein-1
4. Interferon Gamma
5. Smooth muscle cells
6. T Lymphocytes

שאלה 4:

מי מהסמנים (מרקרים) הבאים אינו קשור בהגברת הסיכון לאירועים קרדיו-וסקולרים ותמותה קרדיאלית?

1. IL-6
2. Soluble CD 40 ligand
3. BNP
4. Angiotensin type II receptor
5. CRP

שאלה 5:

מה מהבאים אינו מאפיין רובד רגיש (vulnerable plaque)?

3) ליבה שומנית (lipid core)
4) תכולת קולגן גבוהה
5) ייצור NO נמוך ע"י האנדותל המצפה
6) Fibrous cap דק
7) ריבוי וזה-וזורום (vasa vasorum)

What, Me Worry?