MECHANISMS OF ATHEROSCLEROSIS

Hossein Mehrani

Professor of Clinical Biochemistry

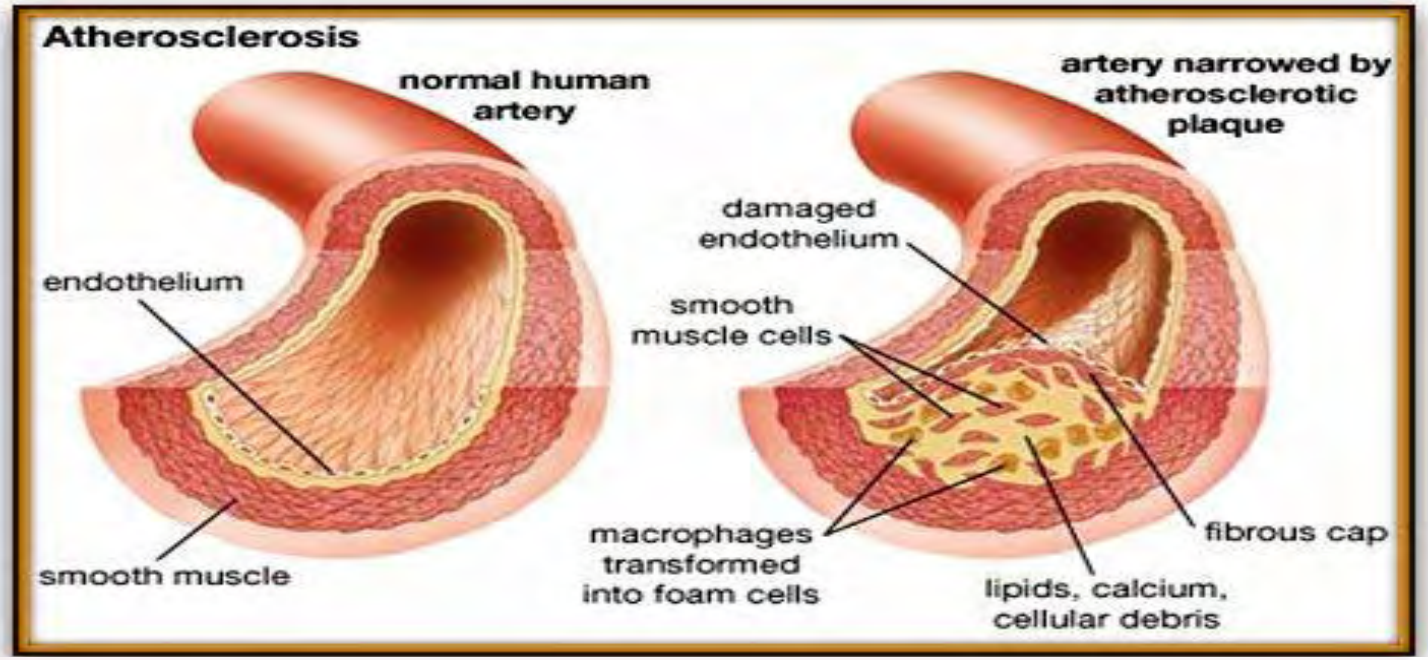
DEFINITION

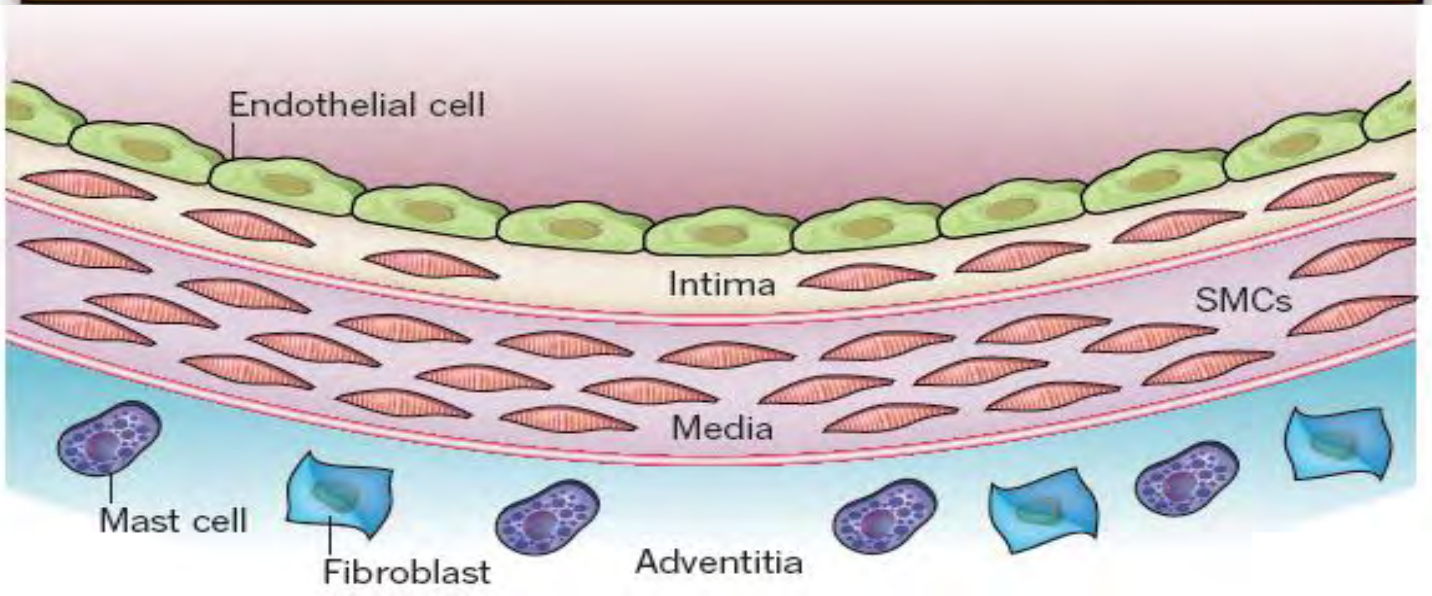
Atherosclerosis: atherosclerosis, is a Greek words atheros (meaning "gruel" or "paste") and sclerosis (meaning "hardness"), is a type of arteriosclerosis in which arteries are narrowed by fatty deposit

Arteriosclerosis: is a hardening of the artery walls, resulting in thickening and calcification

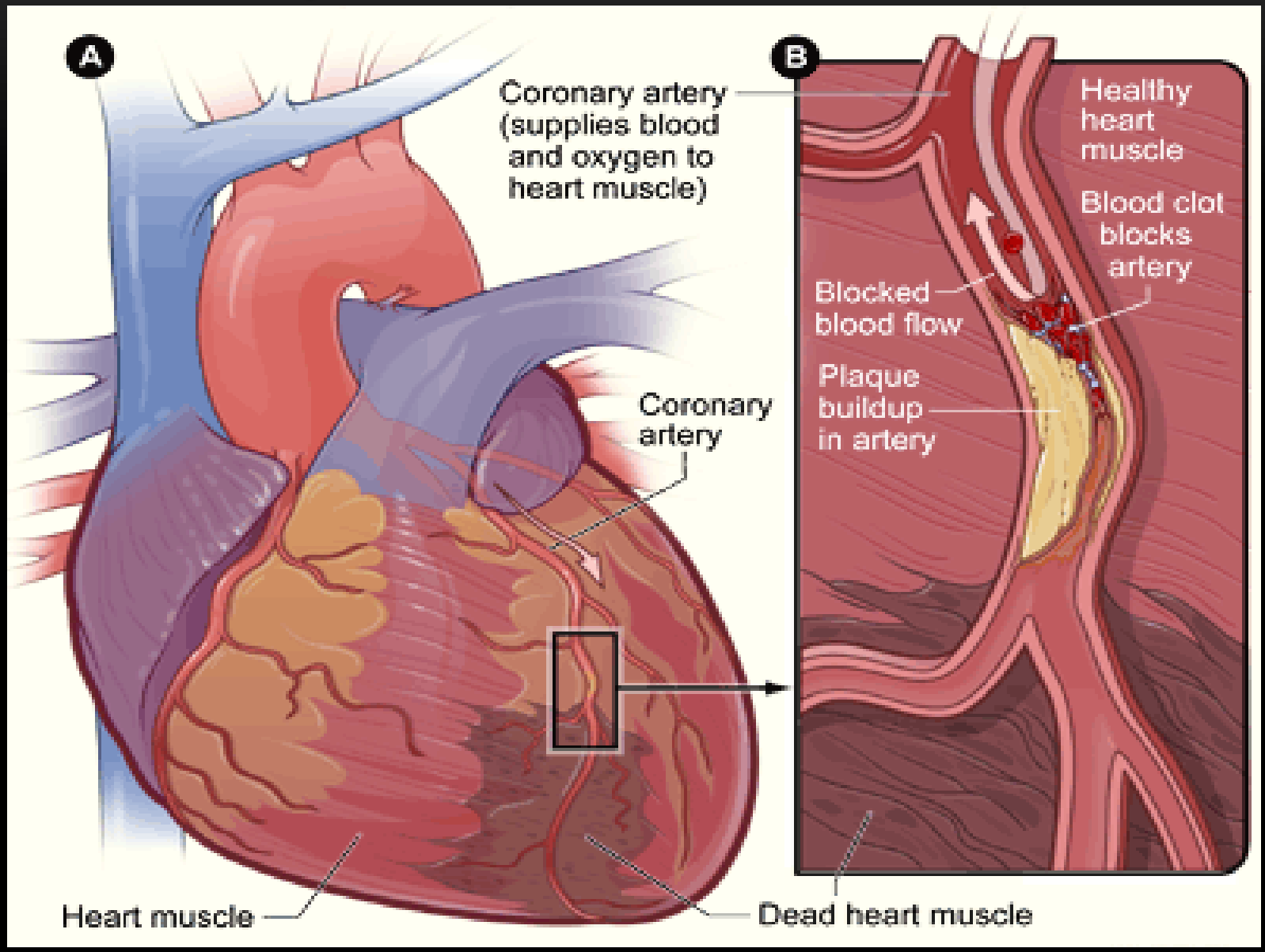
Atherosclerosis is a multifactorial disease process and is the principal cause of myocardial infarction, stroke, and peripheral vascular disease, accounting for almost 40% of all mortality in the western Society

ATHEROSCLEROSIS

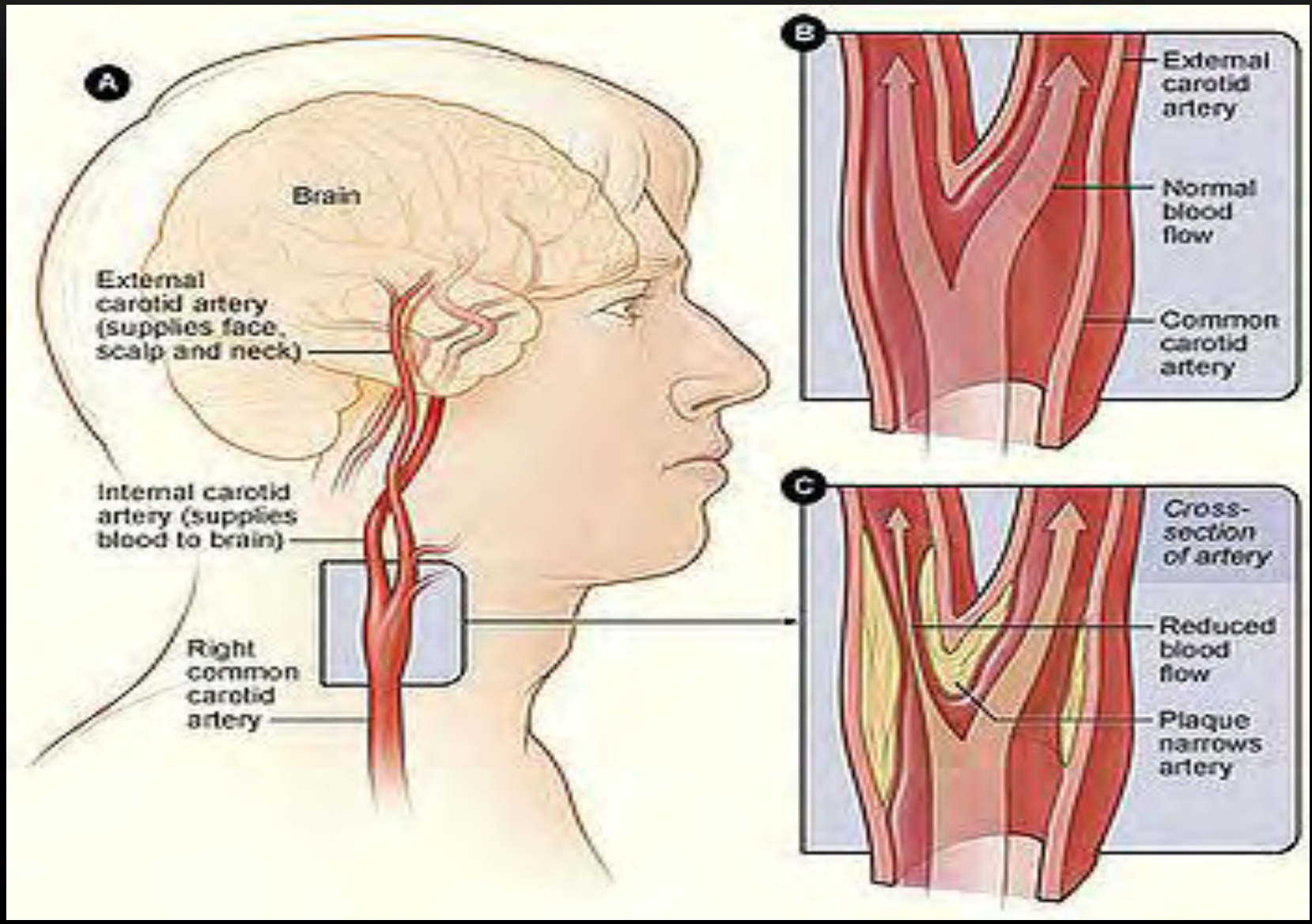




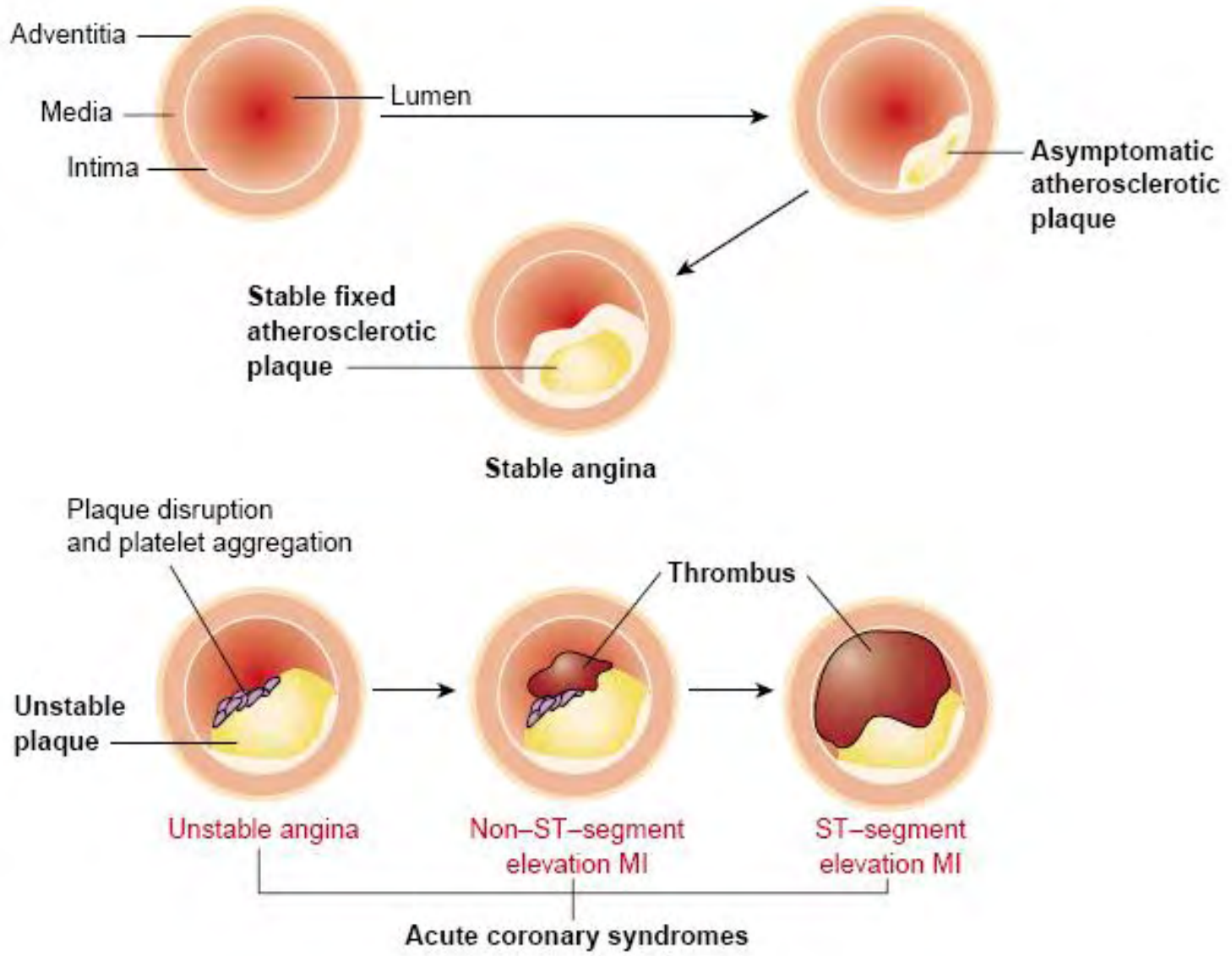
Coronary Atherosclerosis Causes MI



Intracerebral Atherosclerosis Causes Cerebral Infarction



Pathogenesis of Coronary Heart Diseases

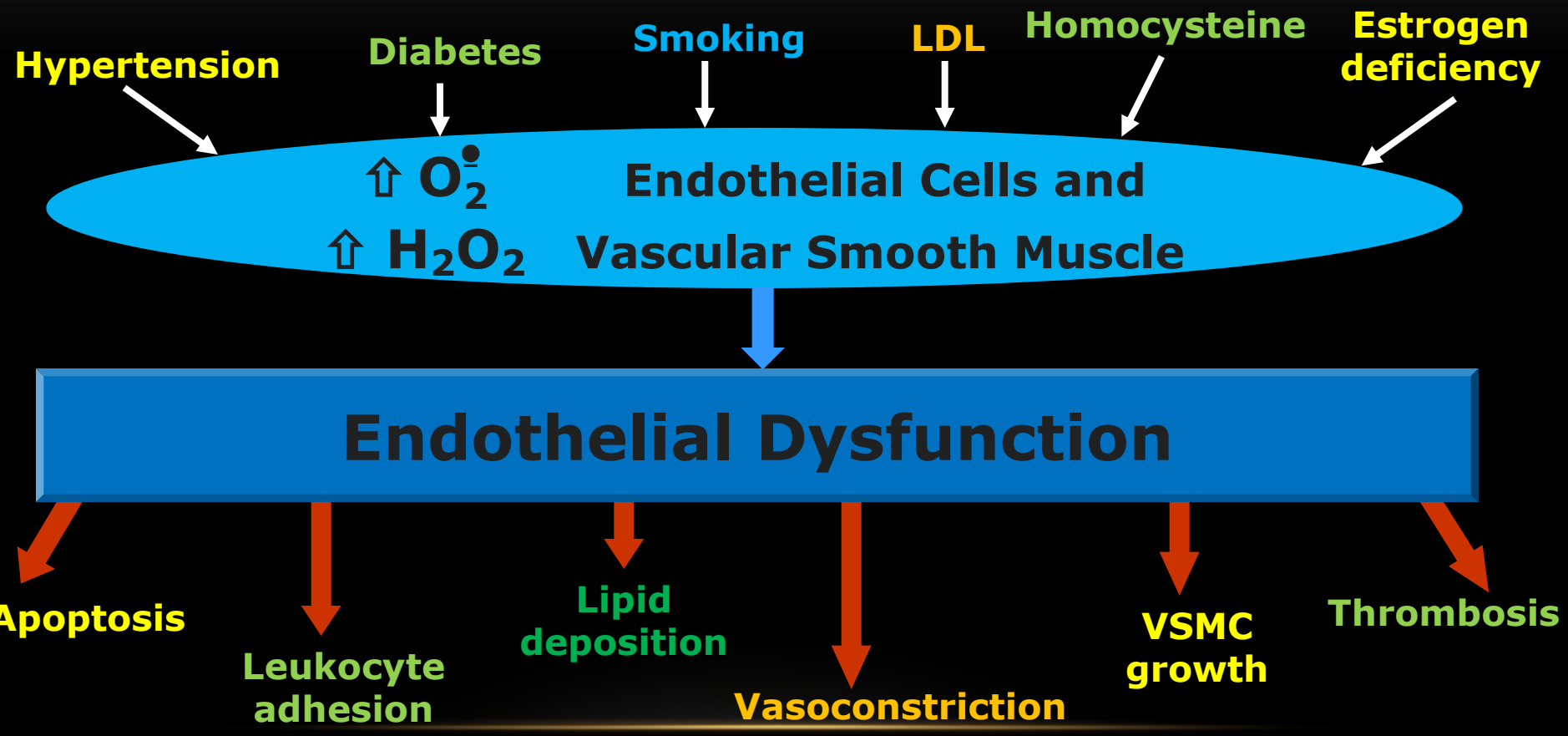


Etiology

1-CAD Risk Factors

2- Oxidative Stress

3-Endothelial Dysfunction



Coronary Arteries Diseases Risk Factors

- **Non modifiable risk factors:**
  - **Increasing age**
  - **Gender**
  - **Family history of premature heart disease**
  - **Genetics Defects**

- **Modifiable risk factors:**
  - **High LDL cholesterol**
  - **Low HDL cholesterol**
  - **High blood pressure**
  - **Diabetes**
  - **Obesity (especially abdominal obesity)**
  - **Physical inactivity**
  - **Cigarette smoking**
  - **Diet high in saturated fat, *trans* fat, cholesterol, low in fruits, vegetables and whole grains**

Genetic Defects of Lipid Metabolism

- **1-Monogenic:**

  Familial Hypercholesterolemia

  (homozygous or heterozygous)

  defect: inactive LDL receptor

  Familial Hypertriglyceridmeia

  defect: inactive lipoprotein lipase

  Familial Combined Hyperlipidemia

  defect: unknown

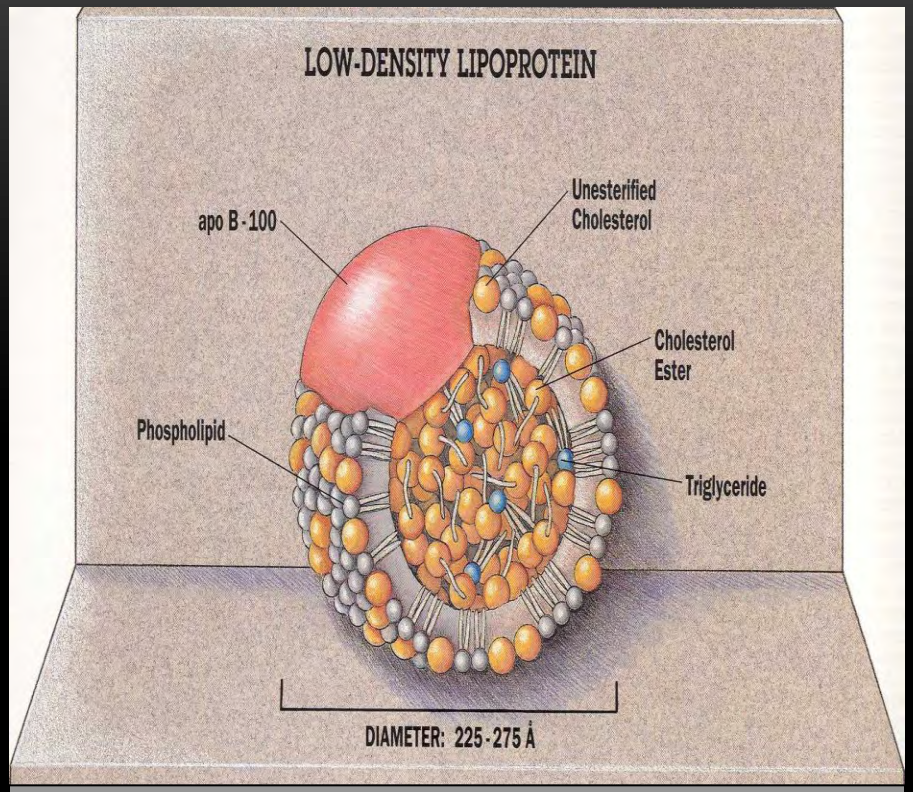
- **2- Polygenic/Multifactorial:**

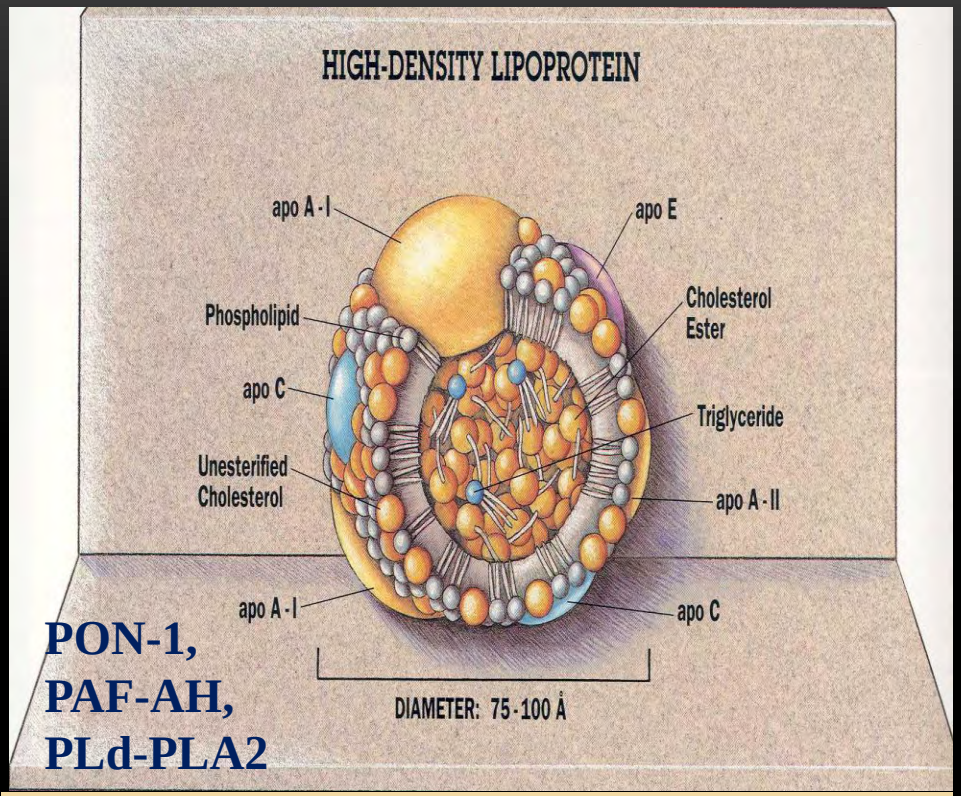
  Hypercholesterolemia,

  Hypertriglyceridemia

SMOKING

- Twice the risk of stroke and heart attack
- Lowers HDL
- Produces free radicals
- Promotes ↑fibrinogen
- Increase plasminogen activator inhibitor





PON-1,
PAF-AH,
PLd-PLA2

Surface Monolayer
Phospholipids (25%)
Free Cholesterol (15%)
Protein (22%)

Hydrophobic Core
Triglyceride (5%)
Cholesteryl Esters (35%)

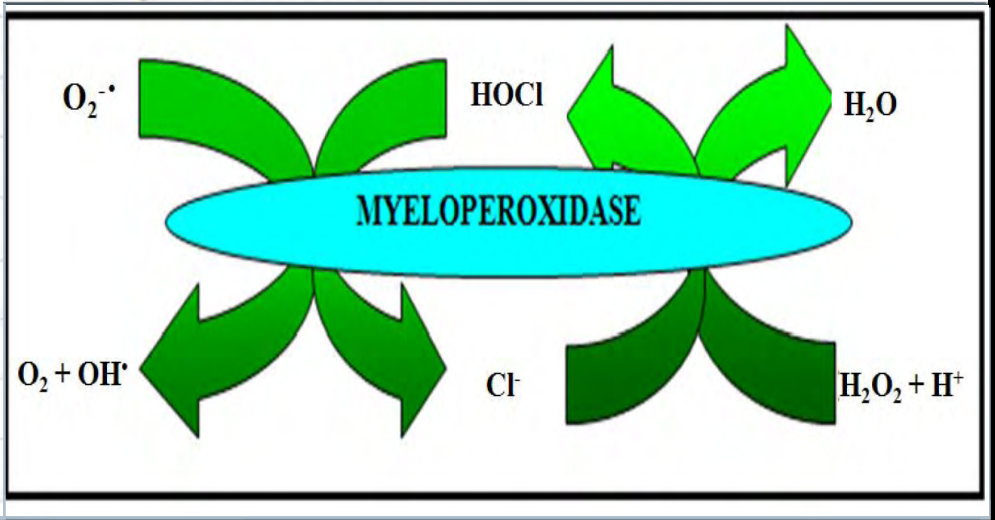
Surface Monolayer
Phospholipids (25%)
Free Cholesterol (7%)
Protein (45%)

Hydrophobic Core
Triglyceride (5%)
Cholesteryl Esters (18%)

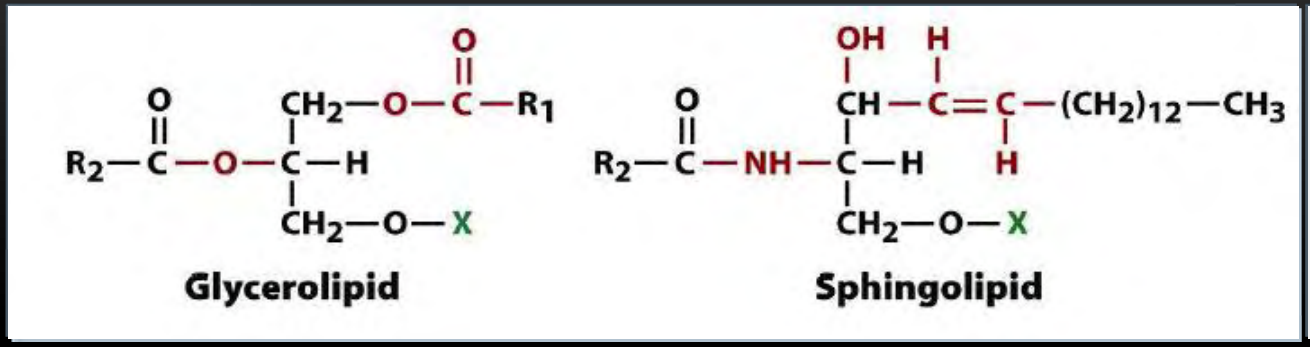
Most Important Reactive Oxygen and Nitrogen Species

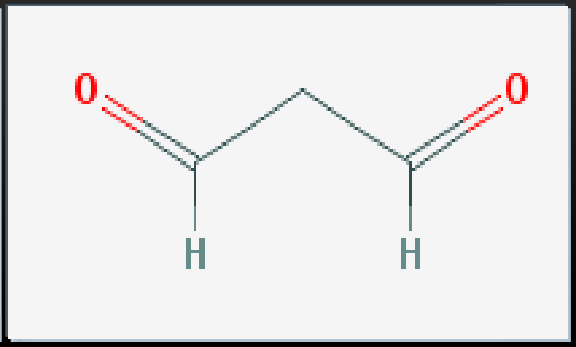
Reaction	Note
$O_2 + e^- \rightarrow O_2^{\cdot -}$	Superoxide formation (various sources, see text)
$2\,O_2^{\cdot -} + 2\,H^+ \rightarrow H_2O_2 + O_2$	Hydrogen peroxide formation, catalyzed by SODs
$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {\cdot}OH + OH^-$	Fenton reaction
$O_2^{\cdot -} + H_2O_2 \rightarrow {\cdot}OH + OH^- + O_2$	Haber-Weiss reaction (iron-catalyzed)
L-arginine $\rightarrow NO^{\cdot}$ + L-citrulline	$NO^{\cdot}$ formation (catalyzed by NOS)
$NO^{\cdot} + O_2^{\cdot -} \rightarrow ONOO^-$	Peroxynitrite formation

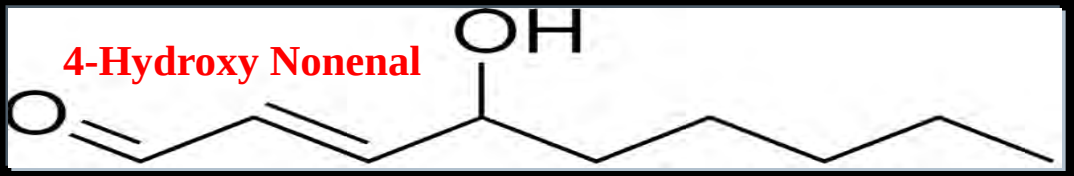
•NO	Nitric Oxide
$\bullet NO_2$	Nitrogen dioxide
$ONOO^-$	Peroxynitrite
$O_2\bullet^-$	Superoxide
•OH	Hydroxyl radical
H_2O_2	Hydrogen peroxide
ROO•	Peroxy radical
HOCl	Hypochlorous acid

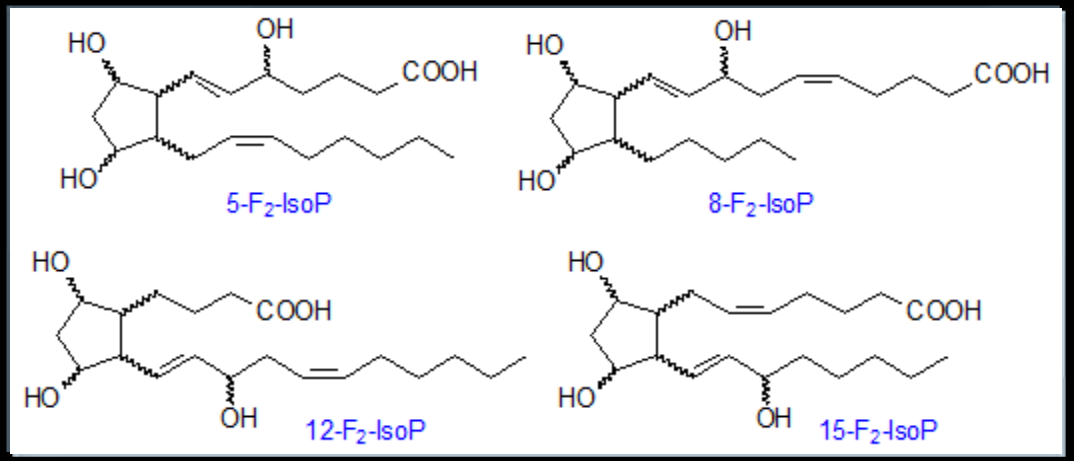


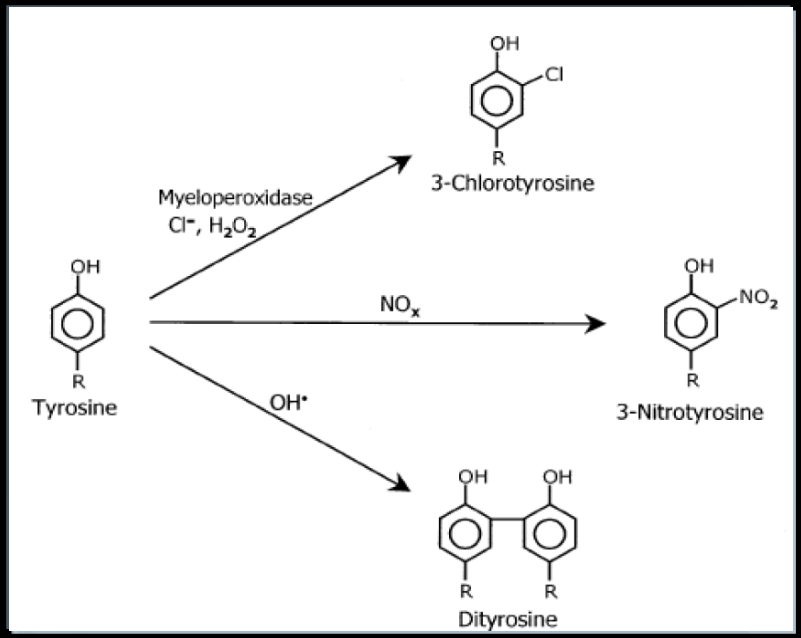
Lipid and Protein Peroxidation











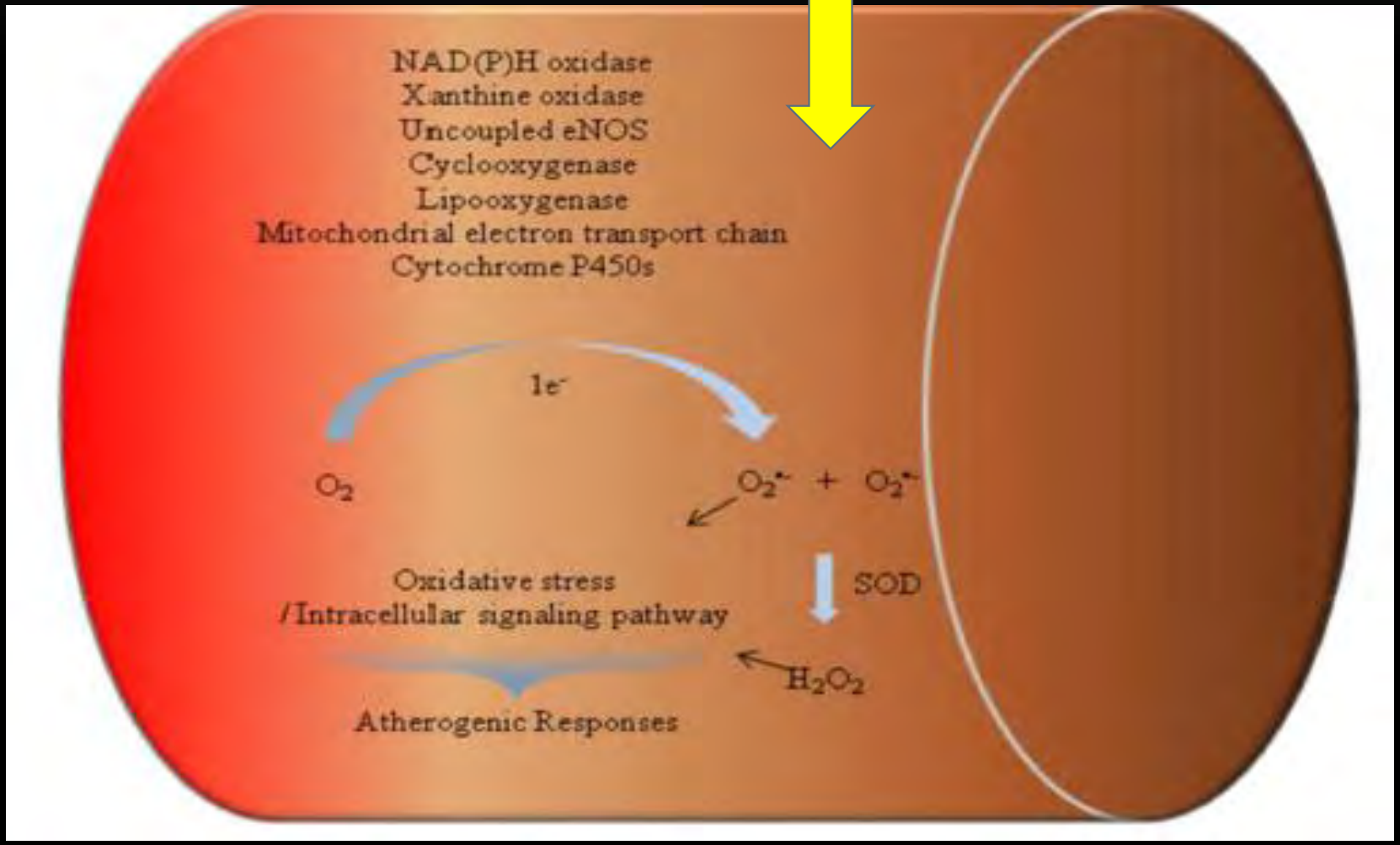
F2-isoprostanes in HDL_2 and HDL_3 were 4- to 6-fold higher than in LDL; HDL_3-contained 50% more F2-isoprostanes than HDL2. Importantly, the amount of arachidonic acid was significantly higher in LDL than in HDL. These observations indicate that HDL is the major carrier of both early and late products of lipid oxidation

Contributing Factors for Generation of ROS

Hypercholesterolemia, Hyperglycemia, Hypertension

Shear Stress, Proinflamatory Cytokines

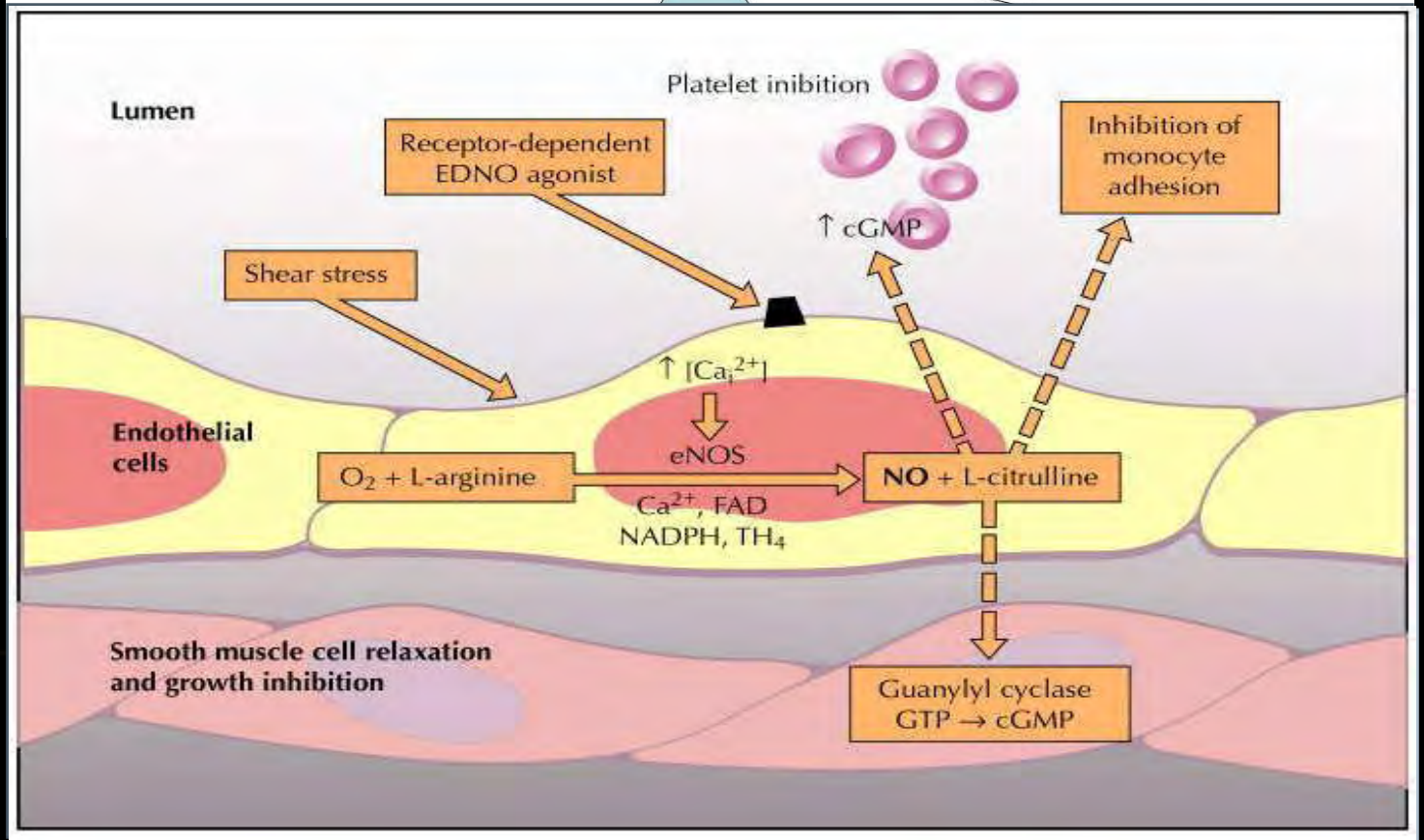
Smoking, Stress



Endothelial Dysfunction

Vasodilation
Thrombolysis
Platelet disaggregation
Antiproliferation
Antiinflammation
Antioxidant

Vasoconstriction
Thrombosis
Adhesion molecules
Growth factors
Inflammation
Oxidant activity



Stepwise Formation of Atherosclerosis

Accumulation of lipids (fatty streak)

↓

Surrounded by proliferating smooth muscle

↓

LDL enters the endothelium

↓

LDL becomes oxidized by several types of cells

↓

The oxidized LDL attracts macrophages, forming foam cells

↓

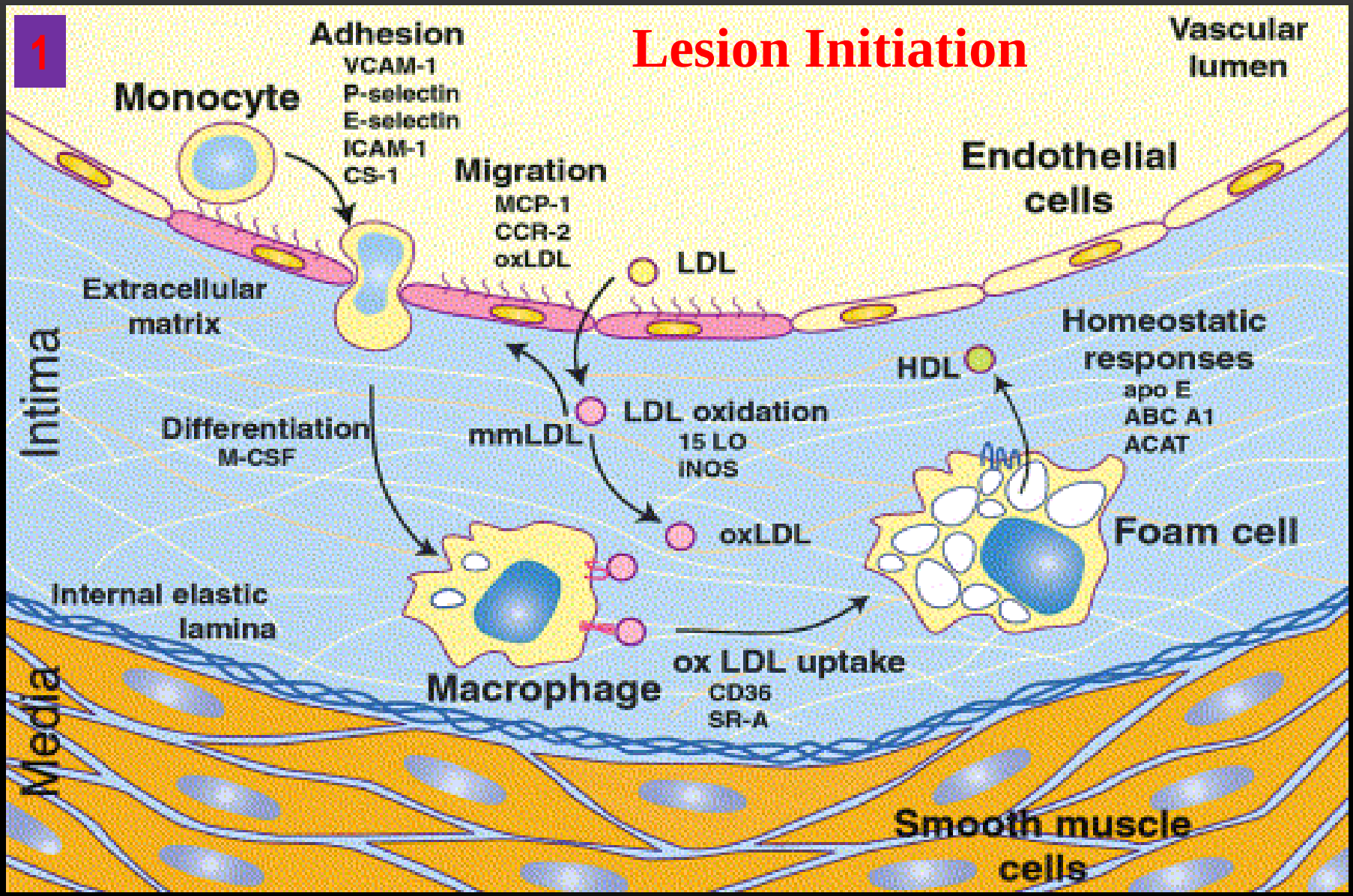
Proliferating smooth muscle, lipids, and connective tissue become incorporated into the maturing Plaque

↓

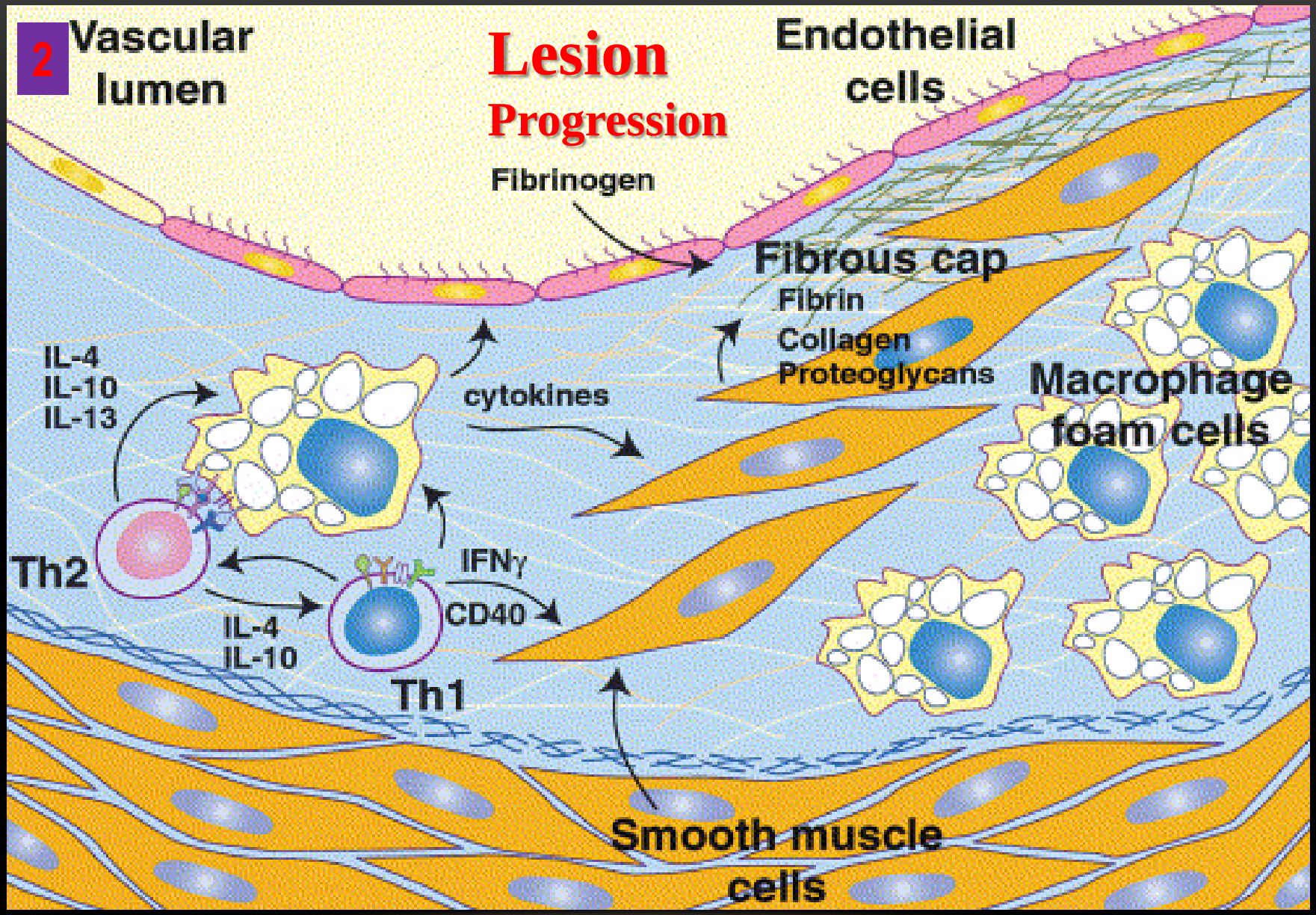
Formation of a fibrous cap, having areas of cell necrosis and calcifation

↓

Narrowing of the arterial's lumen diameter

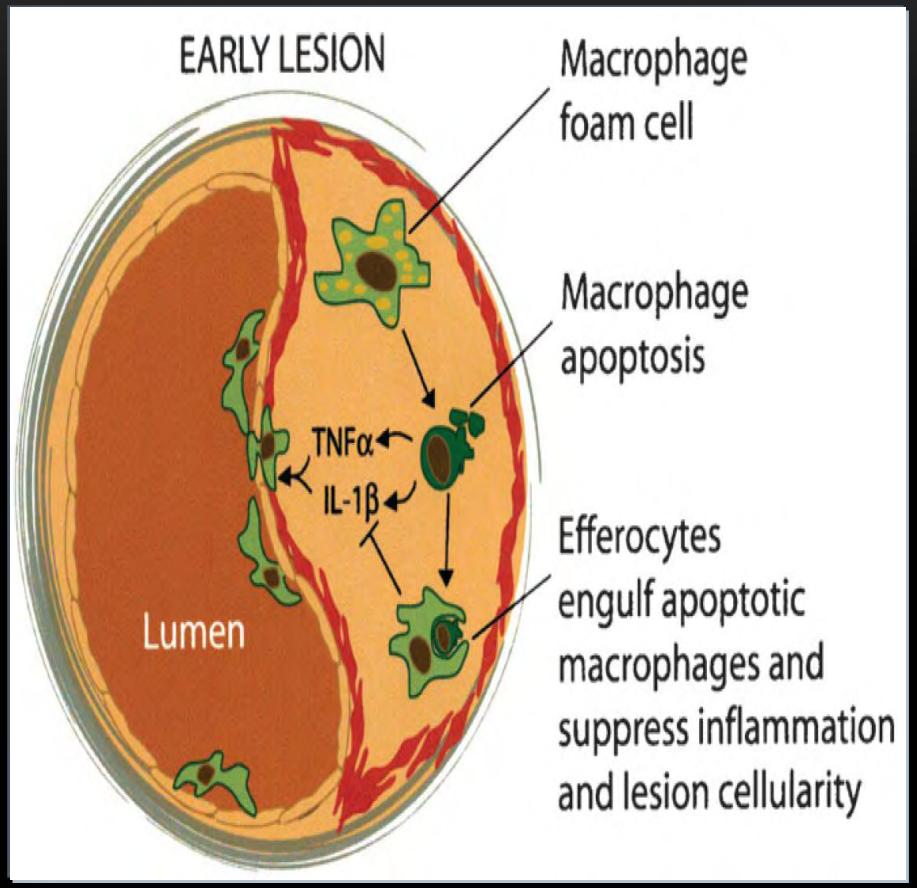


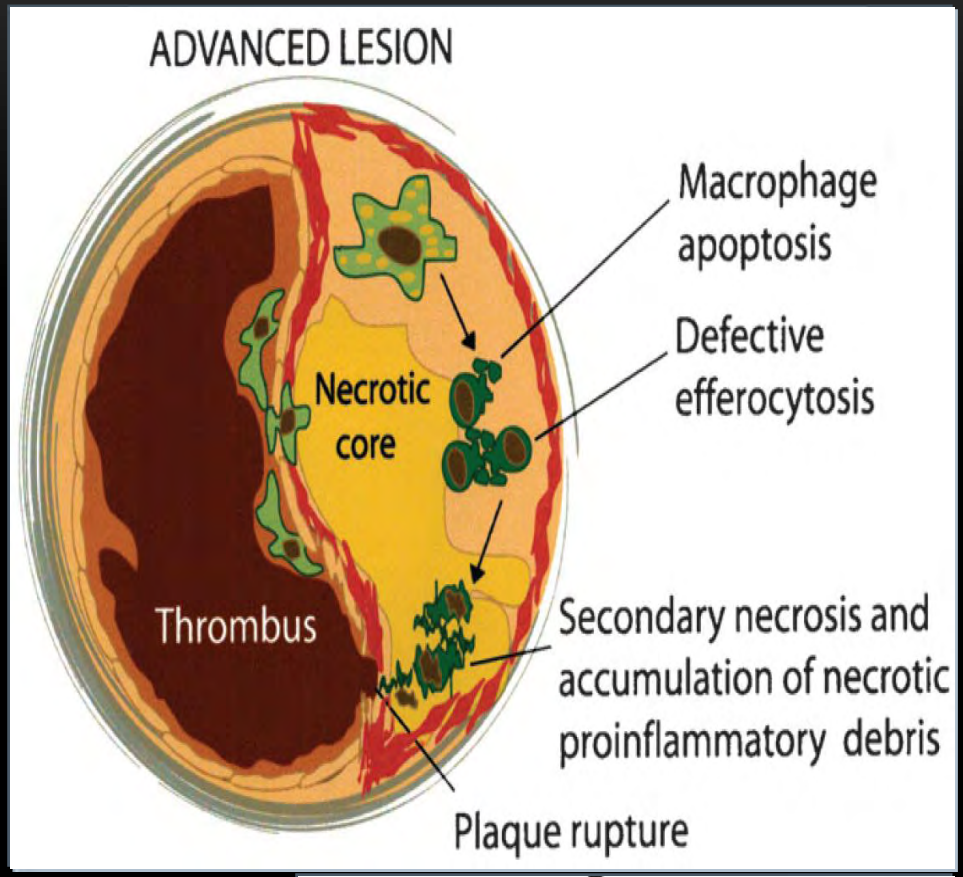
Minimally Modified LDL induces expression of cell adhesion molecules



Smooth muscle cells migrate into the Intima, proliferate and secrete extracellular matrix proteins that form a fibrous plaque

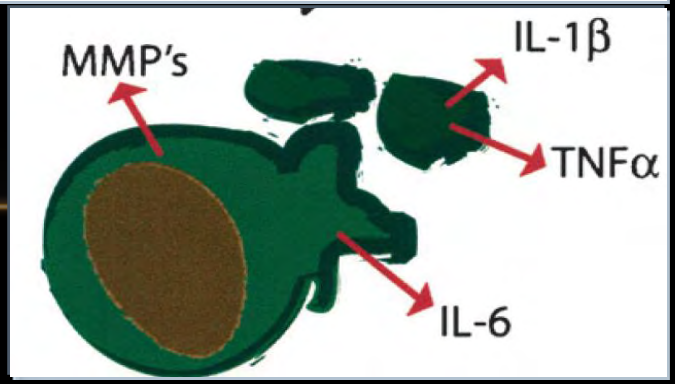
Macrophage death as a factor that limits lesion cellularity

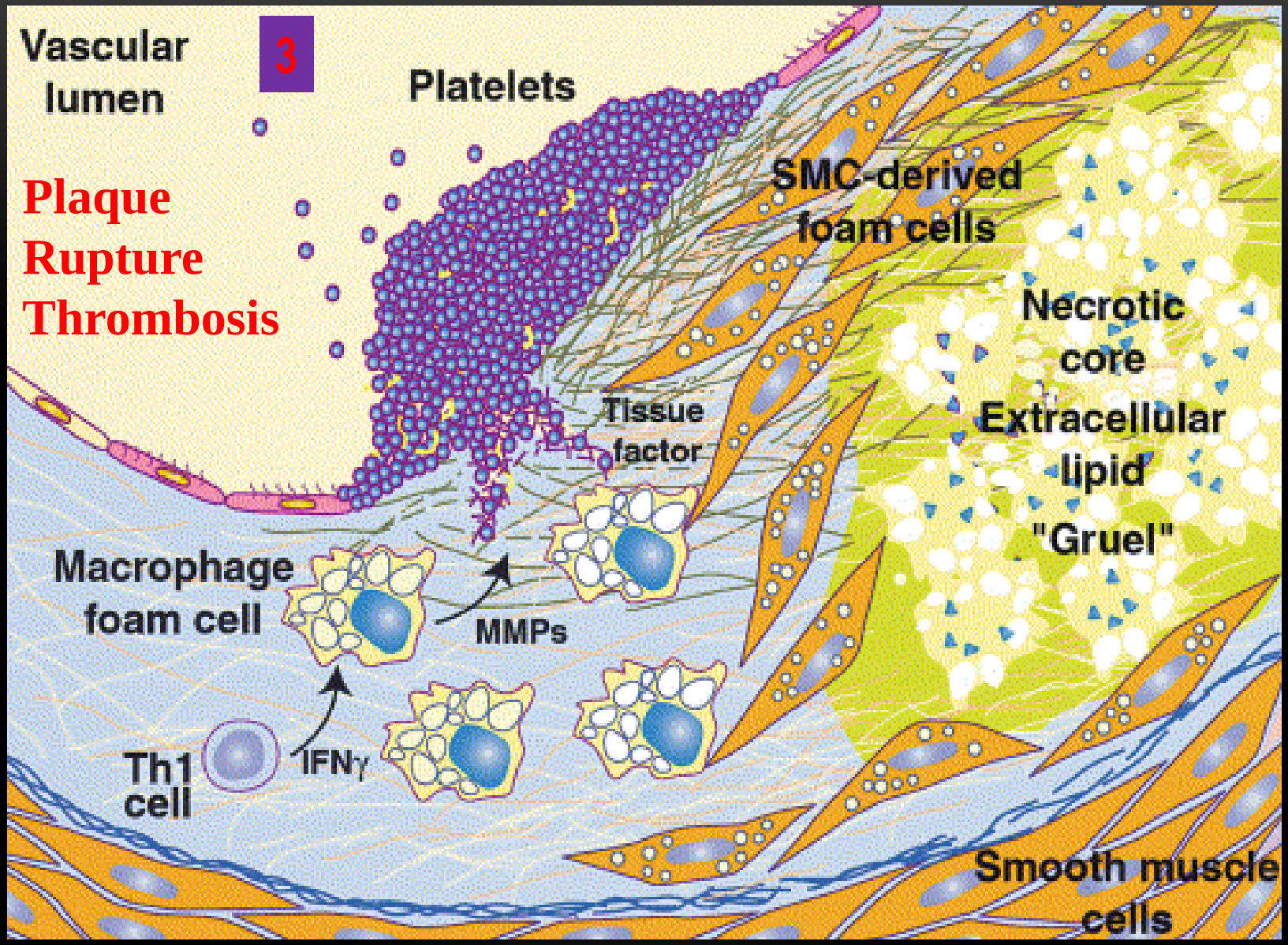




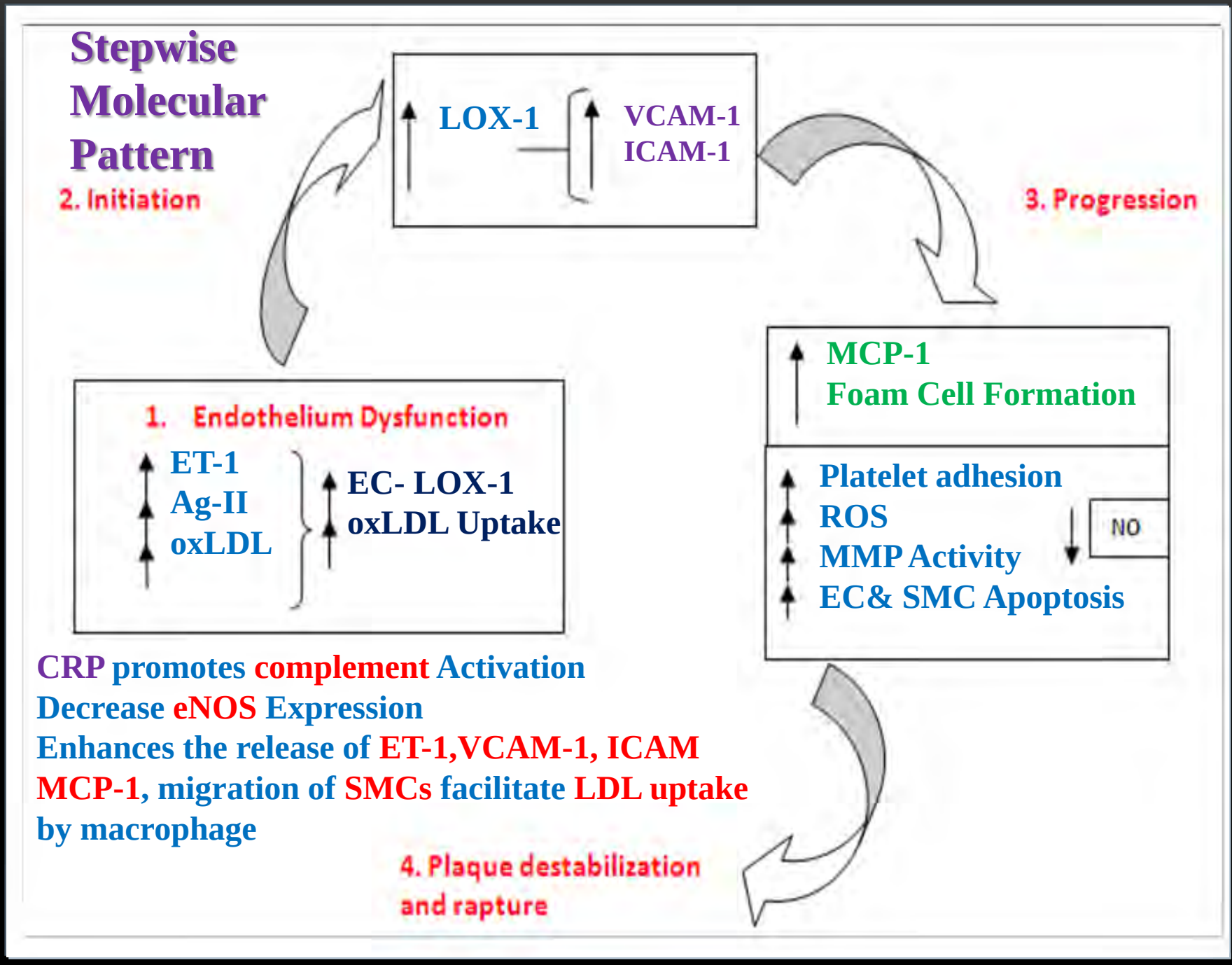
Apoptotic Inducers:

TNFα, Fas Ligand, Growth factor withdrawal, Oxidized LDL, Oxidized Phospholipids Oxysterol (7-ketocholesterol)

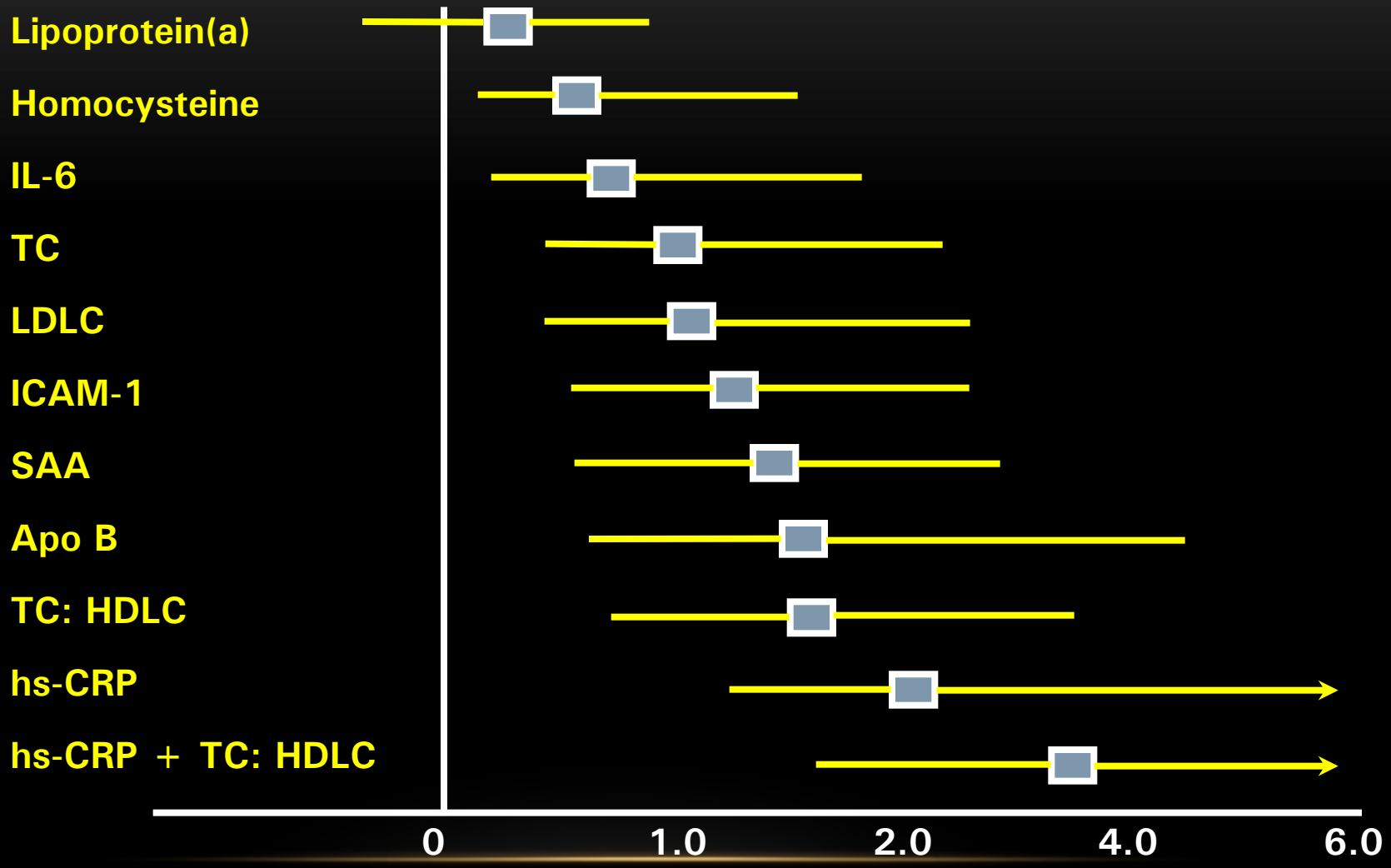




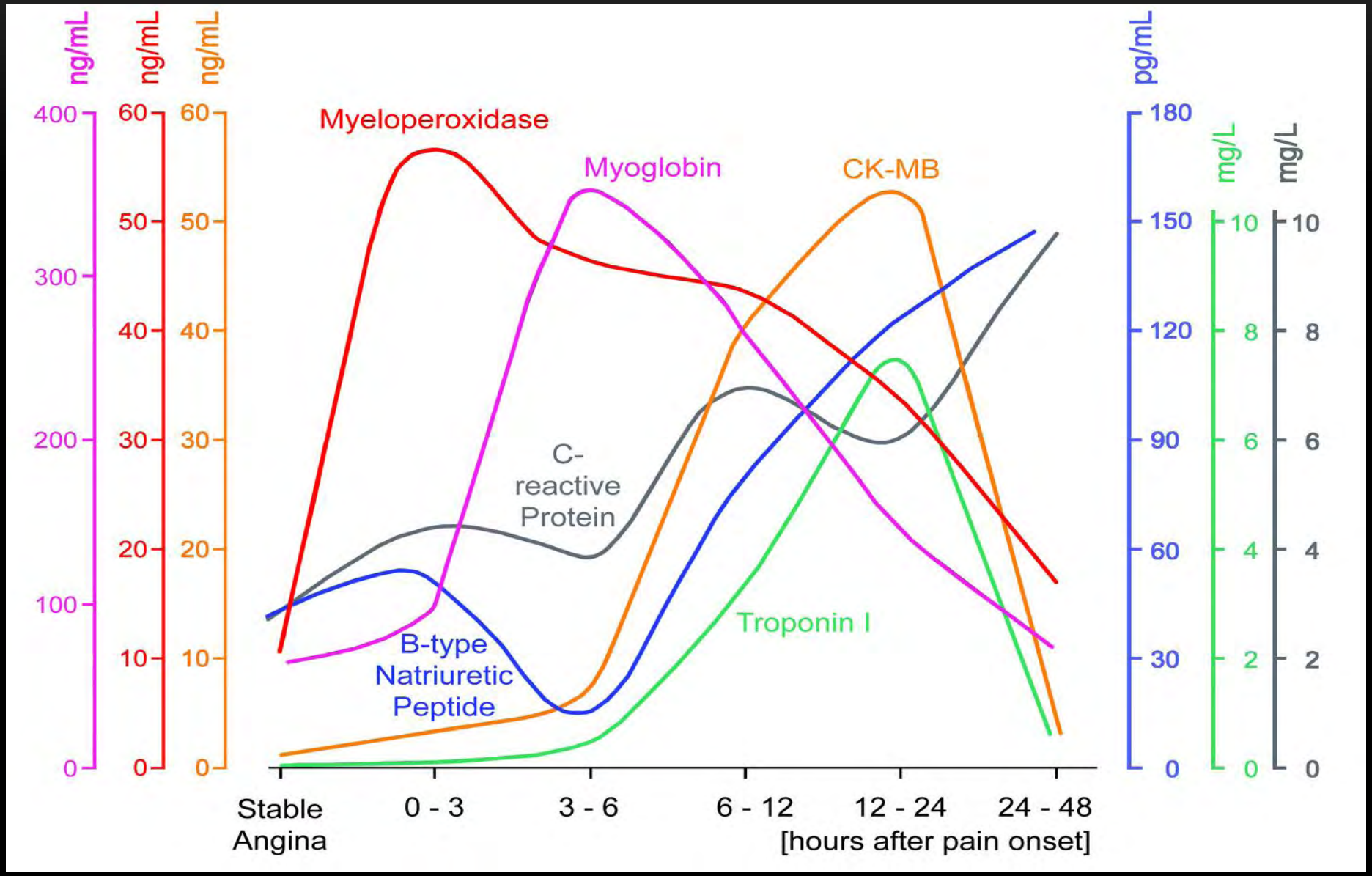
Fibrous Cap is weakened, tissue factors are released, recruitment of platelets and formation thrombosis


Stepwise Molecular Pattern
2. Initiation
LOX-1
VCAM-1
ICAM-1
3. Progression
MCP-1
Foam Cell Formation
Platelet adhesion
ROS
MMP Activity
EC& SMC Apoptosis
NO
1. Endothelium Dysfunction
ET-1
Ag-II
oxLDL
EC- LOX-1
oxLDL Uptake
CRP promotes complement Activation
Decrease eNOS Expression
Enhances the release of ET-1,VCAM-1, ICAM
MCP-1, migration of SMCs facilitate LDL uptake
by macrophage
4. Plaque destabilization
and rapture

Relative Risk Factors for Future Outcomes



Myeloperoxidase Early Indicator of Acute Coronary Syndrome and Predictor of Future Cardiovascular Events



Lipid Lowering Agents

Subclass	LDL	HDL	TG	Side effects/problems
Bile acid resins (cholestyramine, colestipol)	↓↓	—	↑	Tastes bad and causes GI discomfort
HMG-CoA reductase inhibitors (lovastatin, atrovastatin, pravastatin, simvastatin)	↓↓↓	↑	↓	Safety unknown for long term use; Most expensive
VLDL secretion inhibitor (Niacin)	↓↓	↑↑	↓	Evokes flushing; itchiness and GI discomfort
Lipoprotein lipase stimulants (Fibrates: clofibrate, gemfibrozil, fenofibrate)	↓	↑	↓↓↓	More effective in reducing TG than cholesterol; long-term effect not known
Probucol	↓	↓	—	HDL decrease, not effective in single drug therapy; no long term clinical data.