ATHEROSCLEROSIS

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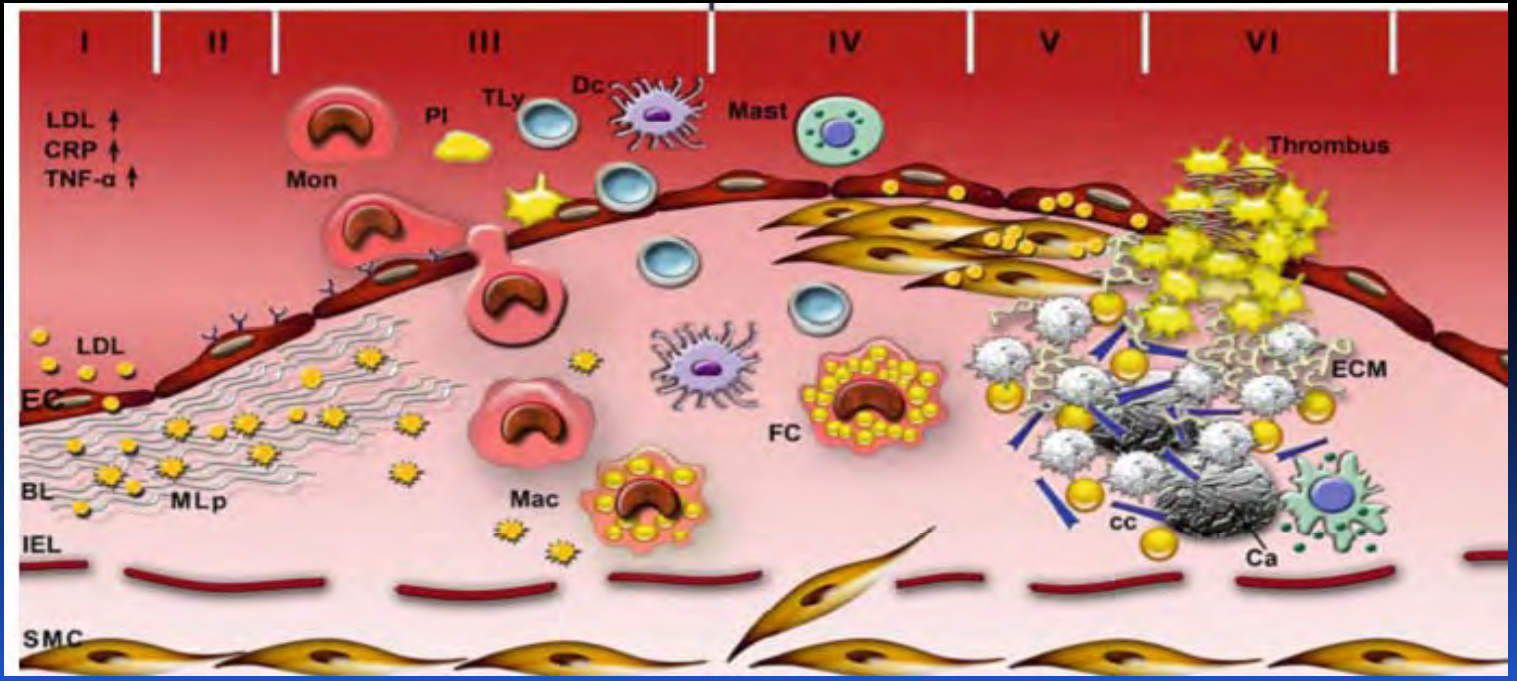
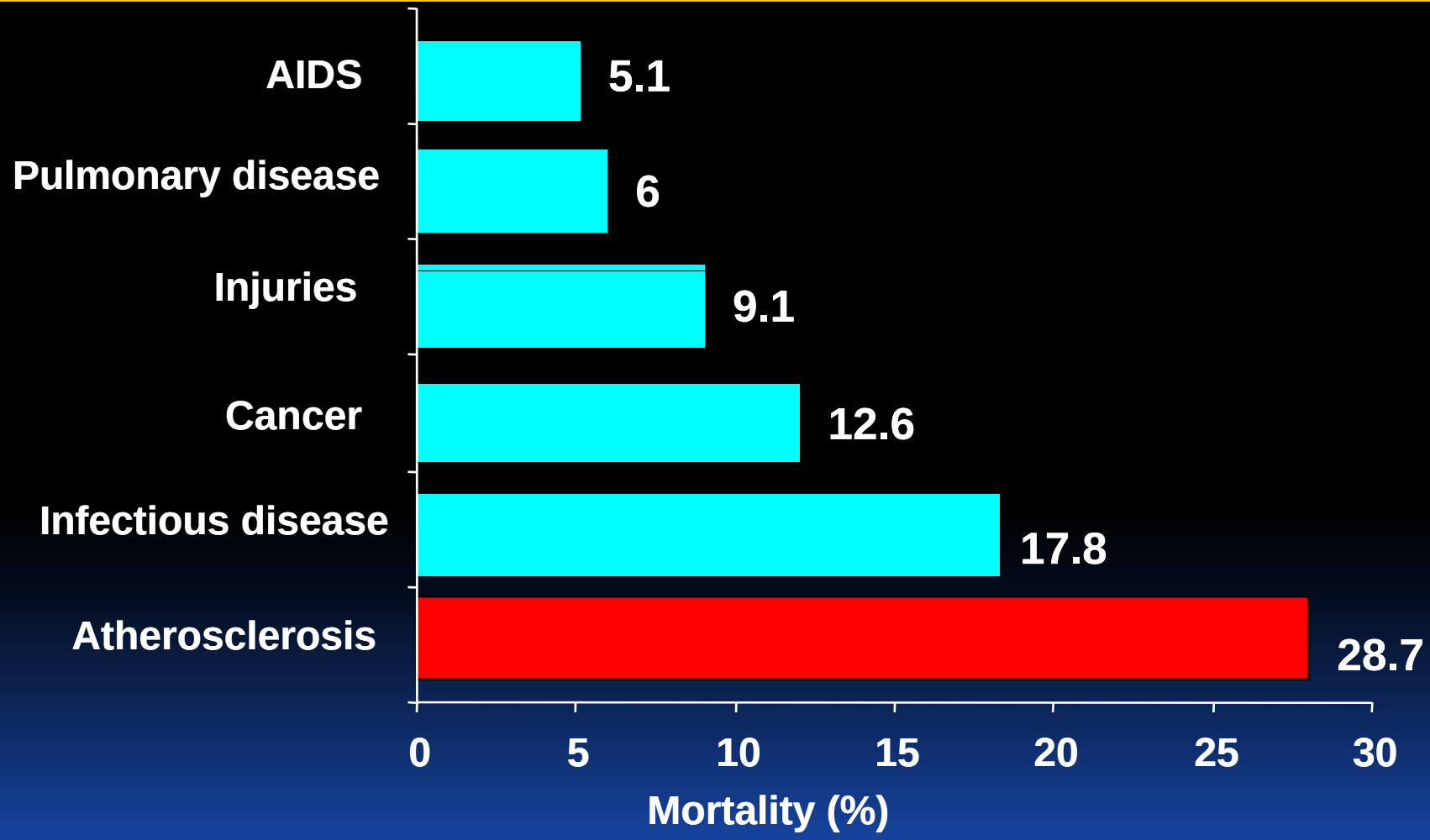


Definition

Atherosclerosis: Is a chronic inflammatory process characterized by plaque formation within the vessel wall of arteries and extensive necrosis and fibrosis of surrounding tissues

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

Atherosclerosis is a Leading Cause of Death Worldwide



THEORY AND CONCEPT OF ATHEROSCLEROSIS

Concept — **Theory** — **Disease**

- Dyslipidemia
- Endothelial dysfunction
- Free radicals
- Immunologic

→ **Inflammations** → **Atherosclerosis/ CAD**

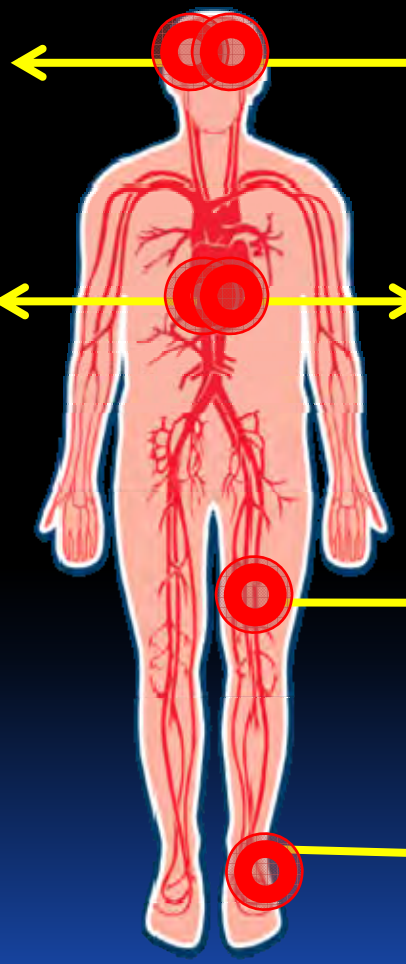
MAJOR CLINICAL MANIFESTATIONS OF ATHEROTHROMBOSIS

Ischemic Stroke

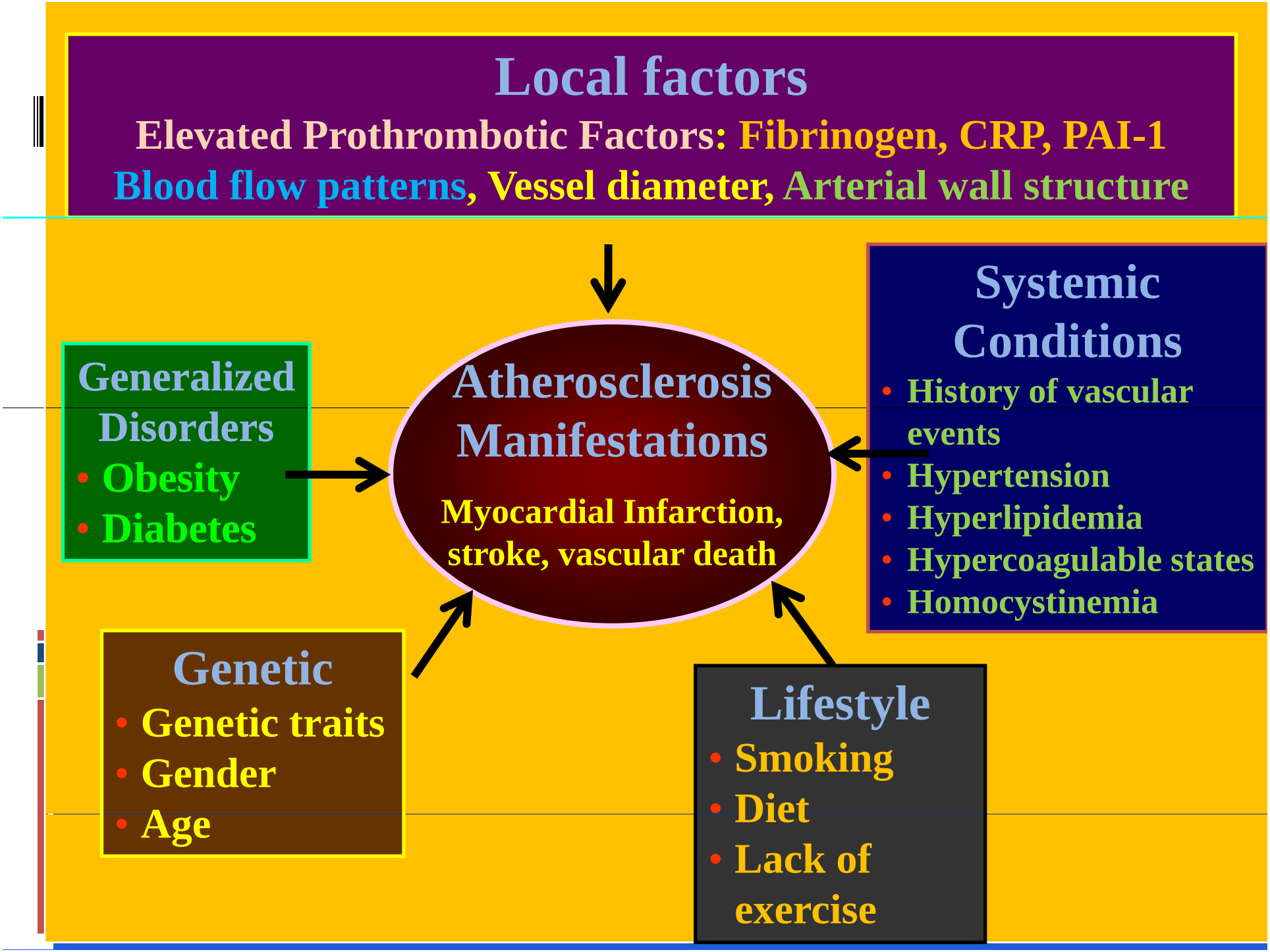
Transient Ischemic attack

Myocardial Infarction

Angina:
- **Stable**
- **Unstable**



Peripheral arterial disease:
- **Intermittent Claudication**
- **Rest Pain**
- **Gangrene**
- **Necrosis**


Local factors
Elevated Prothrombotic Factors: Fibrinogen, CRP, PAI-1
Blood flow patterns, Vessel diameter, Arterial wall structure
Generalized Disorders
• Obesity
• Diabetes
Atherosclerosis Manifestations
Myocardial Infarction, stroke, vascular death
Systemic Conditions
• History of vascular events
• Hypertension
• Hyperlipidemia
• Hypercoagulable states
• Homocystinemia
Genetic
• Genetic traits
• Gender
• Age
Lifestyle
• Smoking
• Diet
• Lack of exercise

Coronary Arteries Diseases Risk Factors

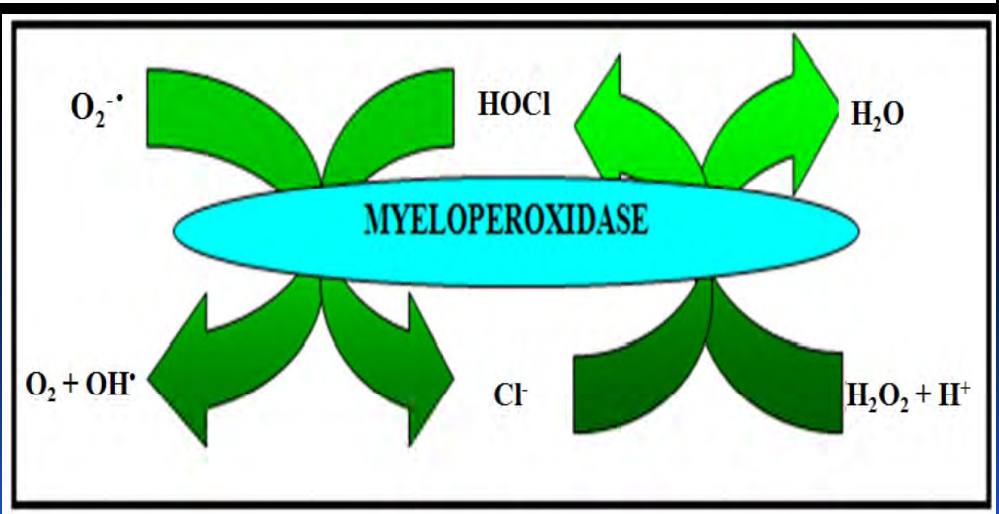
- **Non modifiable risk factors:**
  - **Increasing age**
  - **Gender**
  - **Family history of premature heart disease**
  - **Genetics Defects**

- **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**

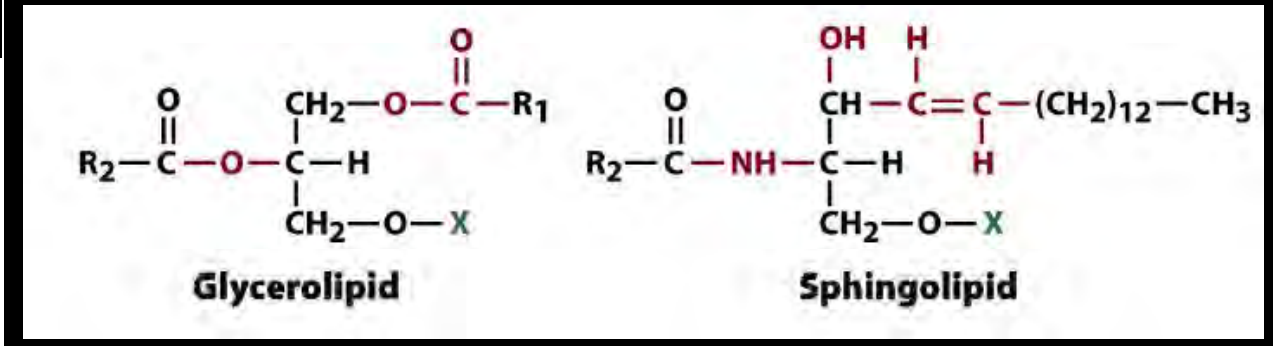
Most Important ROS and RNS

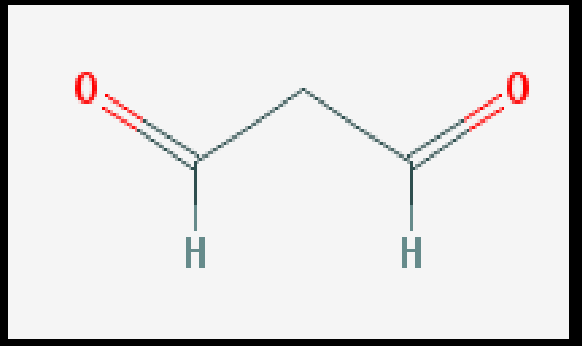
Reaction	Note
$O_2 + e^- \rightarrow O_2^{\cdot -}$	Superoxide formation (various sources, see text)
$2\,O_2^{\cdot -} + 2\,H^+ \rightarrow H_2O_2 + O_2$	Hydrogen peroxide formation, catalyzed by SODs
$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {\cdot}OH + OH^-$	Fenton reaction
$O_2^{\cdot -} + H_2O_2 \rightarrow {\cdot}OH + OH^- + O_2$	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

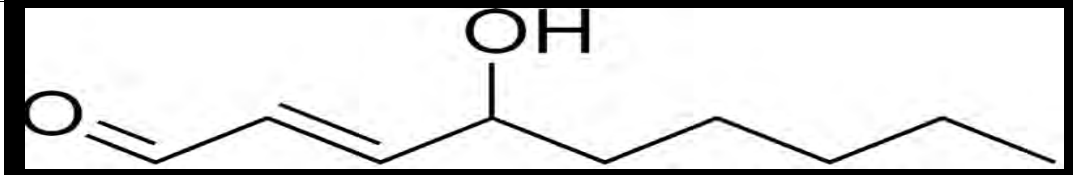


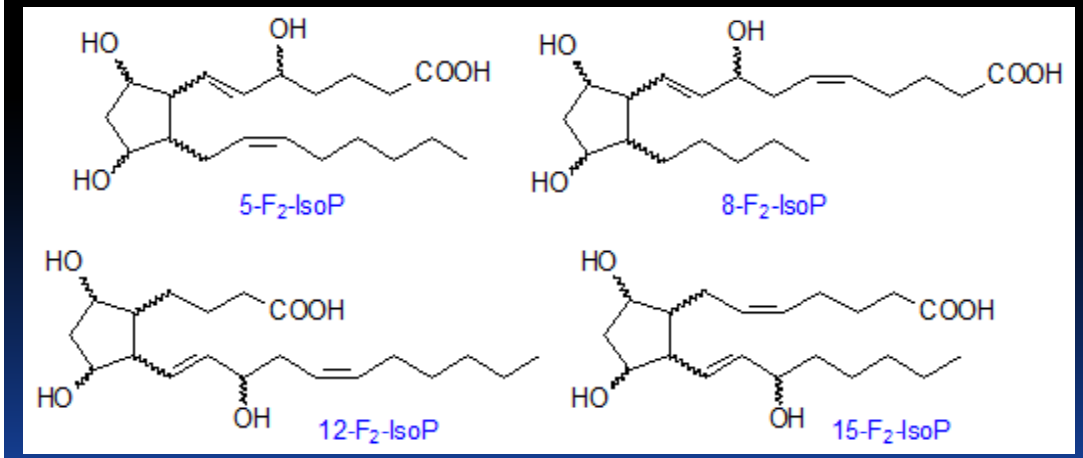
Lipid and Protein Peroxidation

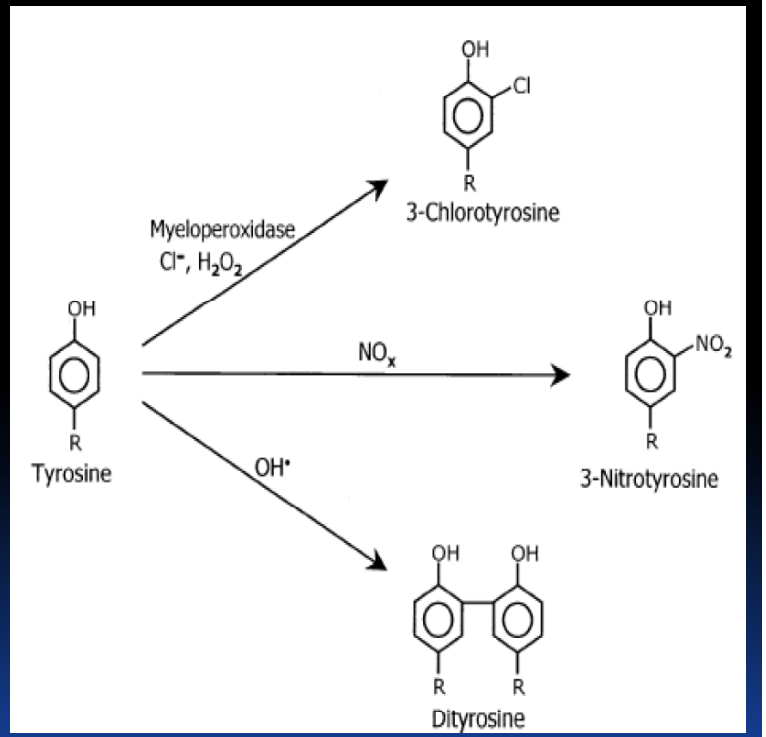




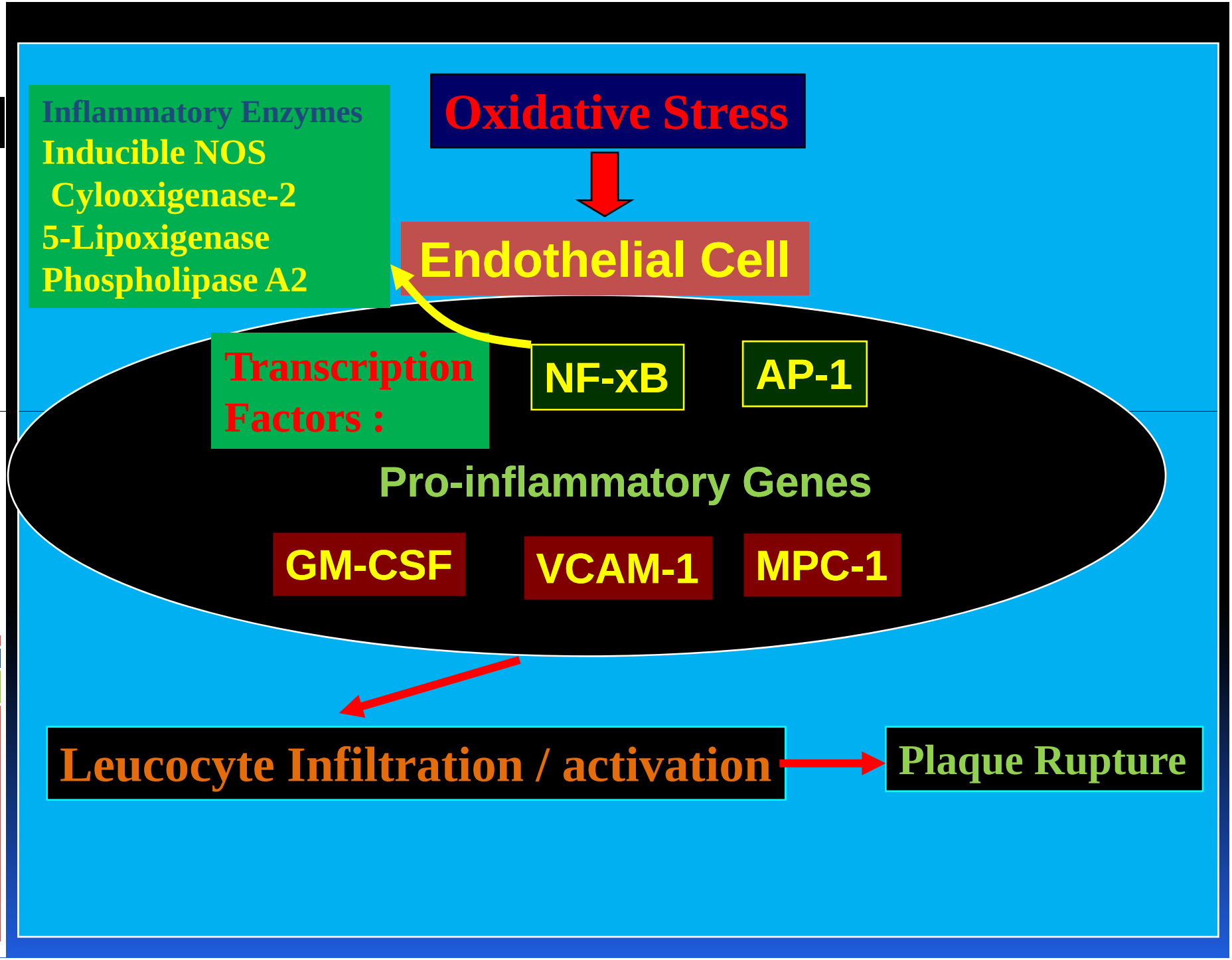
4-Hydroxy Nonenal





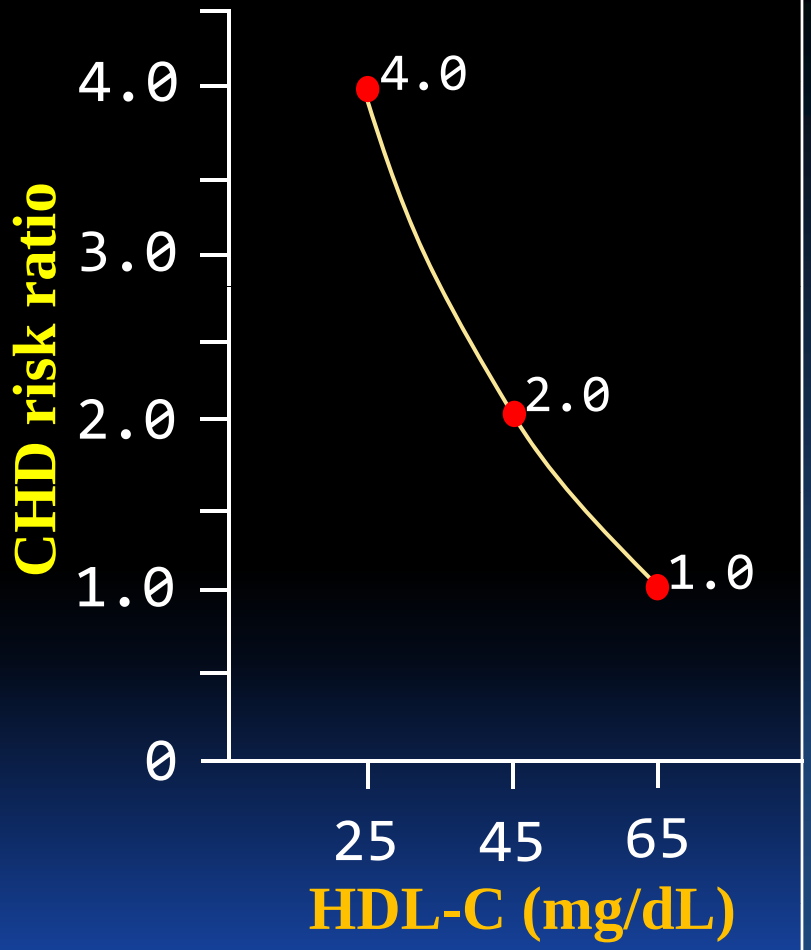


F2-isoprostanes in HDL2 and HDL3 were 4- to 6-fold higher than in LDL; HDL3-contained 50% more F2-isoprostanes than HDL2

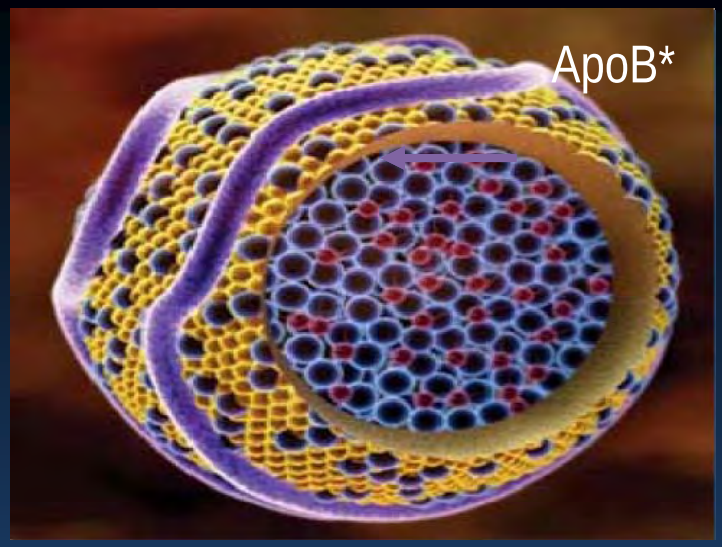

Inflammatory Enzymes
Inducible NOS
Cylooxigenase-2
5-Lipoxigenase
Phospholipase A2
Oxidative Stress
Endothelial Cell
Transcription Factors :
NF-xB
AP-1
Pro-inflammatory Genes
GM-CSF
VCAM-1
MPC-1
Leucocyte Infiltration / activation
Plaque Rupture

LDL and HDL in Atherosclerosis

HDL

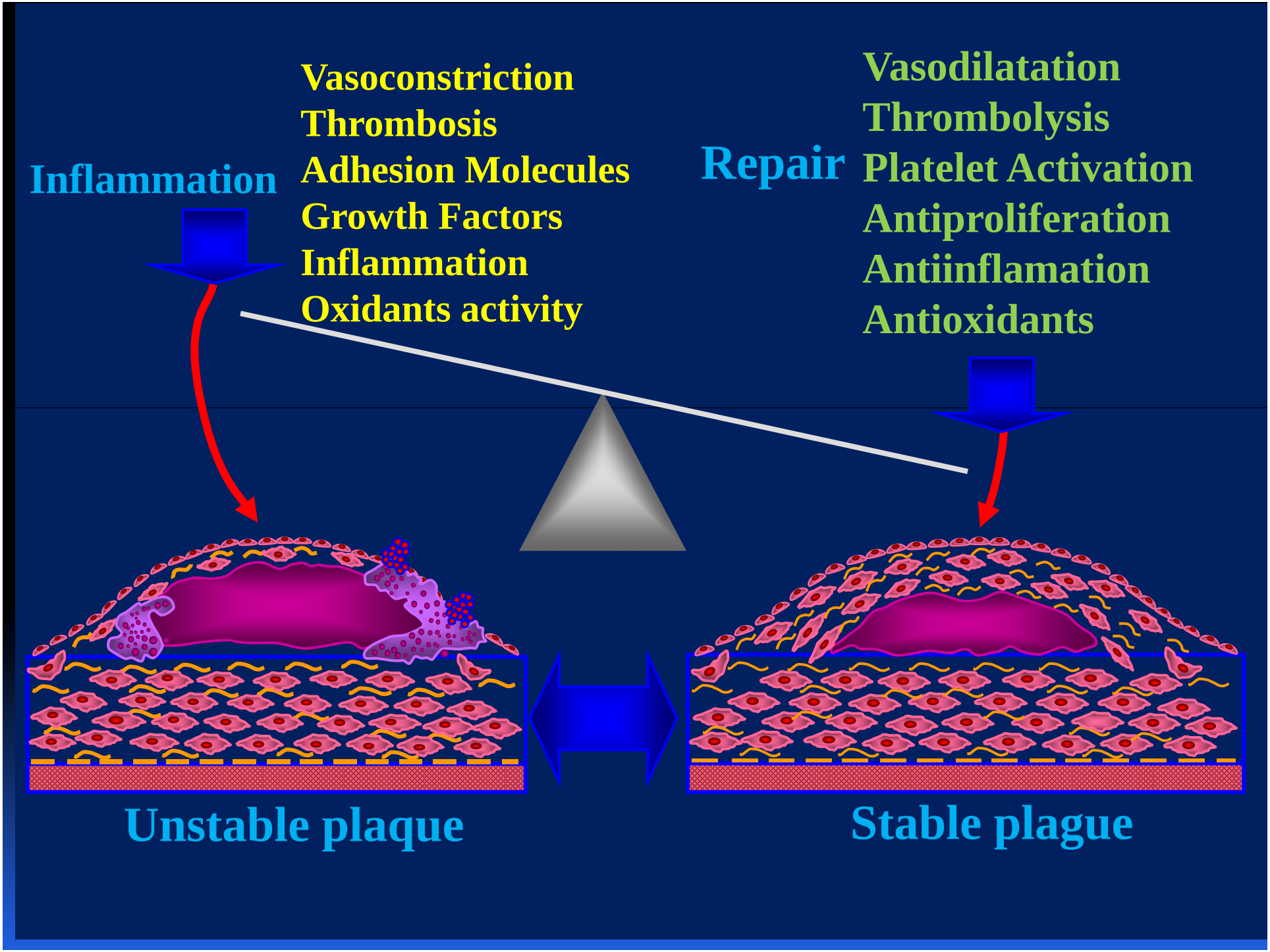


LDL

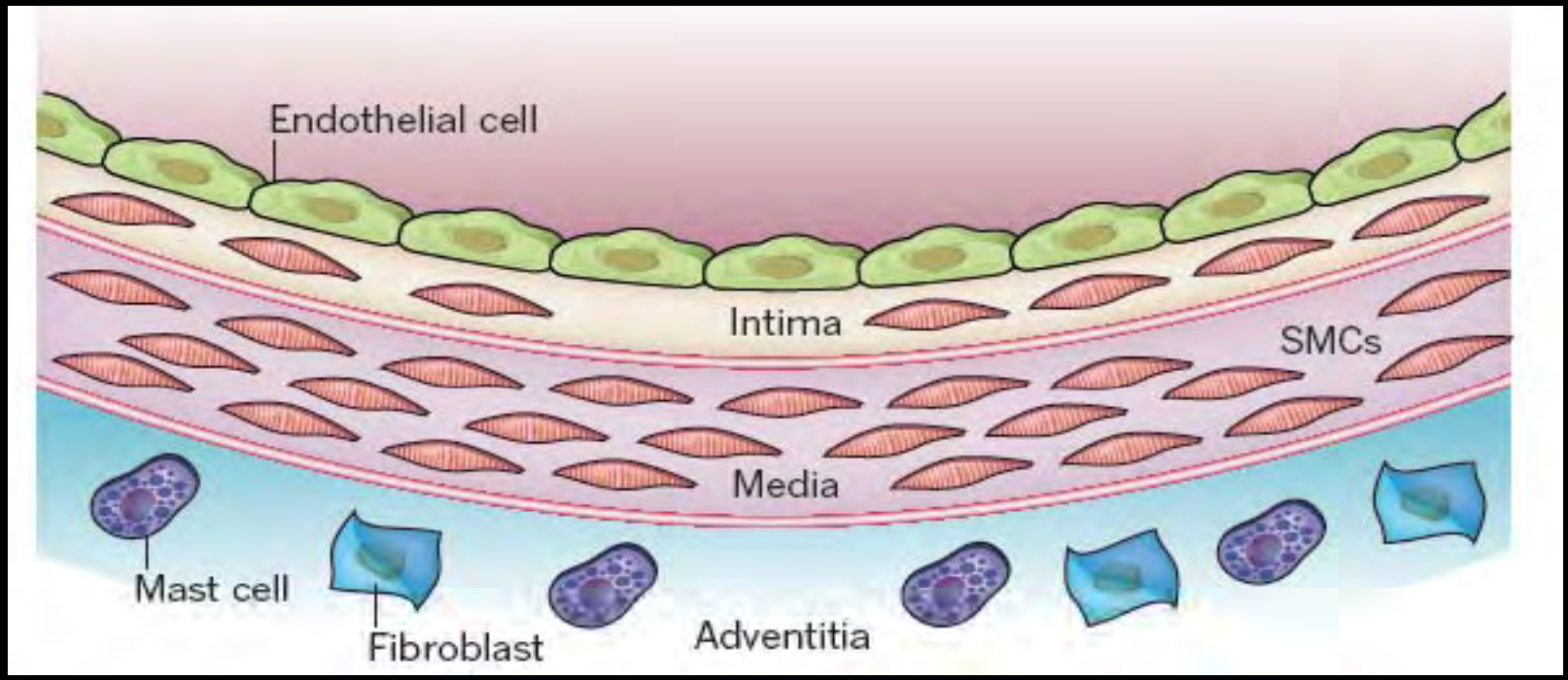


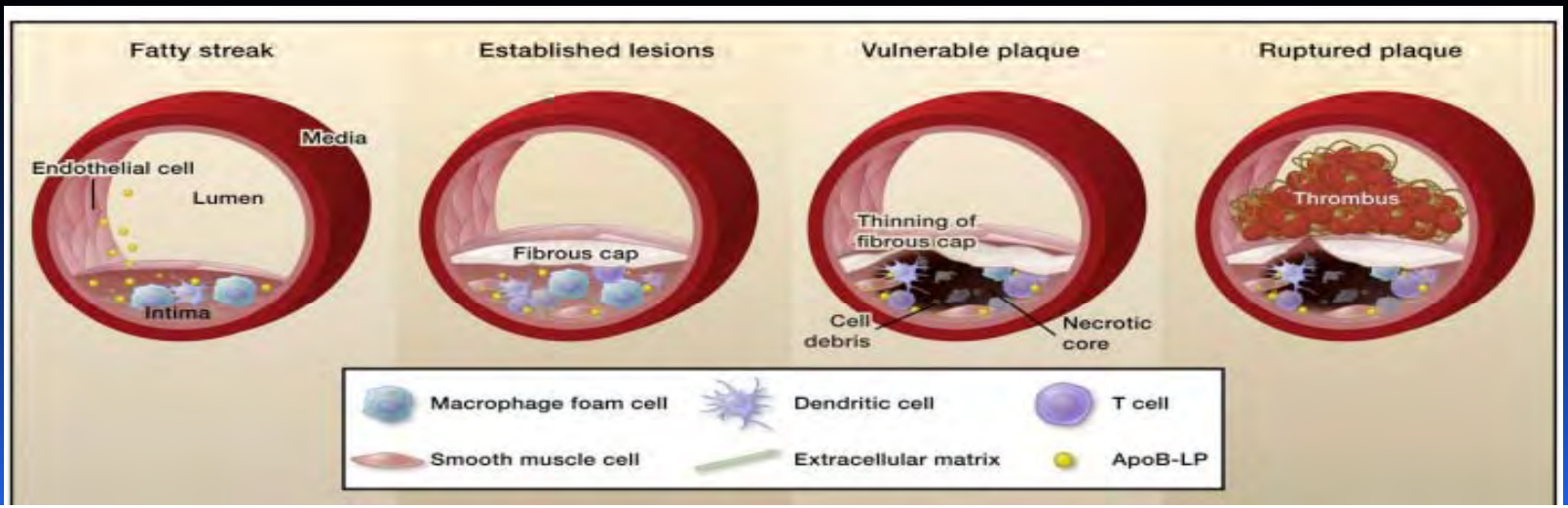
ApoB-containing lipoproteins

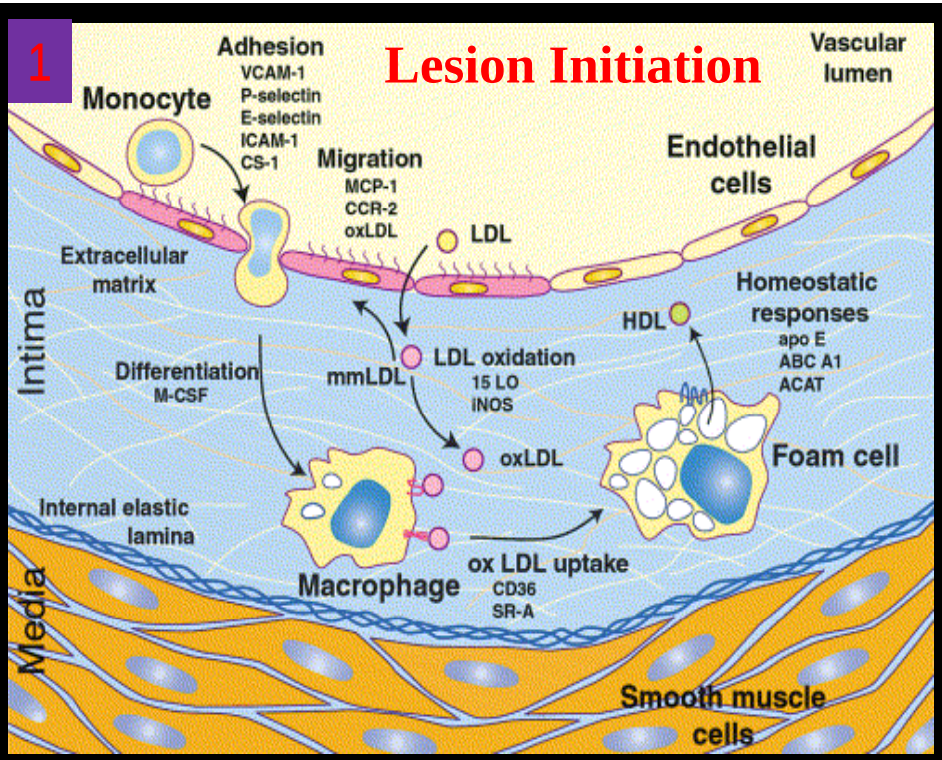
- LDL—most common/most important
- IDL
- VLDL /VLDL remnants
- Chylomicron remnants
- Lp(a)

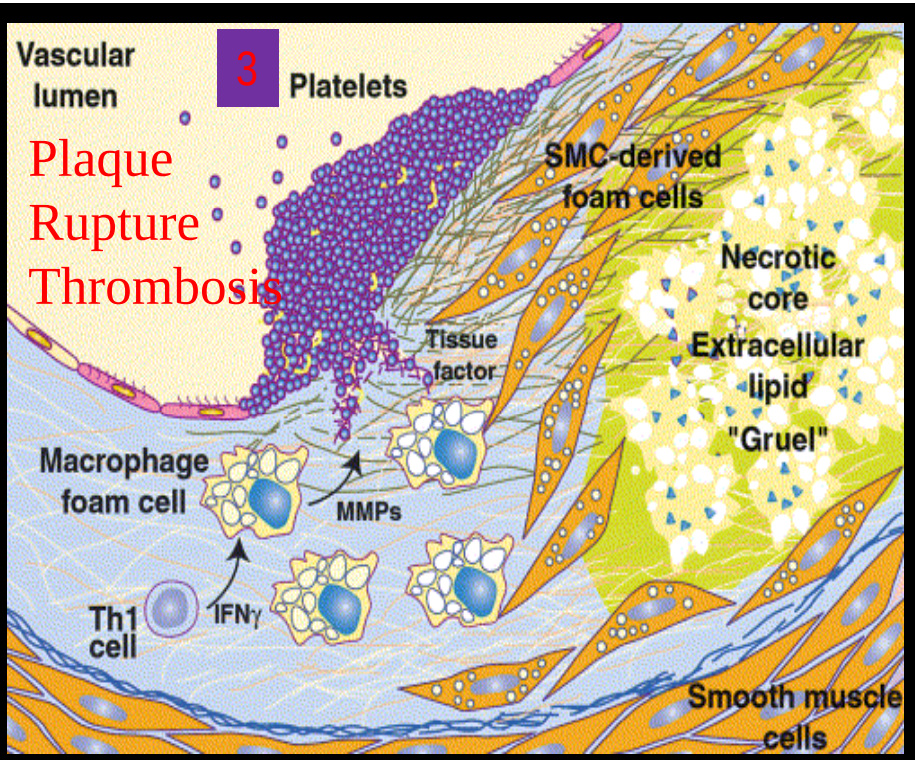

Inflammation
Vasoconstriction
Thrombosis
Adhesion Molecules
Growth Factors
Inflammation
Oxidants activity
Repair
Vasodilatation
Thrombolysis
Platelet Activation
Antiproliferation
Antiinflamation
Antioxidants
Unstable plaque
Stable plague

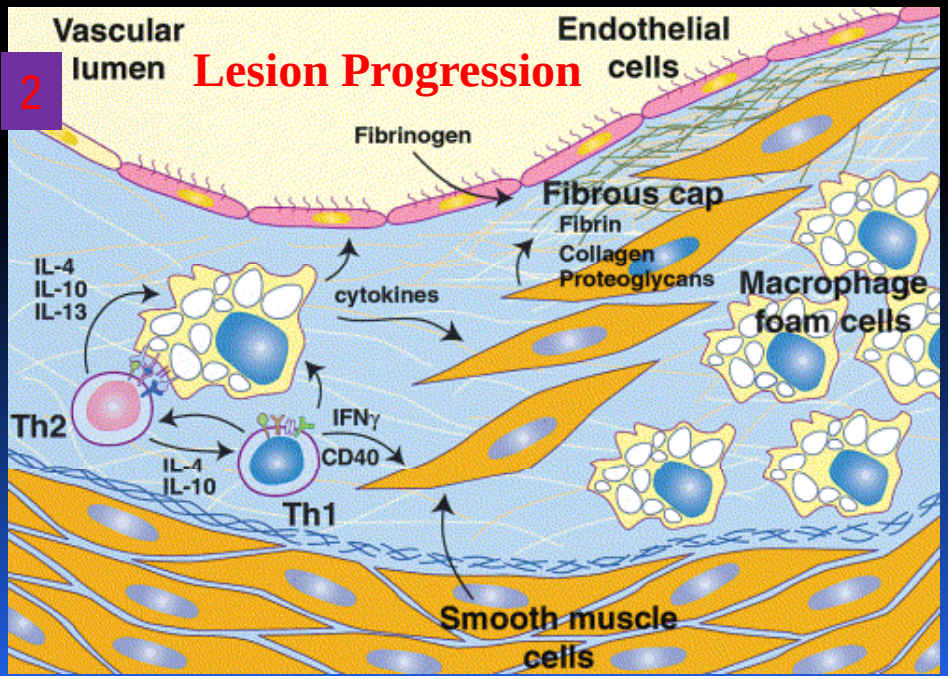
Anatomy of Arterial Vessel Membrane









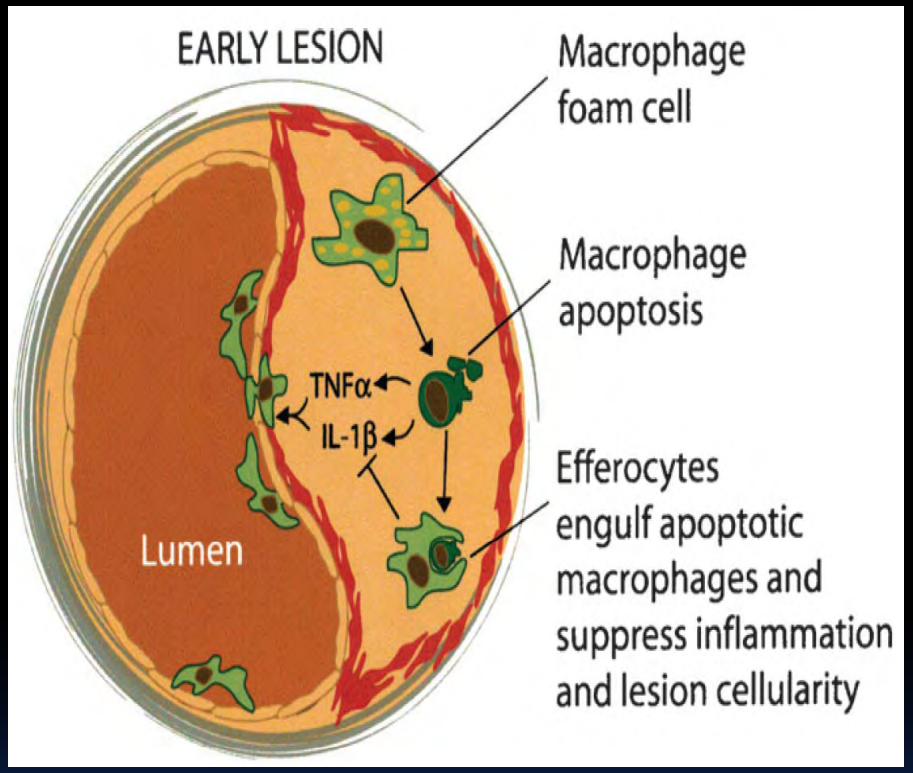


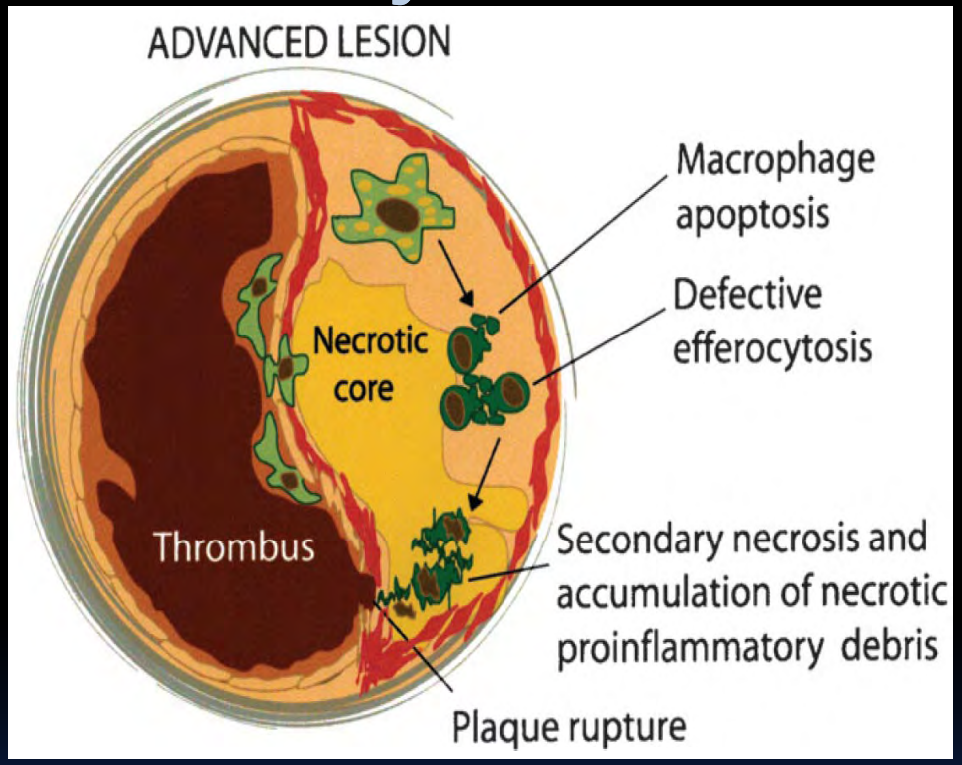
1-Minimally Modified LDL induces expression of cell adhesion molecules

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

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

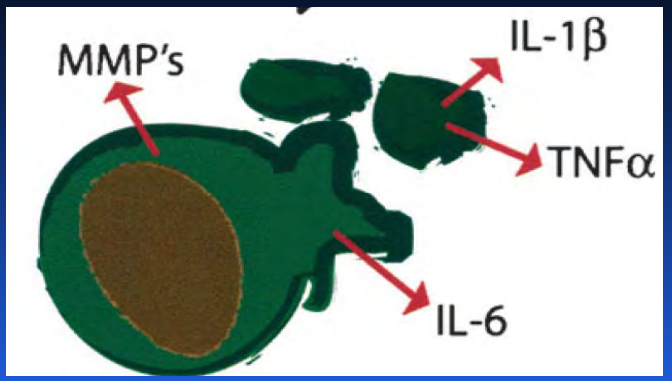
Macrophage Death as a Factor that Limits Lesion Cellularity



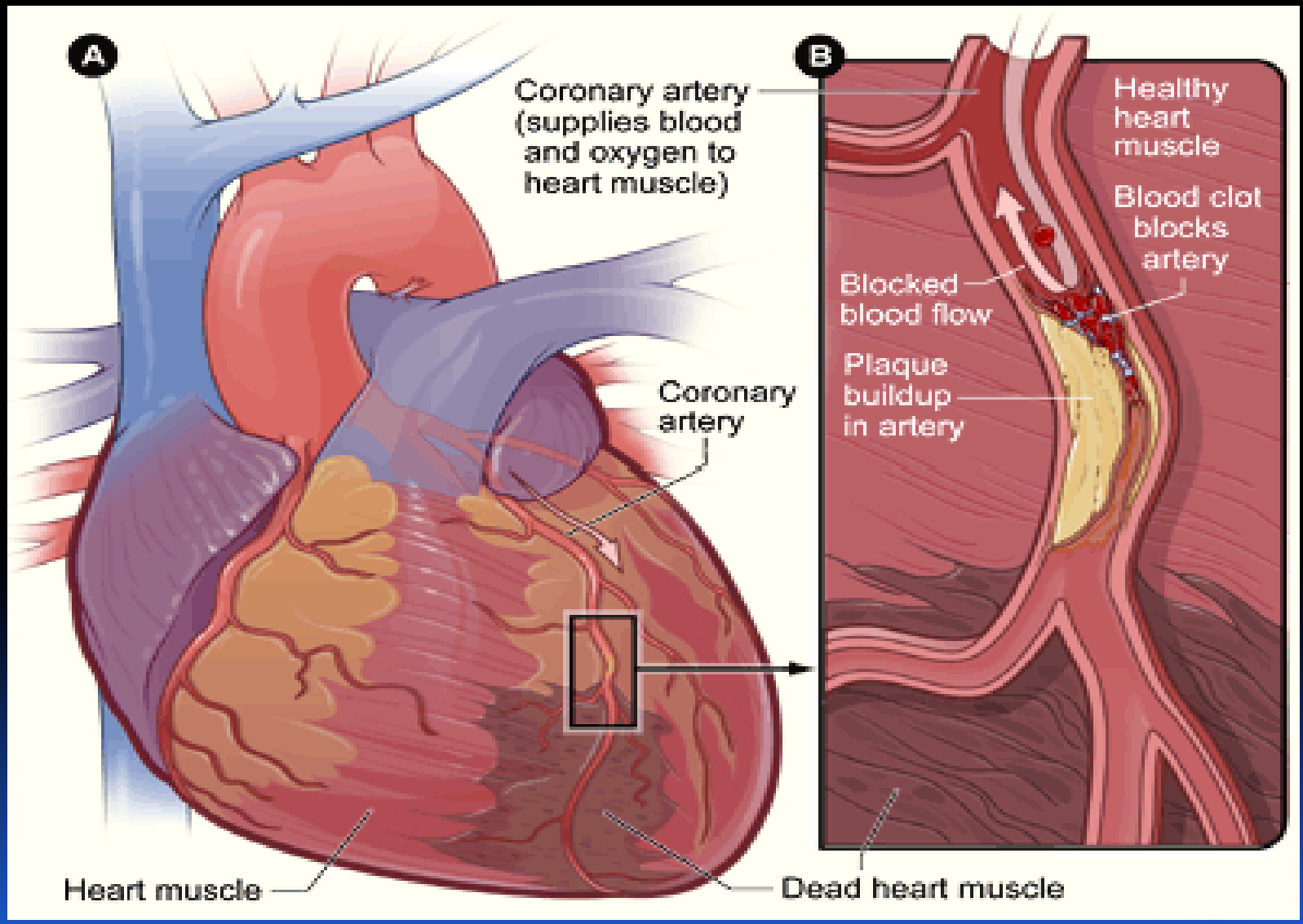


Apoptotic Inducers:

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



Coronary Atherosclerosis Causes MI



Summary of Biochemical Events Following Coronary Artery Occlusion

Coronary Artery Occlusion

↓

Myocardial Ischemia

↓

Anoxia/Energy Deficit

↓

Loss of Metabolic Control

↓

Reversible Damage

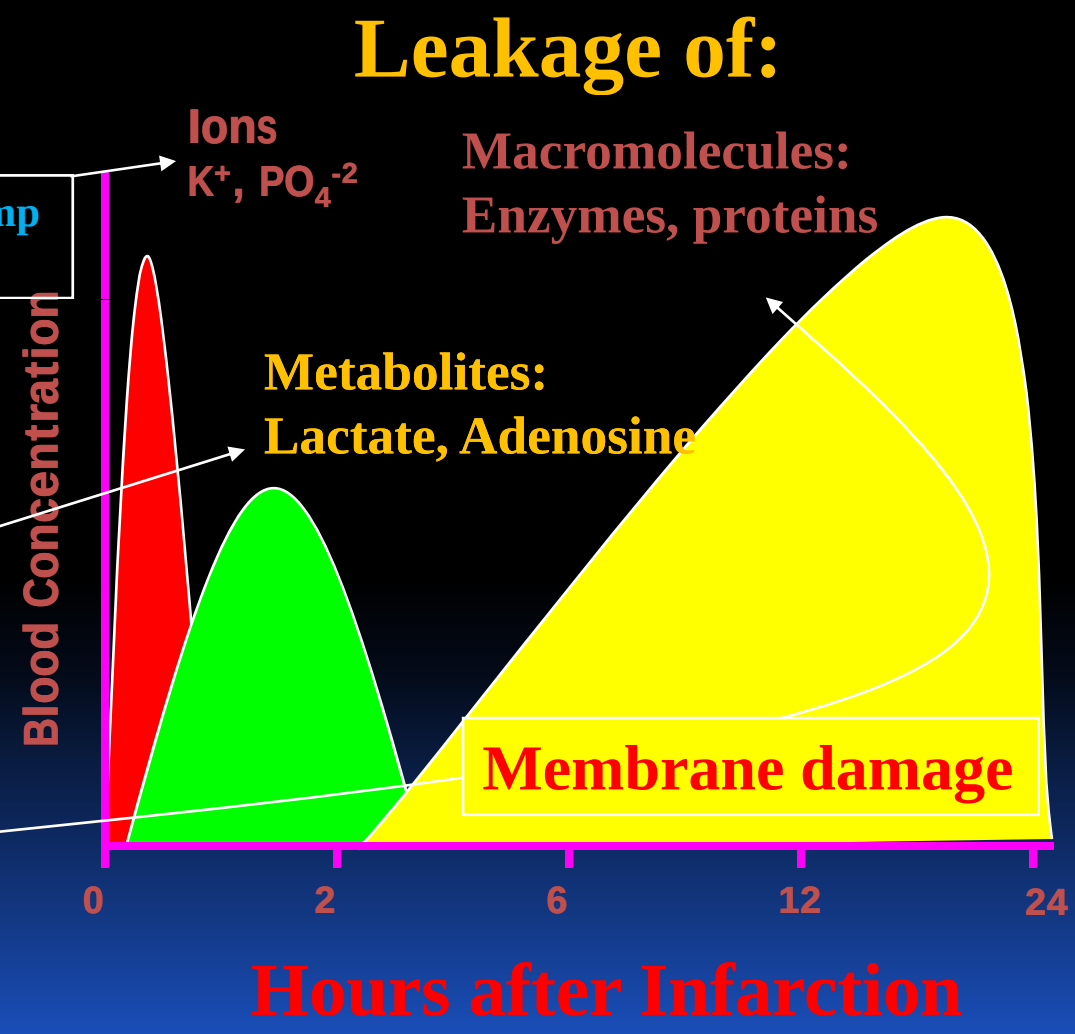
↓

Irreversible Damage

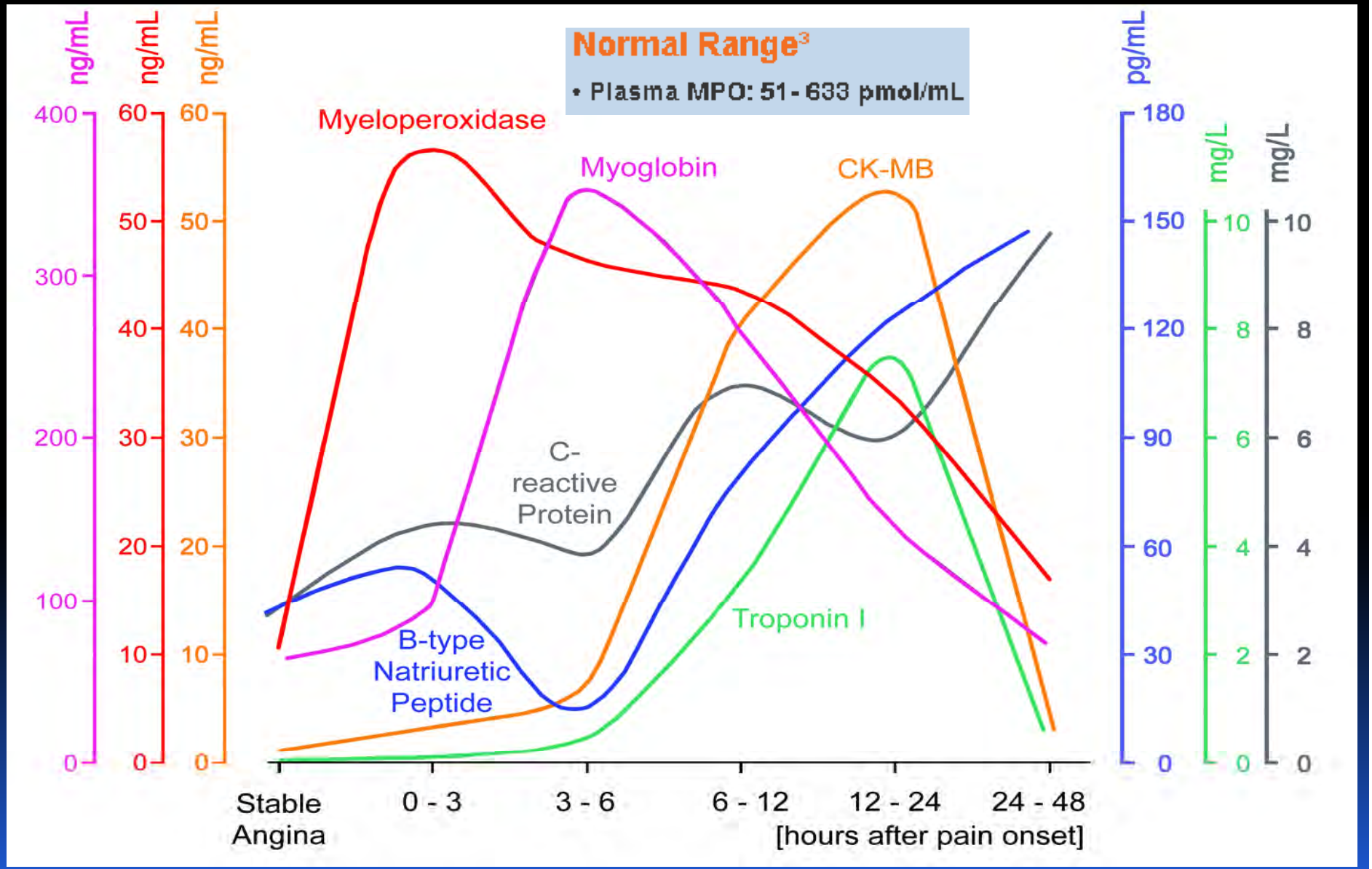
↓

Cell Death and Tissue Necrosis

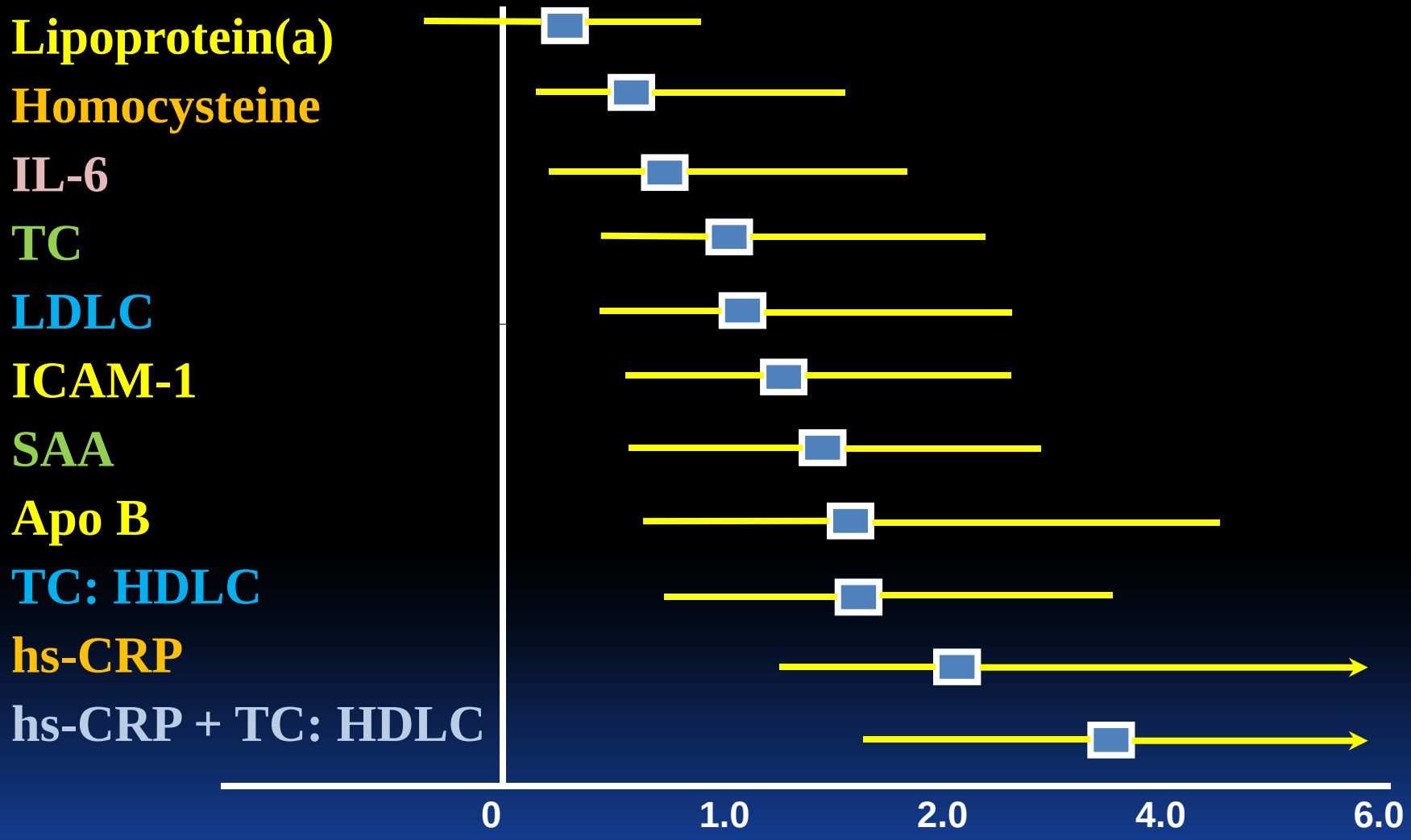
ATP Pump Failure



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



Relative Risk Factors for Future Outcomes



More Than a Biomarker: Dose CRP Plays Direct Role in Atherosclerosis?

CRP localizes in atherosclerotic but not normal intima

CRP induces Complement activation

CRP induces production of MCP-1, ET-1

CRP recruits monocyte into arterial wall

CRP attenuates NO production and decreases eNOS expression

CRP induces production of tissue factor in monocytes

CRP induces PAI-1 expression stabilizes PAI-1 mRNA

CRP blunts endothelial vasoreactivity

CRP triggers oxidation of LDL cholesterol

CRP mediates LDL uptake by macrophages

Biomarker Assessment of high Risk Patients may Include

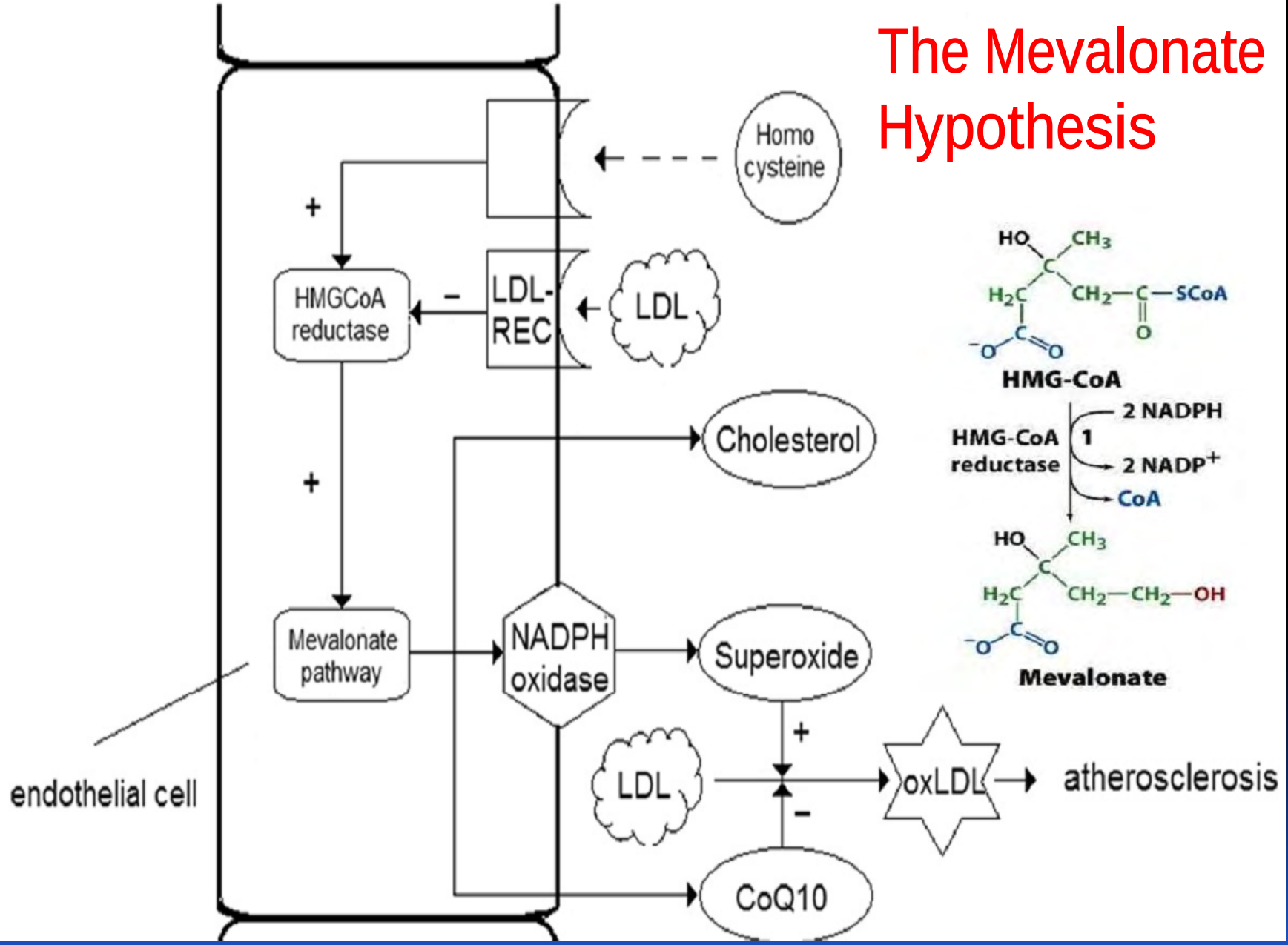
- Inflammatory cytokines (IL-6, IL-8)
- Cellular adhesion molecules (Integrins, Selectins, VCAM)
- Acute-phase Reactants (hs-CRP)
- Biomarkers of ischemia (Ischemia Induced Alb)
- Biomarkers of myocardial stretch (BNP)
- Biomarkers of myocardial necrosis (Troponin, CK-MB, Myoglobin)

Available Lipid Lowering Agents

Agent	HDL-C ↑	Primary Use
Nicotinic acid	15-35%	HDL ↑
Fibrates	5-20%	TG ↓
Statins	5-15%	LDL ↓
Prescription Om-3	*2-10%*	TG ↓
Bile-acid resins	*2-5%*	LDL ↓
Estrogens	*10-25%*	Hot flashes

CETP Inhibitors	Dose (Mg/day)	HDL-C (%)	LDL-C (%)	TG (%)
Torcetrapib	60	61	-24	-9
Anacetrapib	100	138	-40	-7

The Mevalonate Hypothesis



Thank You for Your Patience