تفريغ علم وظائف الأعضاء المرضي

اسم الموضوع:

Hyperlipidemia-3

إعداد الصيدلاني /ة:

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لجان الدُّفعات

* أغلب الـ deposited بكون Fatte

Atherosclerosis → تصلب الشرايين

- Definition: literally means "hardening of the arteries"; it is a generic term reflecting arterial wall thickening and loss of elasticity.

- There are three general patterns:

1. **Arteriolosclerosis,** affects small arteries and arterioles and may cause downstream ischemic injury. ← ضغط

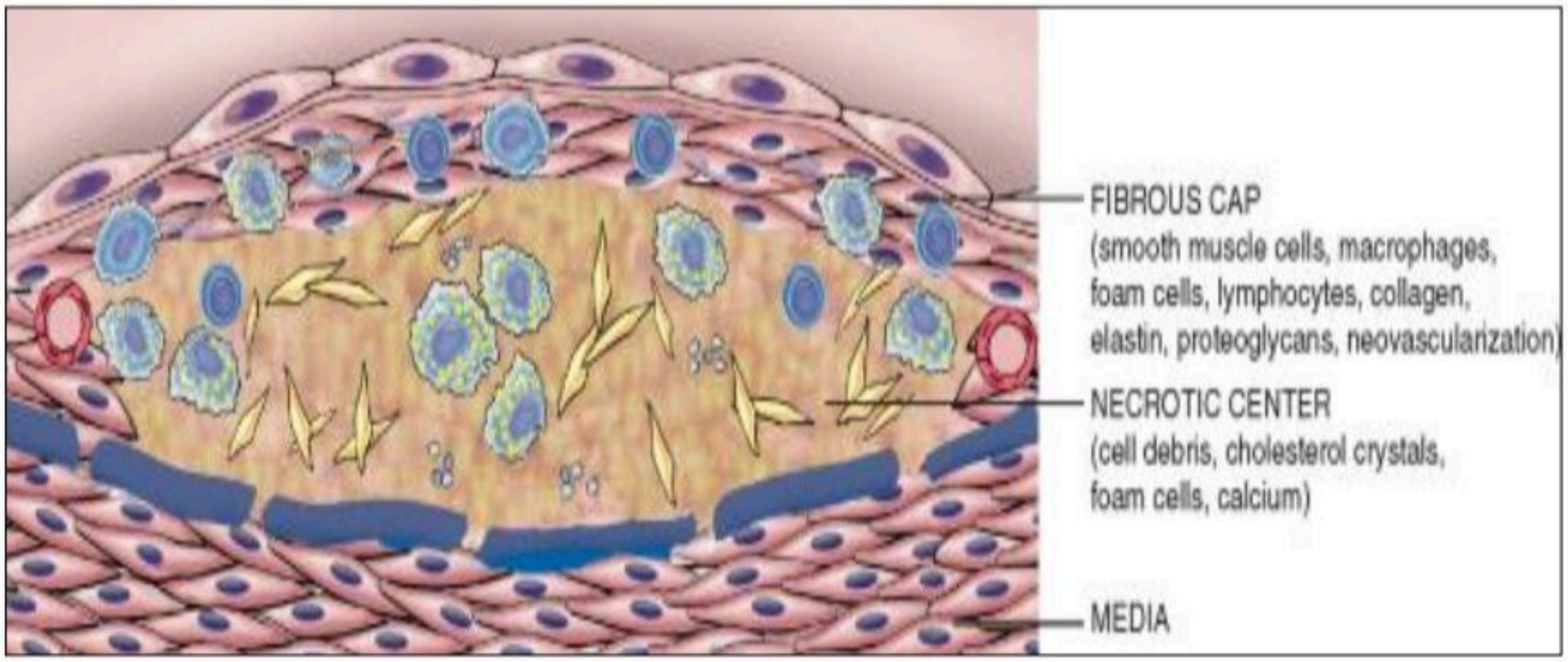
2. **Mönckeberg medial sclerosis**, is characterized by calcific deposits in muscular arteries in persons typically older than age 50. ← ترسبات كلسية

3. **Atherosclerosis,** from Greek root words for "gruel" and "hardening," is the most frequent and clinically important pattern. ← قاسية

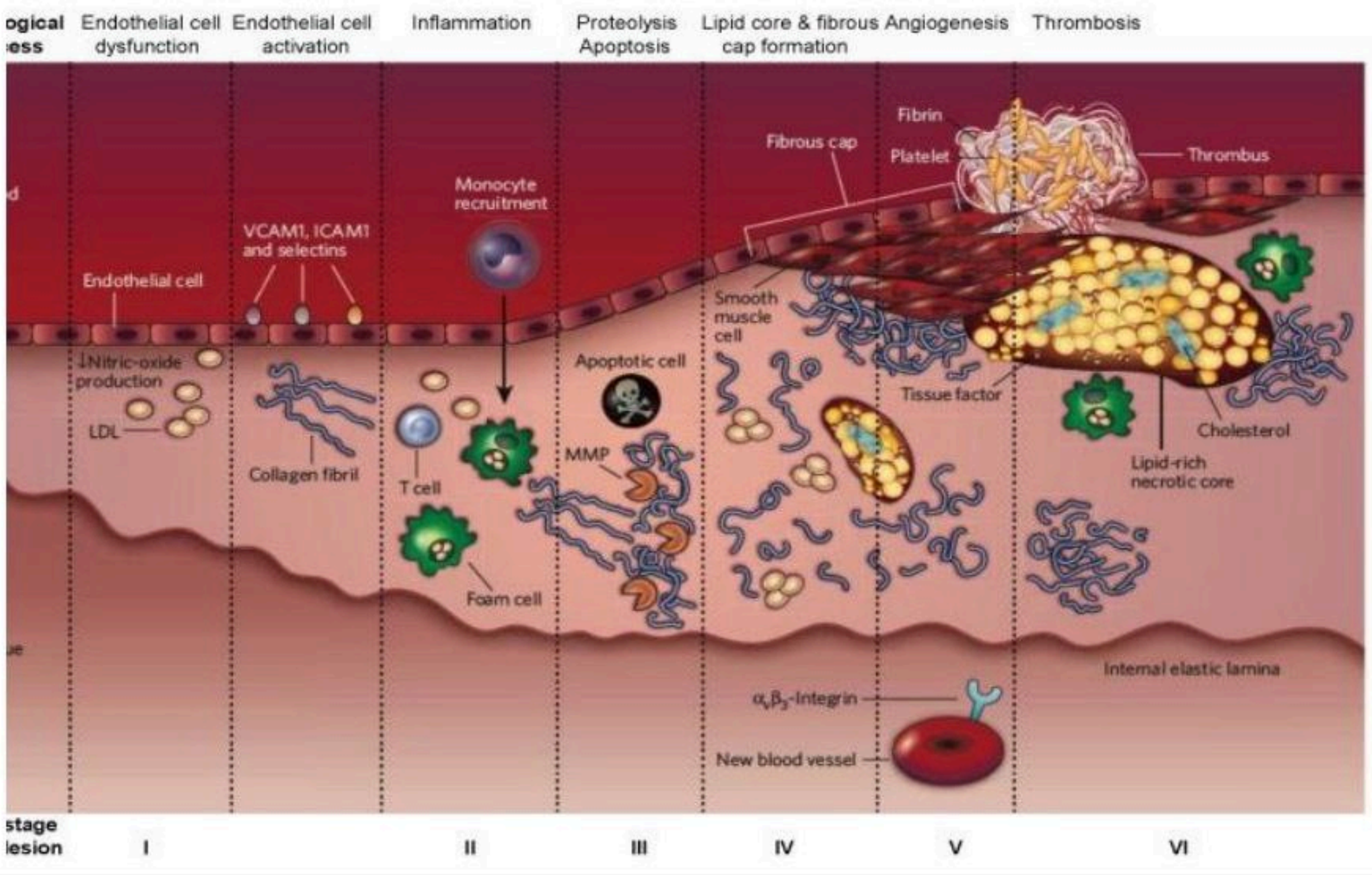
- **Atherosclerosis** is characterized by intimal lesions called *atheromas* (also called *atheromatous* or *atherosclerotic plaques*) that protrude into vessel lumens.

- An atheromatous plaque consists of a raised lesion with a soft, yellow, grumous core of lipid (mainly cholesterol and cholesterol esters) covered by a white fibrous cap.

- Atherosclerotic plaques can:
  - obstruct blood flow (عرقلة)
  - rupture leading to thrombosis
  - weaken the underlying media and thereby lead to aneurysm formation. (تمزق)



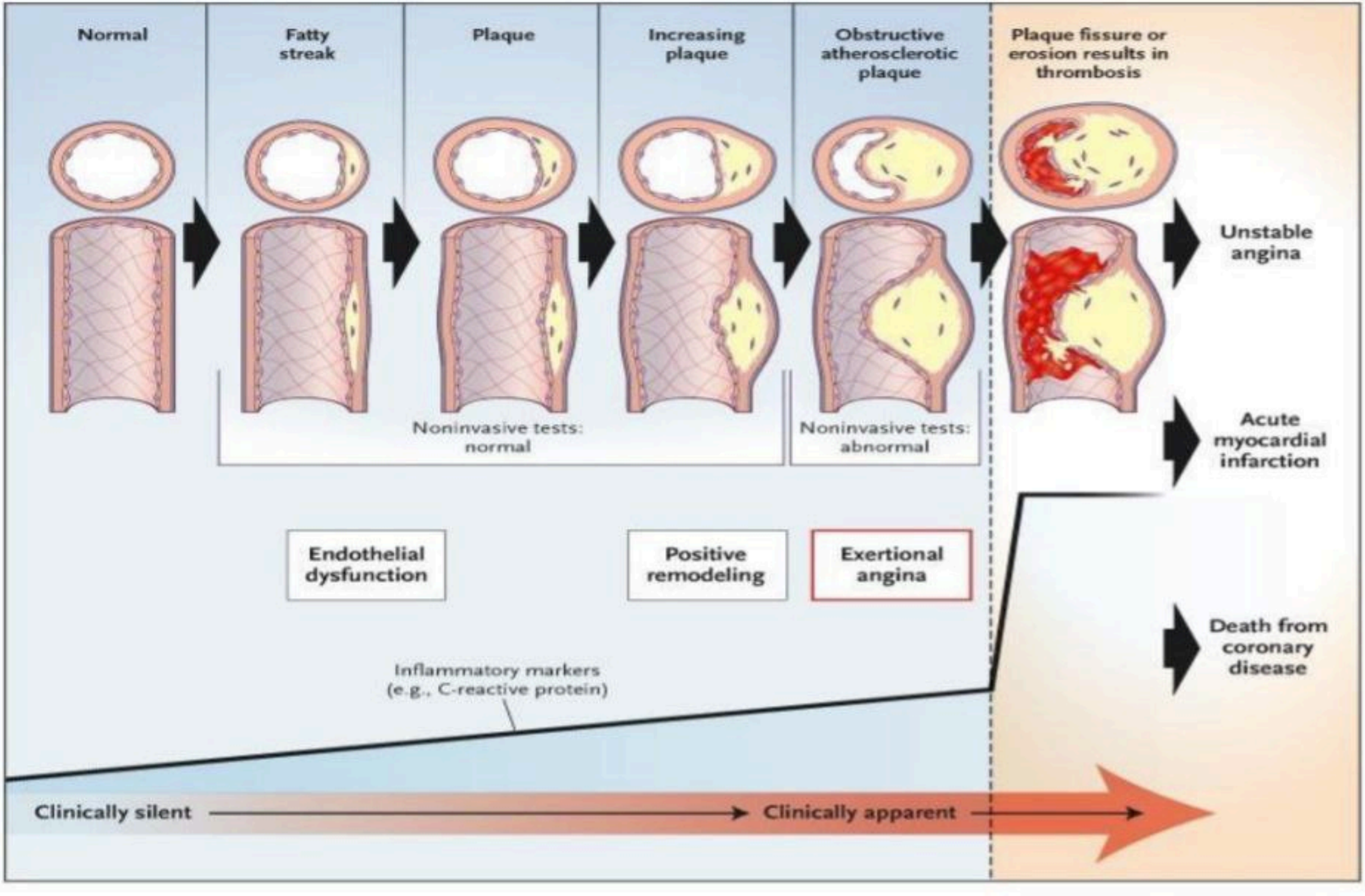
The major components of a well-developed intimal atheromatous plaque overlying an intact media.



Due to endothelial dysfunction,

- **LDL particles migrate** from the blood and accumulate in the arterial intima, forming pro-inflammatory particles.
- This results in the **activation of endothelial cells**, which secrete **adhesion molecules.**
- **Smooth muscle cells, which secrete chemokines and chemoattractants,** thereby recruiting monocytes to the arterial wall.
- Upon entry, **monocytes transform into macrophages**, which engulf the accumulated lipids to form **foam cells** which aggregate to form a lipid core.
- Plaque rupture occurs **when the fibrous cap becomes thin** and partially destroyed which leads to the **development of thrombus and ultimately coronary syndrome.**

collagen protein + smooth muscles


Normal
Fatty streak
Plaque
Increasing plaque
Obstructive atherosclerotic plaque
Plaque fissure or erosion results in thrombosis
Unstable angina
Acute myocardial infarction
Death from coronary disease
Noninvasive tests: normal
Noninvasive tests: abnormal
Endothelial dysfunction
Positive remodeling
Exertional angina
Inflammatory markers (e.g., C-reactive protein)
Clinically silent
Clinically apparent

- The prevalence and severity of atherosclerosis and IHD are related to two groups of risk factors:

I. Constitutional (non-modifiable) risk factors in IHD:

* ممكن نفس شي حكيهم بال Ischemic heart diseas

1 - Age
2 - Gender
3 - Genetics

II. Acquired (Modifiable) risk factors in IHD:

1 - Hyperlipidemia.
2 - Hypertension.
3 - Cigarette smoking.
4 - Diabetes Mellitus.

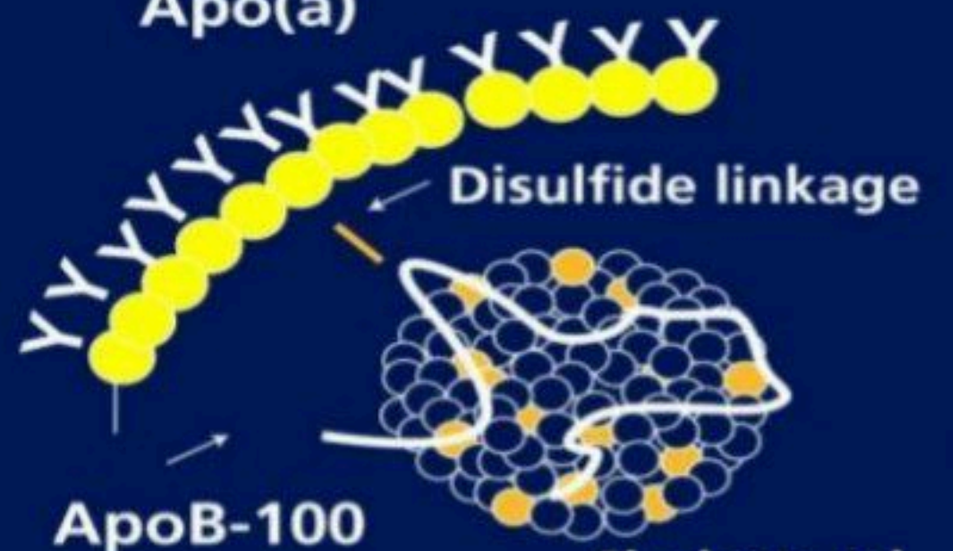
- **Additional risk factors:**

  - Inflammation
  - Hyperhomocystinemia → عبارة عن ارتفاع في بروتين اسمه الـ Homocystine
  - Metabolic syndrome
  - Lipoprotein (a) levels
  - Factors affecting homeostasis
  - Other factors

هدول بكون عندهم ارتفاع بالضغط
Hypertension
ارتفاع بالدهنيات
Hyperlipidemia
ارتفاع بال Sugar
diabetes
ويكونو
obese

بشتغل زي الLDL

Lp(a)



- genetically determined
- marked elevation after acute ischemic coronary syndromes
- structurally homologous to plasminogen
- competes with plasminogen binding sites on endothelial cell surfaces
- oxidized Lp(a) promotes atherosclerosis
- stimulates PAI-1 synthesis
- risk factor for CHD events in men (Lipid Research Clinic) and women (Framingham Heart Study)

Stein JH and Rosenson RS. *Arch Intern Med* 1997;157:1170.

Pathogenesis of Atherosclerosis

- Historically, there have been two dominant hypotheses to explain the progress of the disease:

  - *one emphasizes intimal cellular proliferation.*

  - *the other focuses on the repetitive formation and organization of thrombi.*

- Recently, the *response-to-injury hypothesis* which views *atherosclerosis as a chronic inflammatory and healing response of the arterial wall to endothelial injury was adopted.*

Atherosclerosis is produced by the following pathogenic events:

- **Endothelial injury**, which causes (among other things) increased vascular permeability, leukocyte adhesion, and thrombosis. → التخثر

- **Accumulation of lipoproteins** (mainly LDL and its oxidized forms) in the vessel wall.

- **Monocyte adhesion to the endothelium**, followed by migration into the intima and transformation into macrophages and foam cells.

- **Platelet adhesion.**

- **Factor release from activated platelets, macrophages, and vascular wall cells,** inducing smooth muscle cell recruitment, either from the media or from circulating precursors.

- **Smooth muscle cell proliferation** and ECM (extracellular matrix which contains lots of inflammatory mediators and growth factors) production.

- **Lipid accumulation** both extracellularly and within cells (macrophages and smooth muscle cells).

Atherosclerosis الى بعيد شرايين

Consequences of Atherosclerosis

- The aorta, carotid, and iliac arteries (large elastic arteries) and coronary and popliteal (medium-sized muscular arteries) are targets for atherosclerosis.

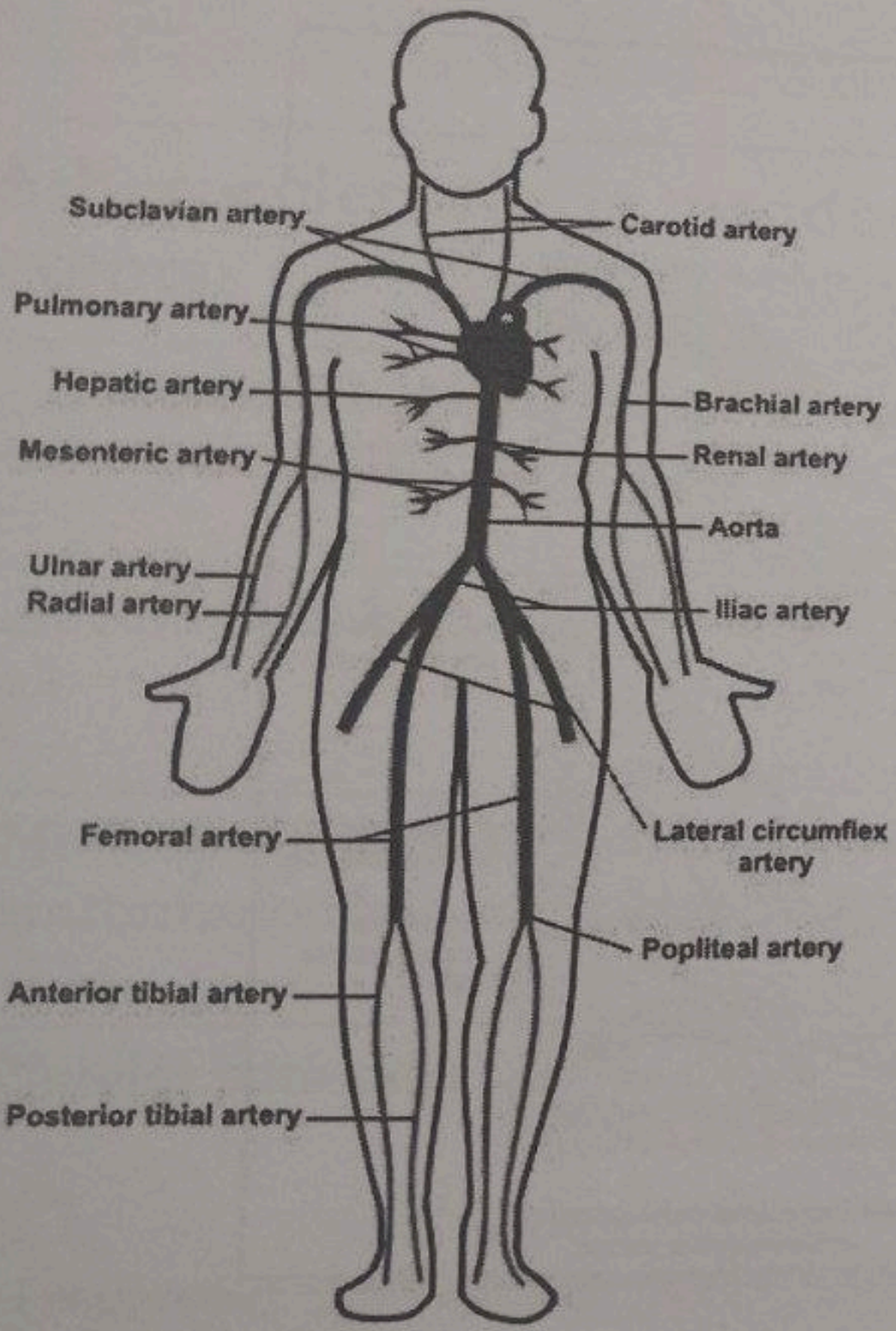
- Heart attack, stroke, aneurysm, and gangrene in the legs are potential consequences of the disease.

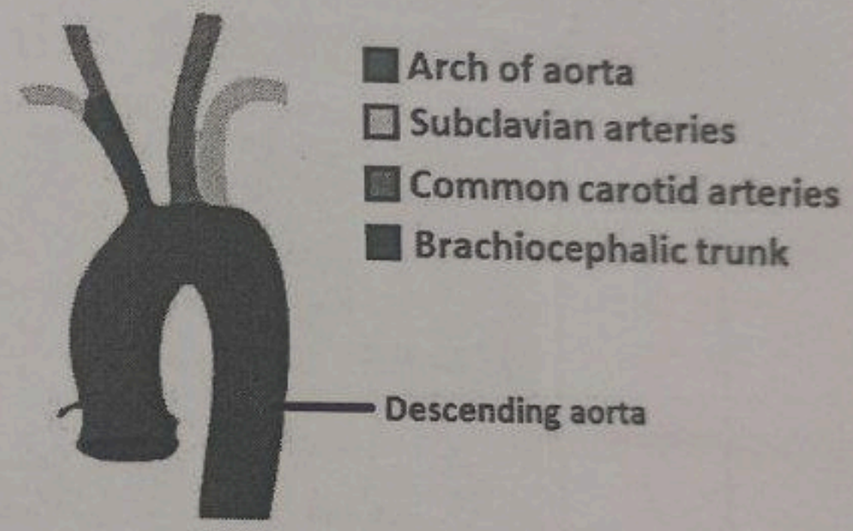
- The principal outcomes depend on:

1 - The size of the involved vessels.

2 - The relative stability of the plaque itself.

3 - The degree of degeneration of the underlying arterial wall.





- The aorta, carotid, and iliac arteries (large elastic arteries) and coronary and popliteal (medium-sized muscular arteries) are targets for atherosclerosis.

1. Atherosclerotic stenosis: → تضييق

- Compromised blood flow WILL lead to ischemic injury secondary to *critical* occlusion of a small vessel.

- Total circumference expansion due to outward remodeling of vessel media is an adaptive mechanism before an injury commences.

- At 70% fixed occlusion, clinical symptoms surface (Stable angina).

- The effects of vascular occlusion ultimately depend on arterial supply and the metabolic demand of the affected tissue.

2. Acute plaque change

- **Plaque rupture is promptly followed by partial or complete vascular thrombosis resulting in acute tissue infarction (e.g., myocardial or cerebral infarction).**

- **Plaque changes fall into three general categories:**

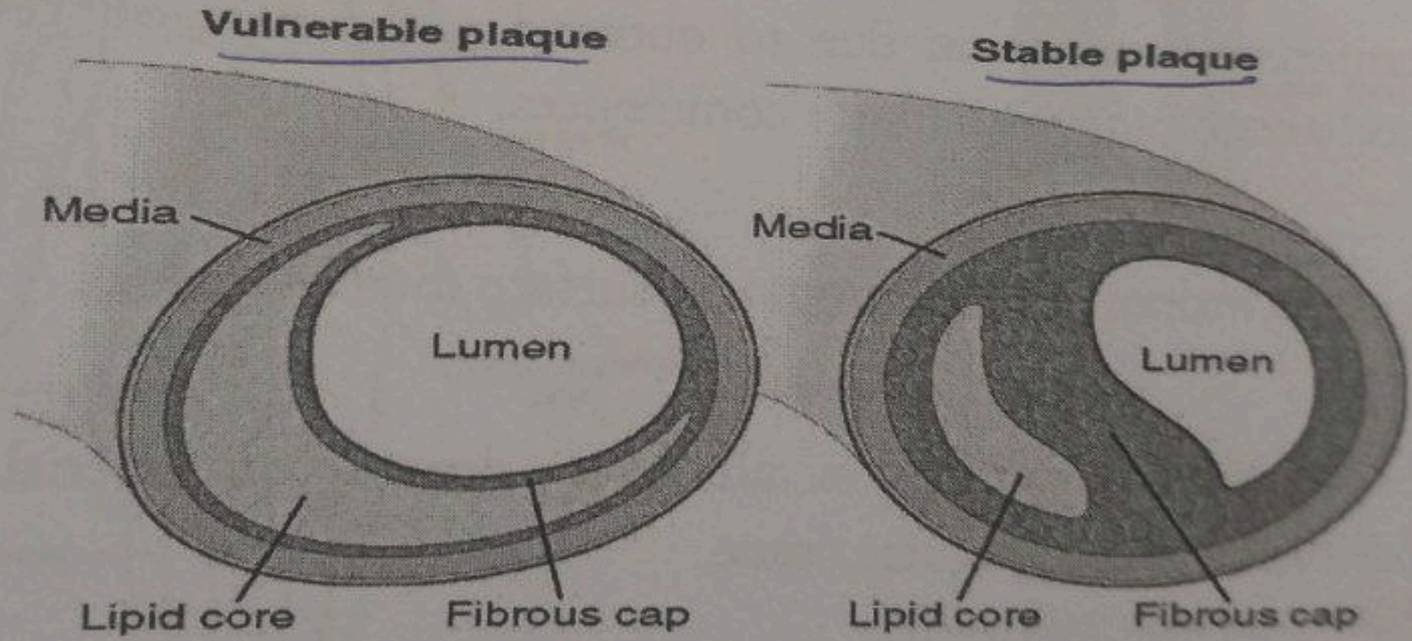
  - **Rupture/fissuring**, exposing highly thrombogenic plaque constituents

  - **Erosion/ulceration**, exposing the thrombogenic subendothelial basement membrane to blood

  - **Haemorrhage** into the atheroma, expanding its volume

إذا فقط تأثرت الطبقة الأدى
وهي endothelium layer

- The events that trigger abrupt changes in plaque configuration are complex and include:
  - Intrinsic factors (e.g., plaque structure and composition)
  - Extrinsic factors (e.g., blood pressure, platelet reactivity)



3. Thrombosis

- Thrombosis (partial/total) associated with a disrupted plaque is critical to the pathogenesis of the acute coronary syndromes.

- Thrombus superimposed on a disrupted partially stenotic plaque converts it to a total occlusion.

- In other coronary syndromes luminal obstruction by thrombosis is usually incomplete and will disappear with time.
- Mural thrombus in a coronary artery can also embolize.

4. Vasoconstriction

- **Vasoconstriction at sites of atheroma is stimulated by:**

(1) circulating adrenergic agonists

(2) locally released platelet contents

(3) impaired secretion of endothelial cell relaxing factors (nitric oxide) relative to contracting factors (endothelin) as a result of endothelial cell dysfunction

(4) mediators released from perivascular inflammatory cells.

Good luck for your exam..

And do the best.