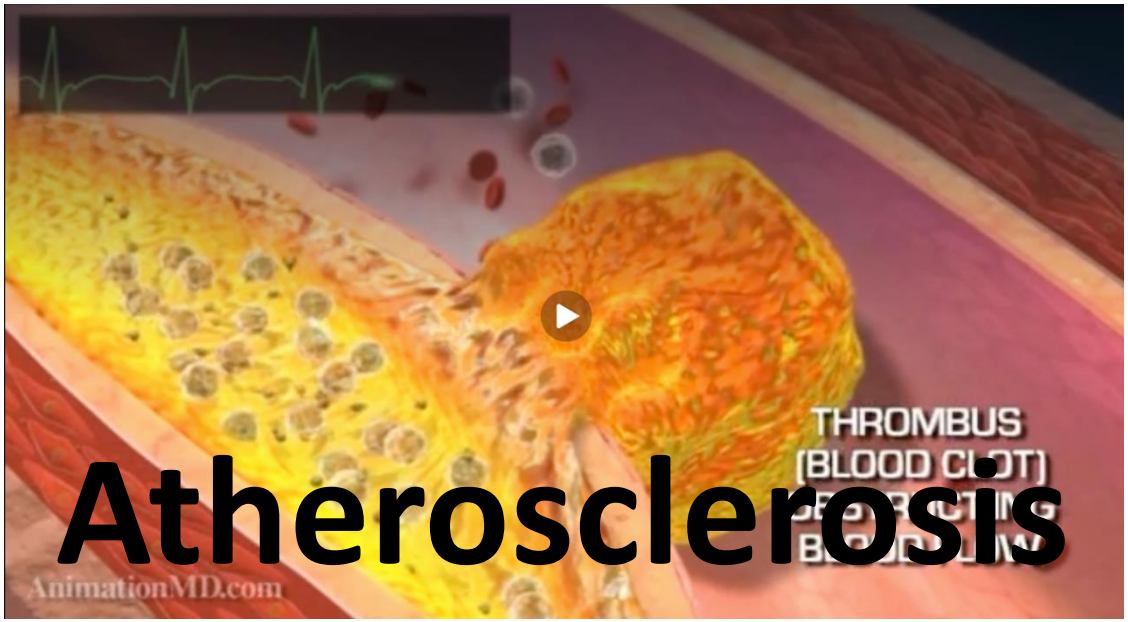


Atherosclerosis

Prof. MUDr. Mária Pallayová, PhD.

maria.pallayova@upjs.sk

19.02.2026

Causes of Death in Europe

1) Diseases of the circulatory system (cardiovascular diseases)

- **Most common cause of death** – about **32–33% of all deaths in the EU in 2022**.
  This includes **ischemic heart disease, myocardial infarction, stroke, hypertension**, and others.
- **Ischemic heart disease and cerebrovascular diseases (stroke)** account for **more than half of the deaths** within this group.

---

2) Neoplastic diseases (cancer)

- **Second most common group of causes** – about **22% of deaths** in the EU.
- Among the most significant are **lung, colorectal, breast, and prostate cancers**.

---

3) Diseases of the respiratory system

- **Third most common category** – approximately **7% of deaths**.
- Includes **chronic obstructive pulmonary disease (COPD)**, **pneumonia**, **bronchitis**, and other chronic respiratory diseases.

Introduction

- **Atherosclerosis (ATS)** has been a medical problem only since the **19th century**:
  - previously **short average life expectancy** due to other diseases
  - **absence of biochemistry** (limited understanding of metabolic mechanisms)
- **Rokitansky (Vienna, 1852)** – incrustation (**thrombogenic**) theory
- **Virchow (Berlin, 1855)** – infiltration (**lipid**) theory
- **Framingham Study (1948)**
- **Since 2000** → more than **25 theories** and numerous **epidemiological studies**

Atherosclerosis – Definition

- **ATS = a chronic inflammatory disease of the intima of large and medium-sized arteries** with **retention of apoB-containing lipoproteins**, **remodeling of the vessel wall**, and **risk of thrombosis**.
- In the intima, an **atheromatous plaque** develops – a structure composed of **lipids**, **cells of the immune system**, **smooth muscle cells**, and **extracellular matrix**.
- **Lipid accumulation + inflammation + healing → scar formation (fibrous cap).**
- It is **not high LDL in the blood**, but its **retention in the intima** that triggers the process.
- **Emphasis:**
- **apoB = number of particles**
- **LDL-C ≠ number of particles**

Introduction

Why atherosclerosis matters

- Leading substrate for MI, ischemic stroke, PAD
- Often silent until thrombosis/critical stenosis

Definition

- Chronic, lipid-driven inflammatory disease of **large/medium arteries**
- Lesion is in the **intima**; evolves over decades

Core concept

- **Necessary condition:** sustained exposure of the arterial wall to **apoB lipoproteins** (LDL, remnants, Lp(a))
- **Amplifiers:** inflammation, disturbed flow, metabolic and toxic insults (smoking, diabetes, HTN)

Atherosclerosis

- **Atherosclerosis** is the underlying cause of most clinical forms of **ASCVD** (coronary, cerebral, and peripheral arterial beds).
- It is **not a passive "fat deposition"**, but a process initiated by **retention of atherogenic lipoproteins** followed by an **inflammatory response of the vessel wall**.
- **"Stenosis" is not the only problem** – **plaque instability and thrombogenicity** are decisive.
- **Complications of atherosclerosis** – **thrombosis after plaque rupture or erosion** – lead to **acute ischemic events** (myocardial infarction, stroke).

Atherosclerosis

- **Trigger:** retention of **apoB-containing lipoproteins** + **endothelial dysfunction**
- **Clinical turning point: thrombosis** due to **plaque rupture or erosion**
- The **core concept** is **retention of LDL/apoB in the intima** followed by a **chronic immune response**
- **Atherosclerosis:** plaque (**lipids + cells + matrix**) in the **intima**
- **Arteriosclerosis:** "hardening" of arteries (**broader term**)
- **ASCVD:** clinical consequences of atherosclerosis (**myocardial infarction, stroke, peripheral artery disease**)
- **Difference between a structural lesion** (plaque) **and a functional consequence** (ischemic events)

Why is apoB important in the pathophysiology of atherosclerosis?

- Atherosclerosis is initiated mainly by **retention of apoB-containing lipoproteins in the intima** (they bind to proteoglycans), followed by **modification** and an **inflammatory response of the vessel wall**. **More apoB = more particles**, which increases the chance of retention.

ApoB vs. LDL cholesterol (LDL-C) – the difference

- **LDL-C:** how much cholesterol is "loaded" inside LDL particles.
- **ApoB:** how many atherogenic particles are circulating in the blood. *In some conditions (e.g.* ***insulin resistance, hypertriglyceridemia****),* ***apoB may be relatively high despite normal LDL-C****, because there are many* ***small, cholesterol-poor particles****.*

Atherosclerosis

- Atherosclerosis begins with **endothelial dysfunction** and in **hemodynamically predisposed sites**, where **apoB-containing lipoproteins** penetrate into the **intima** and are **retained on proteoglycans**.
- Retention leads to **LDL modification** and **endothelial activation**, which **recruits monocytes**.
- **Monocytes differentiate into macrophages**, internalize lipids, and form **foam cells**, which produce cytokines and **sustain inflammation**.
- When **efferocytosis fails**, a **necrotic core** forms, and **smooth muscle cells** create a **fibrous cap**.
- **Plaque stability** depends mainly on the **quality of the fibrous cap** and the **intensity of inflammation**.
  If the cap **ruptures**, there is exposure of the **thrombogenic core** and **thrombosis**; alternatively, **erosion** may occur, where the primary problem is **loss of endothelium** and **thrombosis on the plaque surface**.
  These mechanisms are responsible for **acute ischemic events**.

Atherosclerosis – Summary

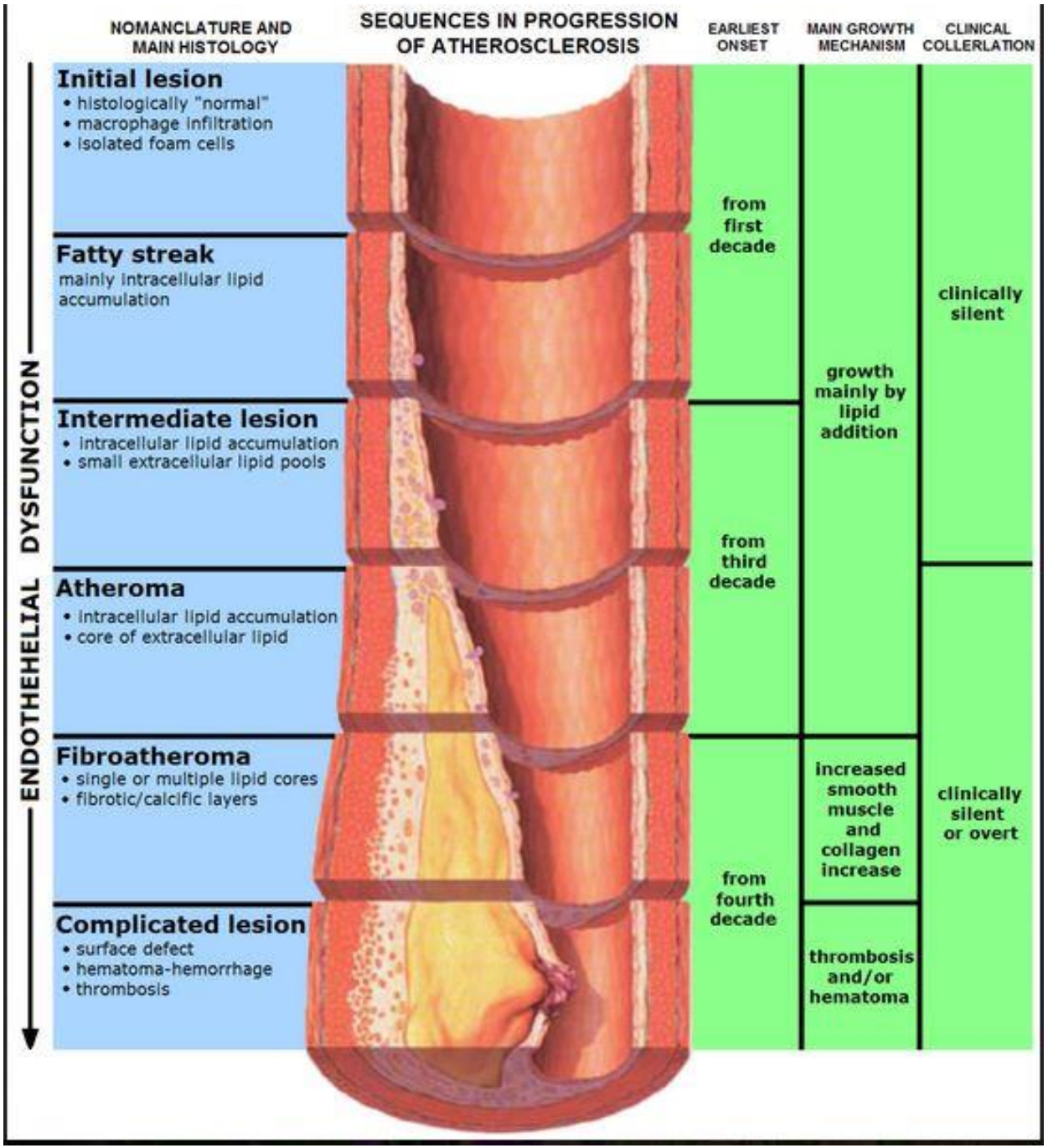
- Atherosclerosis begins in the **intima** and preferentially affects sites with **disturbed shear stress**.
- **Initiation = retention of apoB-containing lipoproteins** in the intima.
- **Inflammation** is a response to locally accumulated and modified lipids.
- **Smooth muscle cells (SMCs)** and the **extracellular matrix (ECM)** form the **fibrous cap** (stability = integrity of the cap).
- A **necrotic core** forms when clearance ("cleanup") of dead cells fails.
- **Complication = thrombosis** (due to **rupture or erosion**).
- A **clinical event is not only a function of stenosis**.
- **LDL-C is a causal driver**: fewer **apoB particles → less retention**.
- **Inflammation is a risk modulator**; there is also **residual inflammatory risk**.
- **Prevention and treatment** target **lipids, blood pressure, glycemia, smoking, and lifestyle**.

Current scientific concepts

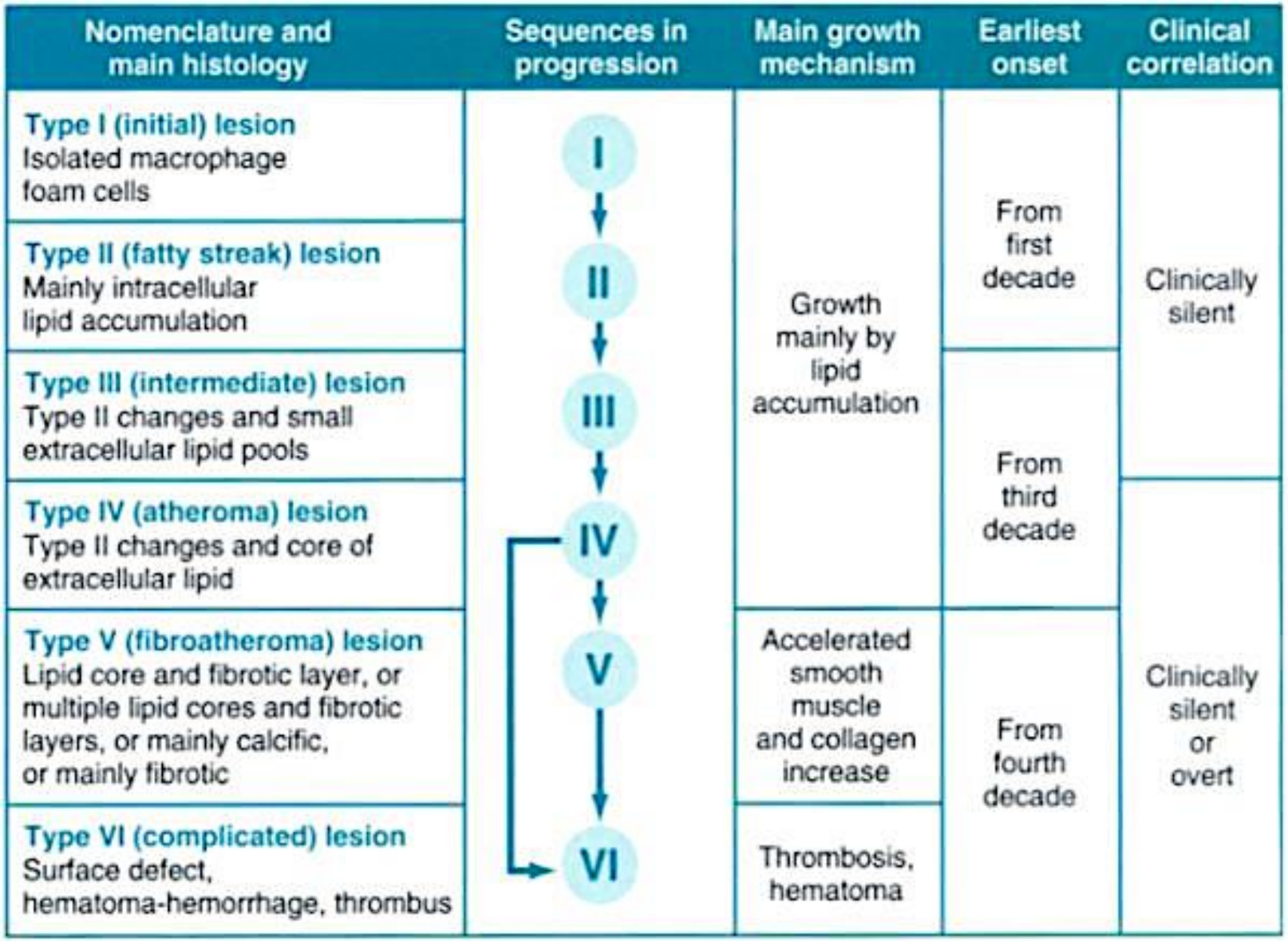
- **Atherosclerosis is a form of chronic inflammation** involving:
  - unfavorably modified lipoproteins
  - macrophages
  - T lymphocytes
  - vascular endothelial cells
  - and possibly other cellular elements
- **Outcome of the inflammatory process:**
- formation of **complex lesions → plaques**
- The **atherosclerotic plaque** is located within the **vessel wall** and usually **protrudes into the lumen**.
- The plaque forms a **soft (atheromatous) core** containing **hydroxyapatite**, especially in later stages (**sclerosis**).

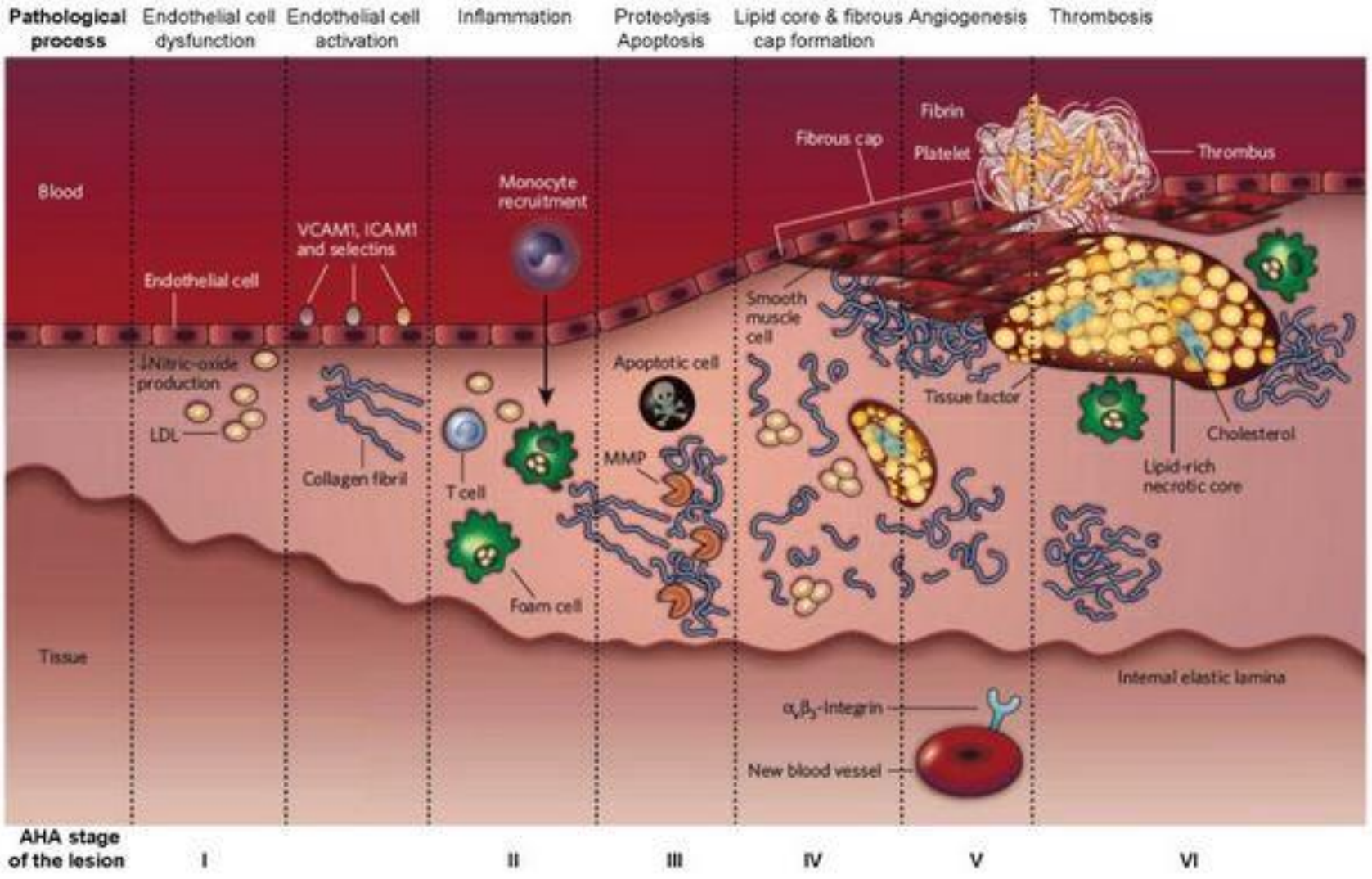
Stages of atherosclerotic plaque development

- **Type I – isolated foam cells**
  – macrophages containing lipid particles in the intima
- **Type II – fatty streaks**
  – bands/stripes of foam cells
- **Type III**
  – increased volume of lipids beneath the layer of foam cells
- **Type IV – atheroma**
  – lipid core, fibrous cap
- **Type V**
  – more collagen and smooth muscle cells in the fibrous cap
- **Type VI**
  – complicated atheroma – thrombosis


NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt

Atherosclerosis




Pathological process
Endothelial cell dysfunction
Endothelial cell activation
Inflammation
Proteolysis Apoptosis
Lipid core & fibrous cap formation
Angiogenesis
Thrombosis
Blood
Endothelial cell
VCAM1, ICAM1 and selectins
Monocyte recruitment
Fibrous cap
Fibrin
Platelet
Thrombus
Smooth muscle cell
↓Nitric-oxide production
LDL
Collagen fibril
T cell
Foam cell
Apoptotic cell
MMP
Tissue factor
Cholesterol
Lipid-rich necrotic core
Tissue
Internal elastic lamina
$\alpha_v\beta_3$-Integrin
New blood vessel
AHA stage of the lesion
I
II
III
IV
V
VI

Atherosclerosis – risk factors

- **Non-modifiable**
  - age
  - male sex
    - in women, the advantage is lost after menopause
  - positive family history
- **Biochemical markers – classic**
  - elevated total cholesterol > 5.0 mmol/L
  - elevated LDL cholesterol > 3.0 mmol/L
  - reduced HDL cholesterol < 1.0 mmol/L
  - elevated triacylglycerols > 2.0 mmol/L

Atherosclerosis – risk factors

- **Biochemical markers – newer**
  - predominance of dense LDL particles
  - high ApoB concentration
  - increased C-reactive protein concentration
    - influences the stability (lability) of the atherosclerotic plaque
  - increased ferritin concentration
    - associated with oxidative damage
  - increased fibrinogen concentration
    - increased clot formation
  - increased homocysteine concentration
    - a probable marker of oxidative damage

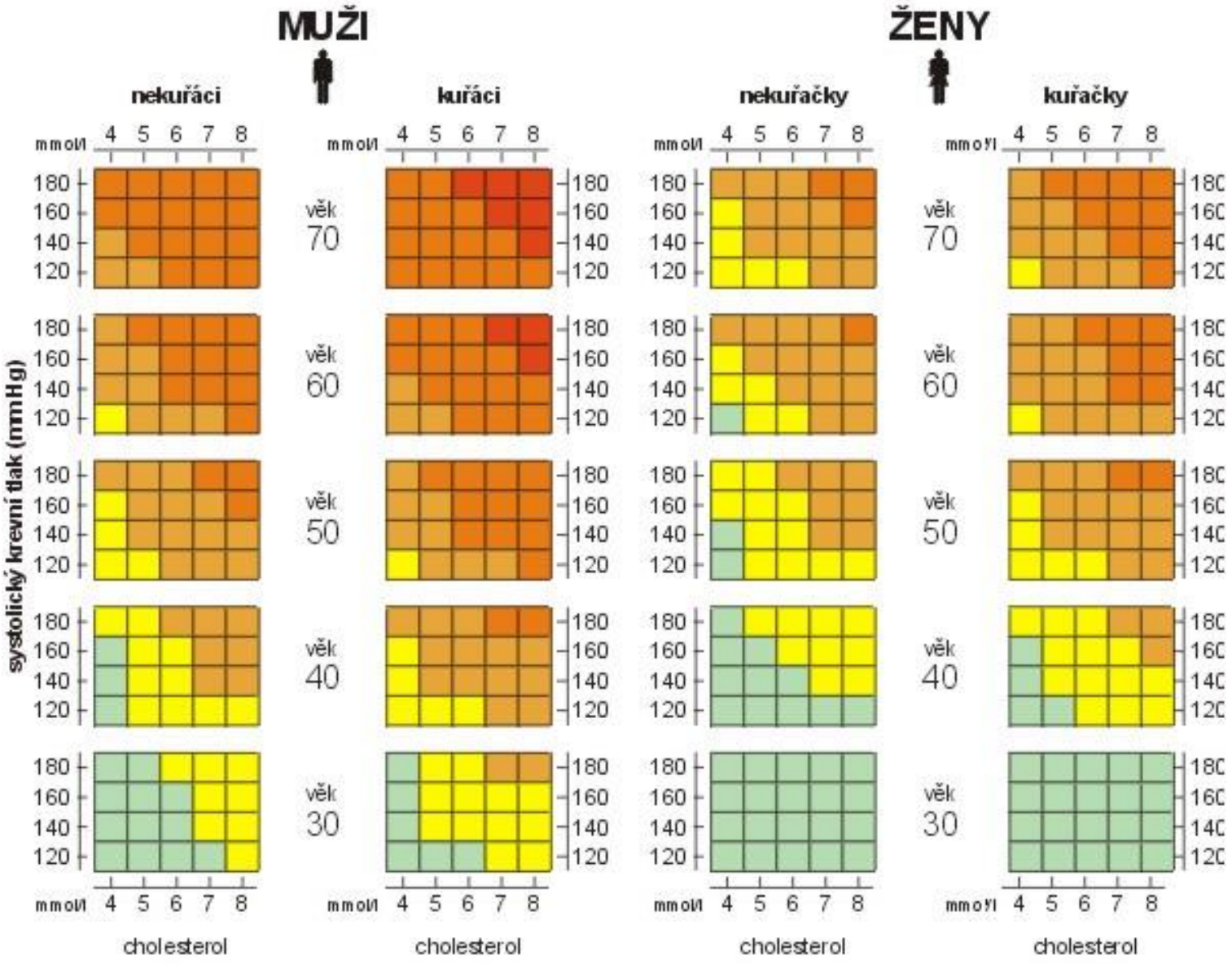
Atherosclerosis – risk factors

- **Diseases**
  - hypertension
  - insulin resistance and diabetes mellitus
  - obesity
  - renal insufficiency
- **Lifestyle**
  - smoking
  - sedentary occupation
- **Nutritional factors**
  - deficiency of exogenous antioxidants
    - vitamins C and E, bioflavonoids
  - magnesium deficiency
  - selenium deficiency
  - excessive alcohol consumption

Atherosclerosis – risk factors

- **Genetic risk factors**
  - presence of the ApoE ε4 allele
  - defective LDL receptor or a mutation in the apolipoprotein B gene

Atherosclerosis – risk factors



Atherosclerosis

- The more risk factors, the earlier the manifestation.
- The disease is progressive and multifocal.
  - The extent of damage differs in individual parts of the vascular bed.
- **Atherosclerosis most commonly affects:**
- coronary arteries
- carotid arteries
- peripheral arteries of the lower limbs
- also the aorta, renal and mesenteric arteries
- **Clinical manifestations include:**
- in coronary arteries: **myocardial infarction**
- in carotid and cerebral arteries: **ischemic attack (TIA)** or **sudden cerebrovascular accident (stroke)**

Atherosclerosis

- A significant indicator of atherosclerotic involvement of the population is **ischemic heart disease**.
- **Harmful factors with an important genetic component:**
- increased LDL and VLDL levels, low HDL levels, increased lipoprotein(a)
- hypertension
- diabetes mellitus
- male sex
- increased homocysteine levels
- increased levels of hemocoagulation factors (fibrinogen)
- metabolic syndrome, obesity
- family predisposition
- systemic inflammation

Atherosclerosis

Environmental factors:

- **smoking**
- **lack of physical exercise**
- **high-fat diet**
- **certain infectious agents**
- **psychological stress**

The arterial wall and "places where plaque forms"

- Intima – site of lipoprotein retention
- proatherogenic flow/low shear stress (bifurcations) → endothelial activation
- “Predilection” sites: coronary, carotid, aortic, femoral
- Hemodynamics explains why the same level of LDL leads to plaques mainly in certain segments.

Endothelium as an organ

- Vasodilation (NO), antithrombotic and anti-inflammatory properties
- Endothelial dysfunction: ↓NO, ↑permeability, ↑adhesion molecules
- Endothelial dysfunction is a “gateway” for atherogenesis: more LDL in the intima and easier adhesion of leukocytes.

“Response-to-retention”: lesion initiation

- ApoB-lipoproteins (LDL and remnants) penetrate the intima
- Retention on proteoglycans → longer residence → LDL modifications
- Triggering the inflammatory response
- Key: it is not just “high LDL in the blood”, but its retention and subsequent biological response of the vessel wall.

LDL Modifications and Why They Are Important

- Oxidation/enzymatic modifications → “neoantigens”
- Activation of endothelial cells and macrophages
- Establishment of a pro-inflammatory microenvironment
- Meaning: modified LDL acts as a danger signal and alters the immune response.

Leukocyte recruitment

- VCAM-1/ICAM-1, selectins → rolling and adhesion
- Chemotaxis (e.g. MCP-1/CCL2)
- Monocytes → macrophages
- This is the “tipping point”: from purely metabolic risk to chronic inflammation in the intima

Foam cells

- Macrophages internalize modified LDL (scavenger receptors)
- Foam cells = basis of “fatty streak”
- Cytokines, ROS, proteases → progression
- Fatty streak can be subclinical for a long time, but creates conditions for advanced plaque.

The role of VSMC (vascular smooth muscle cells)

- Migration into the intima, proliferation
- Synthesis of extracellular matrix (collagen) → fibrous cap
- Phenotypic switch (contractile → synthetic/proinflammatory)
- Modern view: VSMC are an active immunometabolic player, not just a “building cell”.

VSMC as a source of foam cells

- Foam cells do not arise only from macrophages
- A significant proportion of foam cells may originate from VSMC
- Implications: cap stability, plaque composition
- Evidence shift: a cell we consider to be “stabilizing” may contribute to plaque lipid loading and dysfunction under certain conditions.

Necrotic core: why does it arise?

- Apoptosis/necroptosis of cells in the plaque
- Failure of efferocytosis (removal of apoptotic cells)
- Lipid core + tissue factor → thrombogenicity
- The necrotic core is the core of a vulnerable plaque: high thrombogenic potential when exposed to blood.

Fibrous cap: stability vs. risk

- Collagen (VSMC production) vs. degradation (MMP)
- Thinner cover + large necrotic core = “vulnerability”
- Inflammation (macrophages) → cover weakening
- Stability is more about “cover biology” than “stenosis size”.

Calcification: micro vs. macro

- Micro-calcifications in the sheath may increase local tension
- Macrocalcification may be a sign of a “mature” lesion
- Clinically: CT calcium score as a marker of total plaque burden
- Calcification is part of remodeling and inflammation.

Neovascularization and intraplate hemorrhage

- Vasa vasorum → fragile neocoils
- Bleeding into plaque → core growth, more inflammation
- Progression and destabilization
- This mechanism explains the rapid “jumps” in plaque progression.

Innate immunity and the inflammasome

- Cholesterol crystals and DAMPs
- Activation of NLRP3 inflammasome → IL-1β/IL-18
- Linking metabolism and inflammation
- Important for understanding "inflammation as a target"

Adaptive immunity:

- T-lymphocytes (Th1) – pro-inflammatory profile
- B-lymphocytes and antibodies (heterogeneous effects)
- Autoantigens: modified lipoproteins
- Just the basics: plaque is an immunologically active tissue.

"Stable" vs. "unstable" plate

- Stable: thicker cover, more fibrosis, smaller core
- Unstable: thin cover, large necrotic core, intense inflammation
- Clinical: stable angina vs. acute coronary syndrome
- Clinical events often arise not at the largest stenosis, but at the biologically vulnerable plaque.

Plate rupture: mechanism

- Rupture of the sheath → contact of blood with necrotic core
- Thrombosis (within minutes) → occlusion/embolization
- Typically high inflammatory signal
- Rupture is a classic mechanism of MI and some stroke; the link to “instability/rupture” is key.

Plaque erosion: mechanism (different phenotype)

- Without rupture of the sheath
- Loss of endothelial layer → thrombus on “eroded” surface
- Often matrix/VSMC-rich, less lipid core
- Erosion is the second major mechanism of ACS and has a different biology than rupture.

Why does a thrombus form?

- Platelet activation (adhesion, aggregation)
- Coagulation cascade (tissue factor)
- Fibrin stabilization
- Link “platelet” to “acute event”

Risk factors as biological pathways:

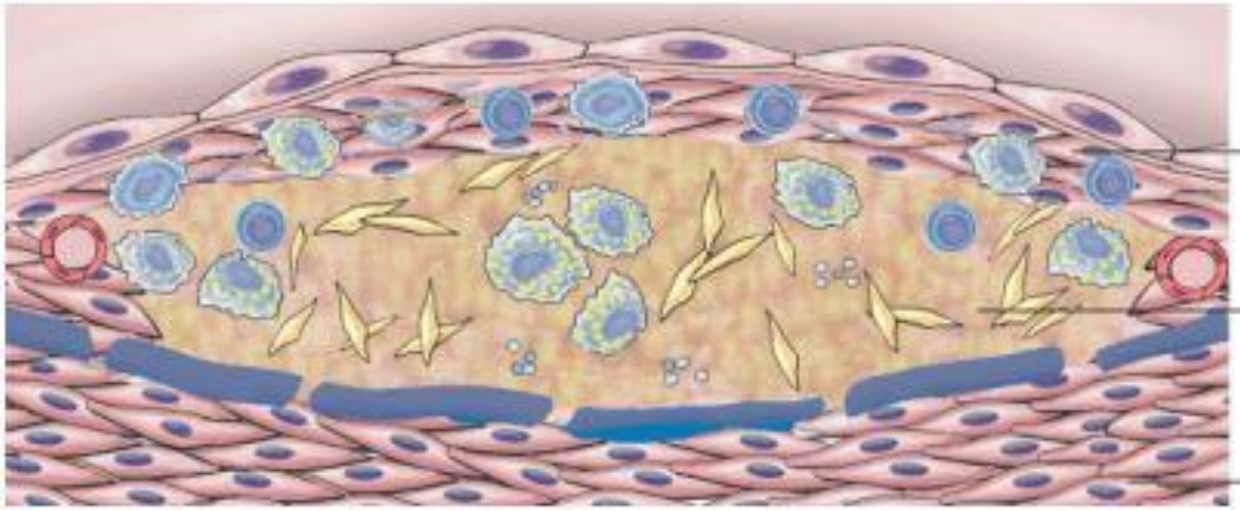
- LDL/apoB: substrate for retention
- HT: mechanical stress of the endothelium
- DM: glycation, oxidative stress, dyslipidemia, inflammation
- Smoking: endothelial dysfunction, procoagulation
- Risk factors = mechanisms that increase retention and inflammation

Biomarkers

- LDL-C as a practical indicator of atherogenic apoB particles
- ApoB (conceptually “particle count”)
- Lp(a) as a genetic risk factor

What does a patient with a history of advanced atherosclerosis "look like"

- History of MI/CMP/PAD, stents, CABG
- DM, CKD, smoking, hypertension
- Drugs: statin, antiplatelet agents, antihypertensives
- Goal: to recognize a high-risk patient and ask the right questions.


FIBROUS CAP
(smooth muscle cells, macrophages,
foam cells, lymphocytes, collagen,
elastin, proteoglycans, neovascularization)
NECROTIC CENTER
(cell debris, cholesterol crystals,
foam cells, calcium)
MEDIA

Atherosclerosis

- structural changes in blood vessels:
- a disease process that leads to deterioration or interruption of blood flow to some areas
- sometimes this fibroproliferative process can accelerate, but also stop or go to regression of the changes created
- from a morphological point of view, two types of changes are observable:
- fatty streaks – macroscopically visible
- are already detected in children
- usually in places with a focal increase in the content of lipoproteins in the intima
- this is the result of the binding of LP to macromolecules of the extracellular matrix $\rightarrow$ its stay in the intima is prolonged
- this is the first step of atherogenesis

Atherosclerosis

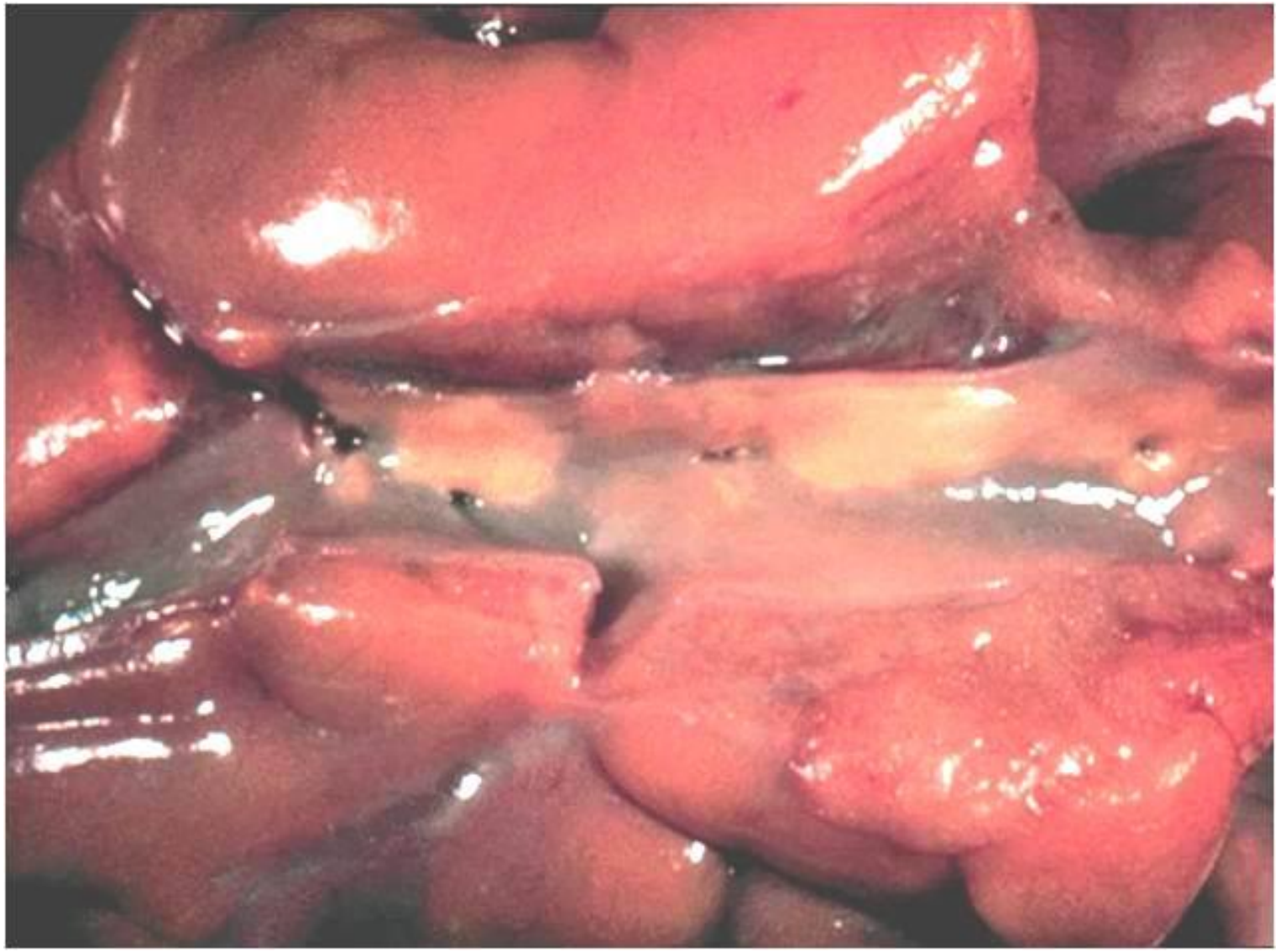
Microscopic findings:

- thickening of the intima
- subendothelial accumulation of cells with a high lipid content – foam cells (mostly macrophages)
- a smaller part of the foam cells are smooth muscle cells with lipid content
- lipids (mainly CHOL) are also present extracellularly to a lesser extent
- T-lymphocytes may also be present
- fatty streaks are not clinically significant, but may develop into a fibrous plaque

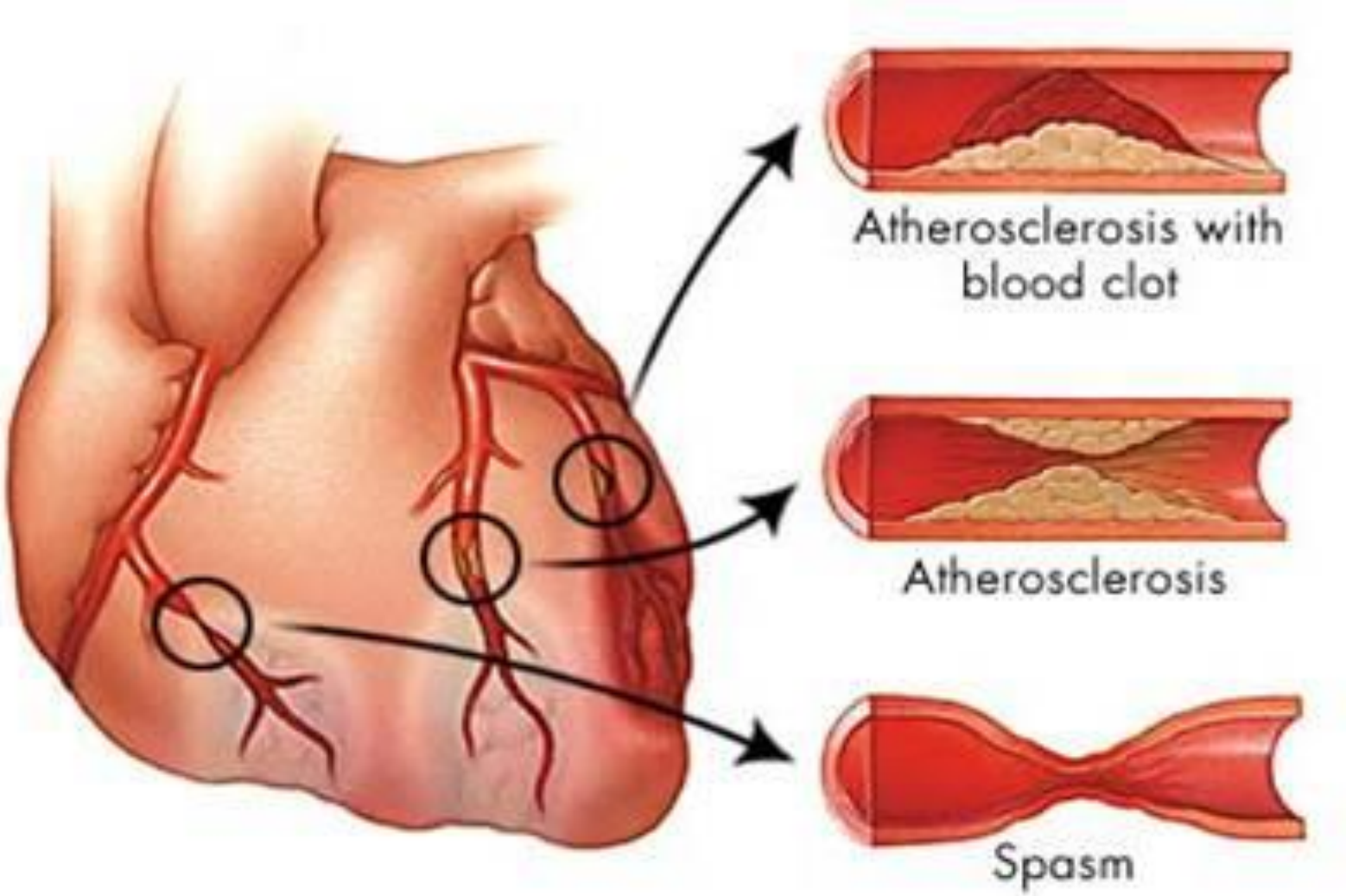
Atherosclerosis

- fibrous plaque
- pale gray elevation in the lumen of the vessel
- typical structure
- on the side facing the lumen is a fibrous cap
- the uppermost part is made up of endothelium
- beneath it are proliferated smooth muscle cells, macrophages, T-lymphocytes, foam cells, extracellular matrix
- on the edges are newly formed vascular channels
- beneath the fibrous cap is the core of the plaque
- necrotic material from cell debris, extracellular lipids with cholesterol crystals and foam cells
- around the necrotic core are calcium compounds
- fissures may form at the edge of the plaque
- site of thrombus formation

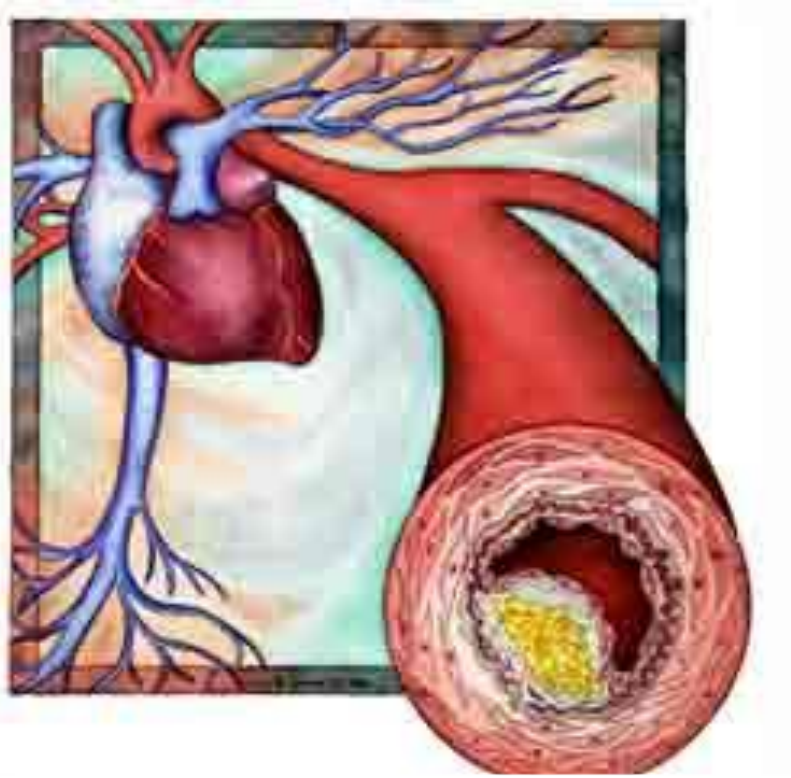
Atherosclerosis - atheromas

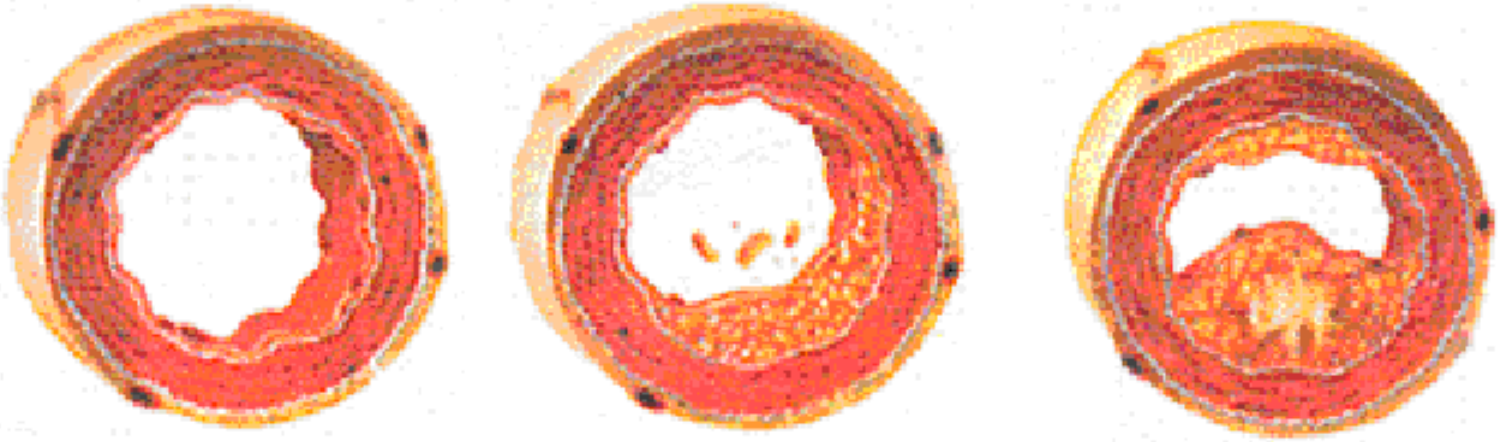


Atherosclerosis



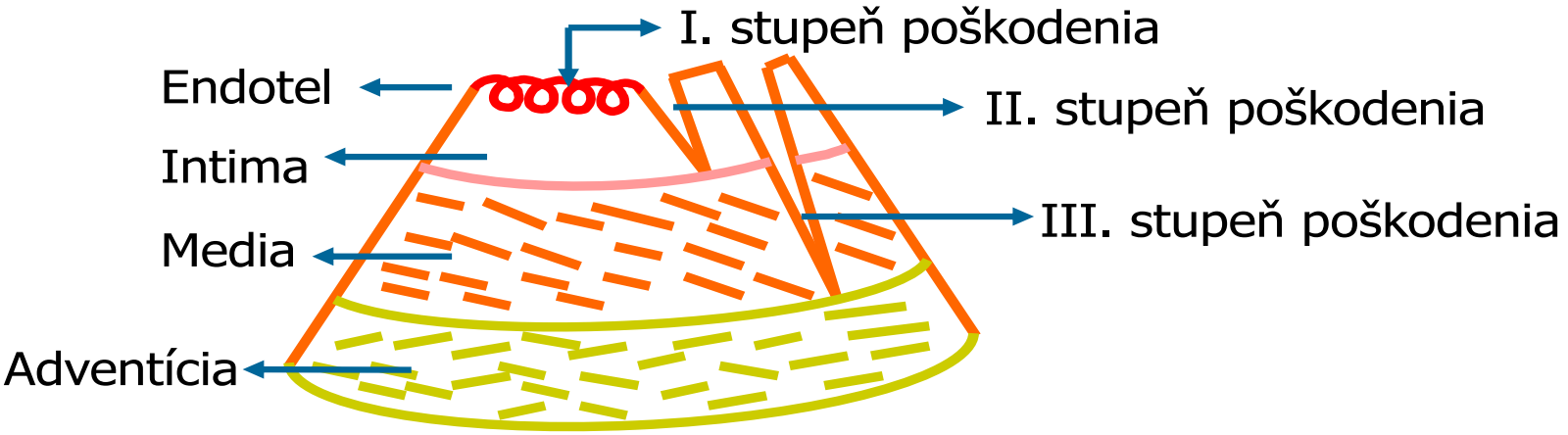
Atherosclerosis





Ateroskleróza

	Akumulácia lipidov a adhézia monocytov	Depozícia doštičiek a trombóza	Proliferácia buniek hladkého svalu
I. stupeň poškodenia	mierna	Nie je	Prítomná – nízka
II. stupeň poškodenia	?	Minimálna	Stredne silná, tvorba „čiapky" na povrchu plátu
III. stupeň poškodenia	?	Mierna	Silná organizácia trombu



Atherosclerosis

- **A thrombus** may completely occlude the vessel lumen or **embolize** to any downstream vessel in the direction of blood flow.
- **Blood can enter the plaque through fissures** in the fibrous cap.
- **Plaque rupture leads to atherothrombosis.**
- **The presence of a plaque may cause an aneurysm.**
- **Plaques most commonly occur in:**
  - abdominal aorta, iliac arteries, epicardial segments of the coronary arteries, thoracic aorta, femoral artery, popliteal artery, carotid arteries, vertebral arteries, cerebral arteries, and the basilar artery.
- **Atherosclerosis does not occur in veins** due to different hemodynamic conditions and **lower endothelial susceptibility**.

Atherosclerosis - origin

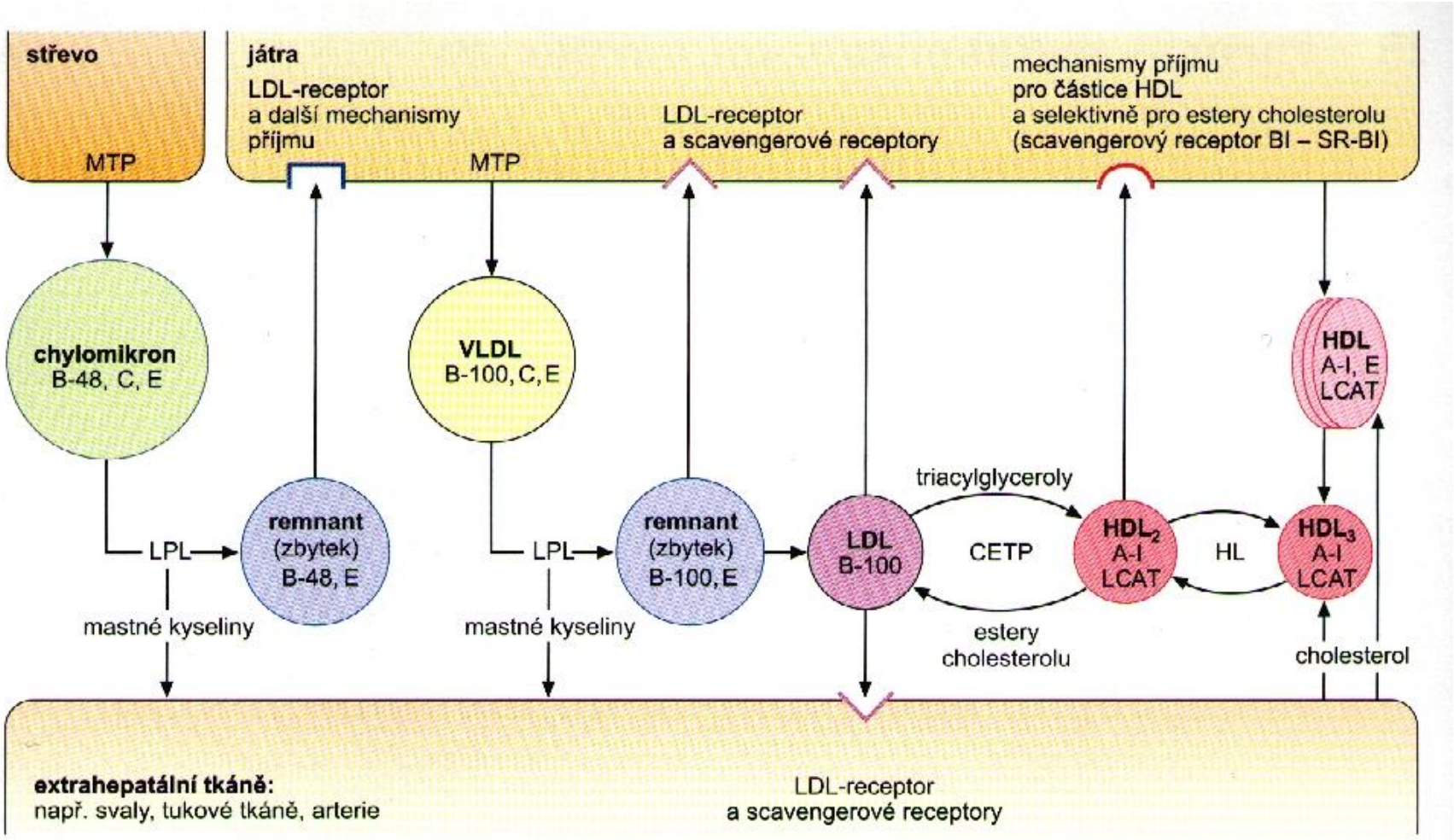
- complex process
- several cell types and many biologically active molecules are involved
- biophysical influences – flow are also important
- among the most important processes for the development include:
  - endothelial damage
  - altered lipoprotein function
  - oxidative stress modifying LDL to oxLDL
  - clonal proliferation of smooth muscle cells
  - chronic infections
  - autoimmune response

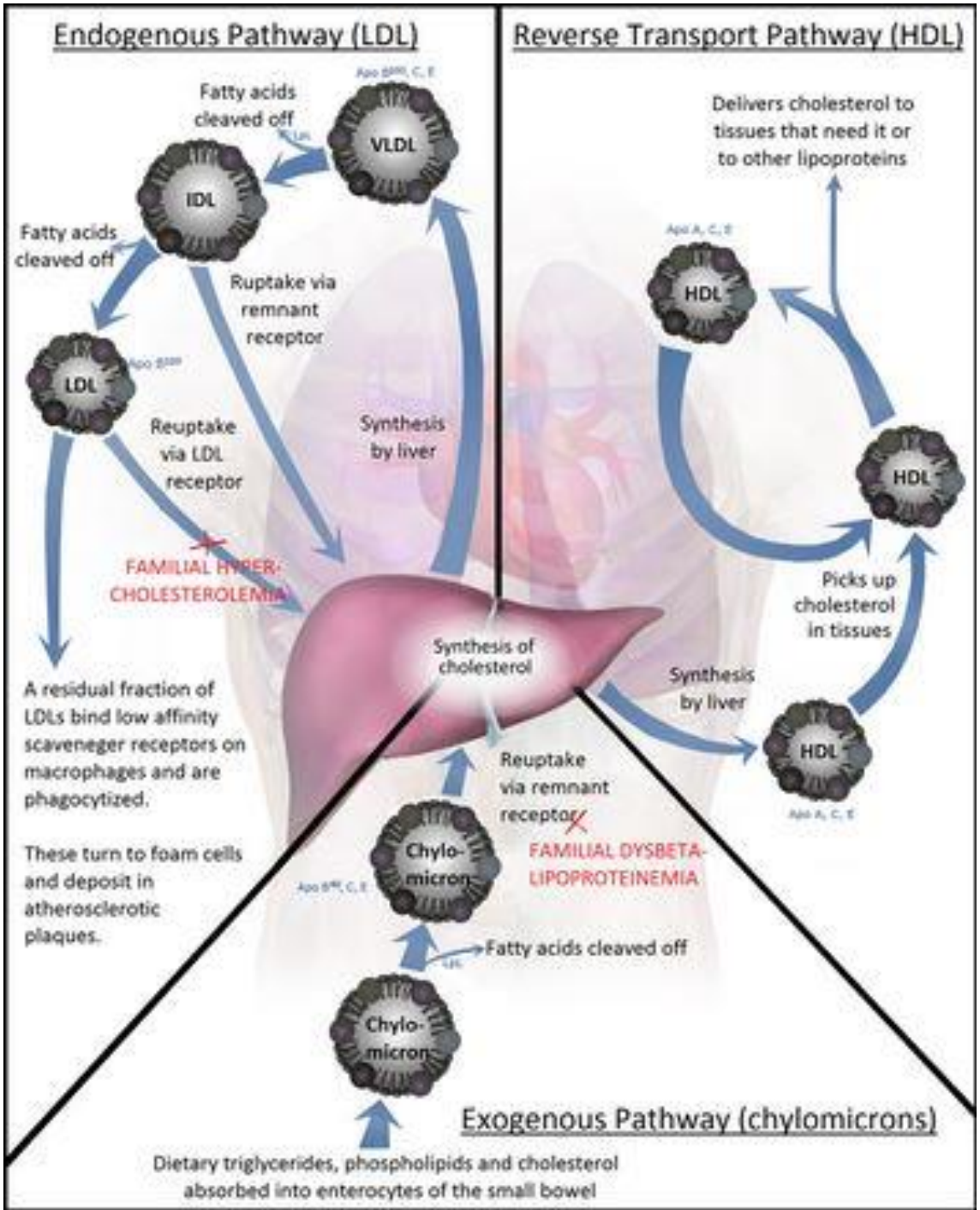
Atherosclerosis - origin

hypercholesterolemia

- essential importance of serum cholesterol – VLDL, LDL, HDL
- chylomicrons – large particles of low density, formed in the intestines, transport lipids from the intestines to the liver
- lipoproteins – transport role for endogenous lipids
- VLDL – rich in TAG, contain apoB-100 and apoE, synthesized in the liver, transfer of MK to tissues and muscles
- after release in tissues, VLDL are metabolized to LDL
- using apoB-100, they bind to LDL receptors and the entire complex enters the cell
- LDL transports about half of the daily cholesterol production back to the liver
- the other half is removed by HDL (transport to the liver)
- produced in the liver, empty discoid particles that capture cholesterol from peripheral tissues

Atherosclerosis - origin




Endogenous Pathway (LDL)
Reverse Transport Pathway (HDL)
Fatty acids cleaved off
VLDL
IDL
Fatty acids cleaved off
Ruptake via remnant receptor
LDL
Reuptake via LDL receptor
Synthesis by liver
FAMILIAL HYPER-CHOLESTEROLEMIA
A residual fraction of LDLs bind low affinity scaveneger receptors on macrophages and are phagocytized.
These turn to foam cells and deposit in atherosclerotic plaques.
Delivers cholesterol to tissues that need it or to other lipoproteins
HDL
HDL
Picks up cholesterol in tissues
Synthesis of cholesterol
Synthesis by liver
HDL
Reuptake via remnant receptor
FAMILIAL DYSBETA-LIPOPROTEINEMIA
Chylo-micron
Fatty acids cleaved off
Chylo-micron
Exogenous Pathway (chylomicrons)
Dietary triglycerides, phospholipids and cholesterol absorbed into enterocytes of the small bowel

Atherosclerosis - origin

- **oxidative stress**
  - arises as a result of a shift in the balance between oxidants and antioxidants
  - their effects in atherosclerosis can be summarized as:
  - oxidation of lipoproteins in the arterial wall
  - reduction of vasodilation capacity by removal of NO (from endothelial cells)
  - stimulation of smooth muscle cell proliferation
  - activation of the inflammatory process through increased production of pro-inflammatory cytokines and adhesive molecules by the cells involved

Atherosclerosis - origin

- **hypertension and homocysteine**
  - in hypertensive patients increased concentration of angiotensin II – vasoconstrictor
  - may promote endothelial dysfunction
  - stimulates growth and constriction of smooth muscle cells
  - increases lipoxygenase activity in them → LDL oxidation → inflammation
  - increased concentration of hydrogen peroxide, superoxide and hydroxyl radicals → ↓ NO availability, ↑ leukocyte adhesion and peripheral resistance
- **homocysteine**
  - is toxic to the endothelium
  - has a prothrombogenic effect
  - ↑ collagen production
  - ↓ NO availability
  - stimulates smooth muscle cell proliferation

Atherosclerosis - origin

- vascular smooth muscle cells
  - from a morphological point of view – division:
  - epithelioid and spindle
  - from a functional point of view:
  - contractile and secretory
  - contractile have receptors for vasodilator and vasoconstrictor substances
  - under the influence of pro-inflammatory cytokines they change into secretory
  - produce collagen, elastic fibers and proteoglycans
  - secretory type is more prone to apoptosis (the faster apoptosis, the faster proliferation)
  - in atherosclerotic sites apoptosis is faster
  - oxidized LDL in high concentrations stimulates apoptosis, low ones increase proliferation $\rightarrow$ one of the triggers of atherosclerosis

Atherosclerosis - origin

- proliferation is also influenced by hemodynamic forces
- biomechanics of flow
- shear stress
- cyclic mechanical pressure
- shear stress stimulates the production of NO and PGI – vasodilators
- cyclic mechanical pressure acts on the endothelium and smooth muscle cells
- insufficient shear stress and mechanical pressure trigger apoptosis
- sites with abnormal hemodynamics are predisposed to atherosclerotic changes

Atherosclerosis - origin

- **angiotensin II in atherogenesis**
- stimulates the formation of NF-kB
- triggers the transcription of several dozen inflammatory genes
- stimulates the formation of collagen
- stimulates the activity of osteopontin (participates in plaque calcification)
- significantly influences the pro-inflammatory activities of macrophages, endothelium and smooth muscle cells
- induces hyperplasia and hypertrophy of smooth muscle cells
- stimulates the release of reactive oxygen species $\rightarrow$ LDL oxidation $\rightarrow$ LDL endocytosis $\rightarrow$ formation of foam cells

Atherosclerosis - origin

infectious diseases

- some infectious agents can be a trigger or enhancing factor of atherosclerosis
- Chlamydia pneumoniae
- Helicobacter pylori
- cytomegalovirus
- EBV

chronic infections

- they result in ↑ inflammatory markers (CRP, IL-1,6, TNF, ICAM, etc.)
- the combination of increased MMP-9 and IL-18 is very unfavorable
- CRP and amyloid A levels are elevated in most patients with AP

Atherosclerosis - origin

autoimmune diseases

- accelerated progression of atherosclerosis is observed in some classic AI diseases
- immunological hypothesis of atherosclerosis
- the essence is an insufficiently regulated local immune response
- the first cells appearing in the arterial intima are lymphoid cells (T-lymphocytes), not foam cells, then macrophages and smooth muscle cells
- in a normal arterial cell, both mast and dendritic cells are present in an immature form
- oxLDL increases the adhesion of dendritic cells to the endothelium and their migration into the intima and stimulates the expression of VCAM-1
- (adhesive and chemotactic molecule for monocytes and T-lymphocytes)

Atherosclerosis - origin

- **endothelial cells**
- damage to the endothelium results in its dysfunction, apoptosis to cell oncosis – development of atherosclerosis
- apoptosis → apoptotic microparticles → need for damage compensation → without the presence of phagocytic cells → inflammation
- endothelial microparticles constitute 30% of circulating particles in the circulation
- their number increases in some diseases, including coronary
- inflammatory mediators bind to them
- they can deposit at the site of endothelial damage
- they are the main component of atherosclerotic plaques

Atherosclerosis - origin

- replacement of damaged endothelium using progenitor circulating endothelial cells (more often) or angiogenesis
- in patients with coronary diseases their number is reduced
- their number can be pharmacologically increased by statins
- laminar shear stress stimulates the expression of anti-inflammatory, antiproliferative, antiapoptotic and antioxidant genes
- for normal endothelial function a stress of 5-20 dyn/dc2 is required
  - ↑ shear stress → ↓ NO formation, ↑ formation of reactive oxygen species → development of atherosclerosis
  - ↓ shear stress → mechanical damage to the endothelium → development of atherosclerosis

Atherosclerosis

- **plaque rupture**
- **plaque vulnerability depends on:**
  - size and consistency of the atheromatous core
  - thickness and integrity of the fibrous cap
  - inflammatory changes in the fibrous cap
  - reduced resistance to hemodynamic stress
  - stable plaque with gradual development contains 70% fibrous core
  - increased core volume positively correlates with plaque vulnerability
  - collagen production depends on the content of smooth muscle cells
  - activity depends on several inflammatory mediators
  - IFNγ inhibits collagen formation and activates matrix. proteinases

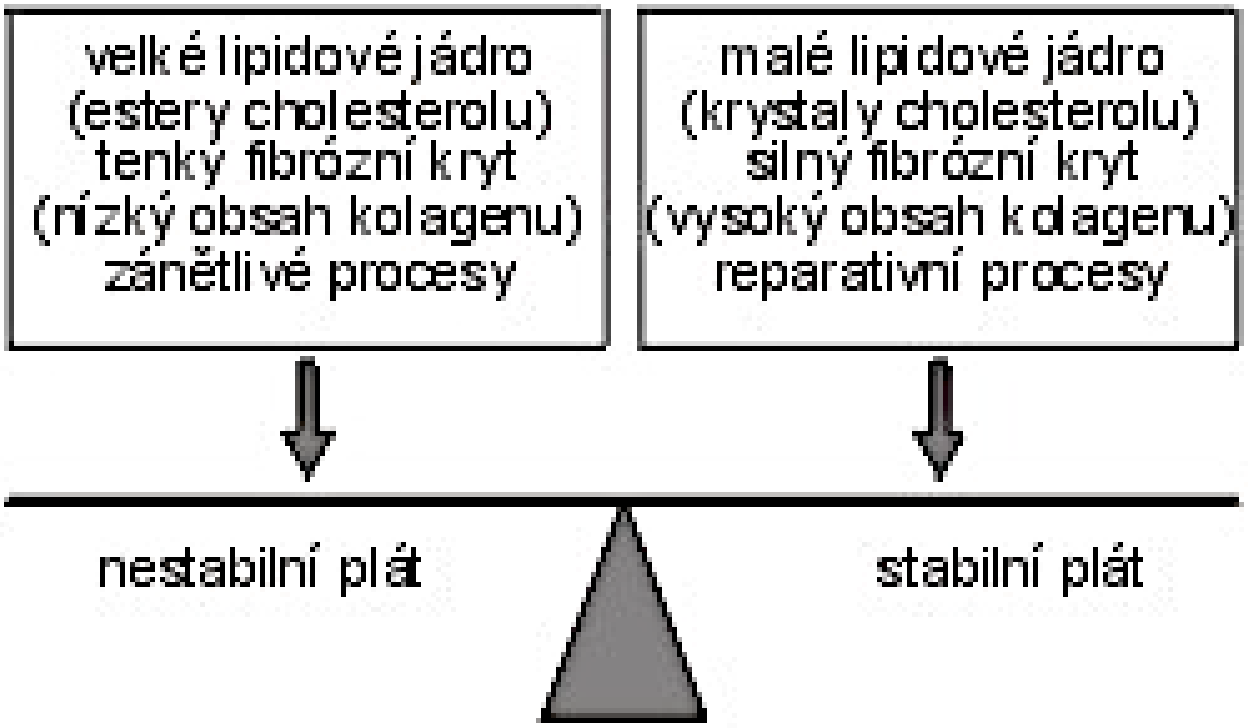
Atherosclerosis

- metalloproteinases degrade collagen, proteoglycans and elastin $\rightarrow \uparrow$ plaque lability
- damage occurs with $\downarrow$ activity of proteinase inhibitors (TIMP)
- the transition zone of plaque and intima is a critical place – changes in kinetics and shear stress
- atheroma has an irregular surface $\rightarrow$ formation of turbulent flow $\rightarrow$ activation of platelets $\rightarrow$ activation of clotting $\rightarrow$ formation of thrombin
- they also produce the factor CD40L, which causes the production of chemotactic factors in endothelial cells $\rightarrow$ inflammation
- plaque enlargement $\rightarrow$ increased turbulent flow

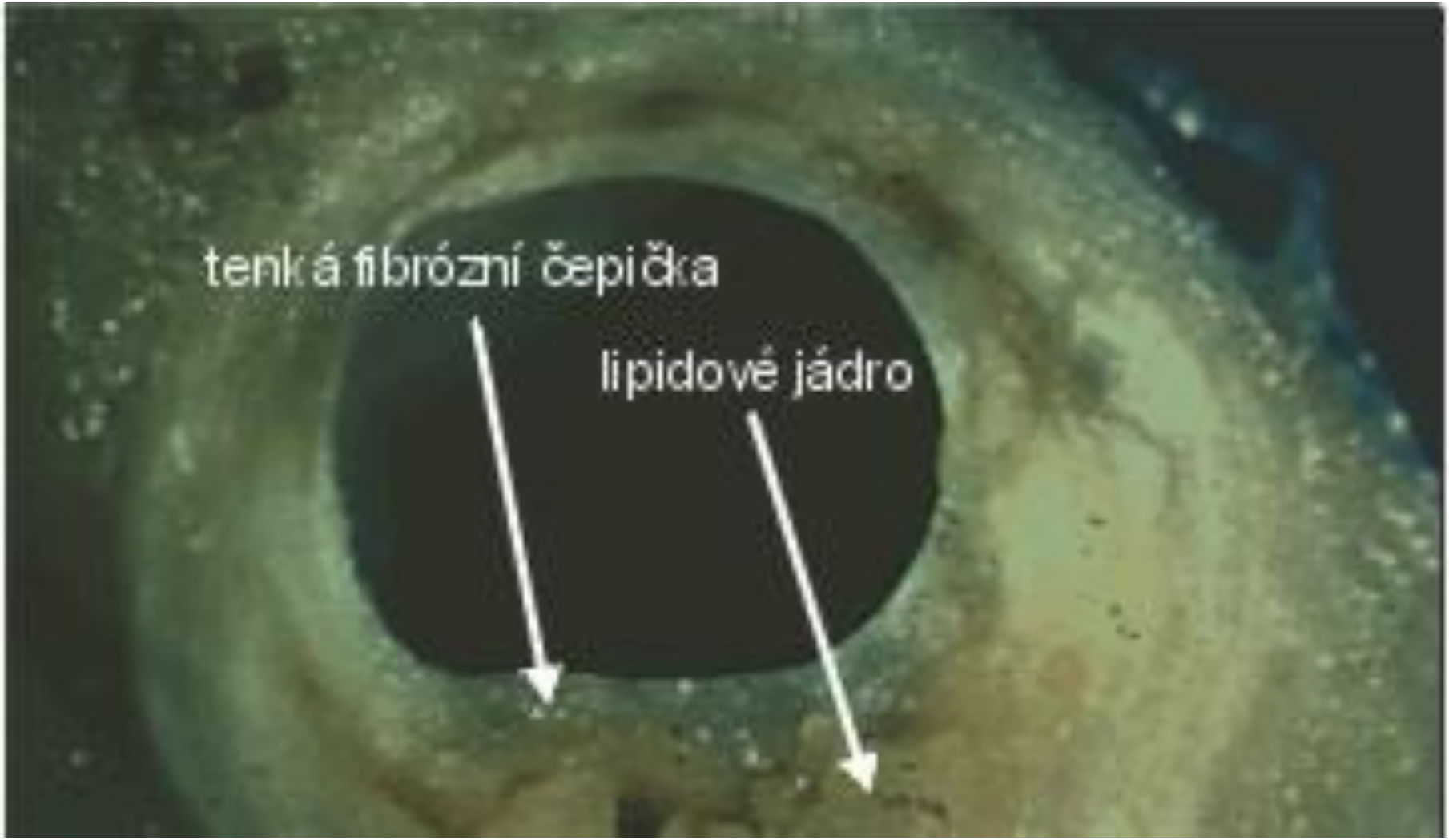
Atherosclerosis

- Rupture can occur:
- by mechanical action of flow
- by vasoconstriction
- by a combination of the above
- a tear is formed $\rightarrow$ bleeding into the thrombogenic core of the plaque $\rightarrow$ thrombogenic material enters the lumen $\rightarrow$ formation of a massive thrombus

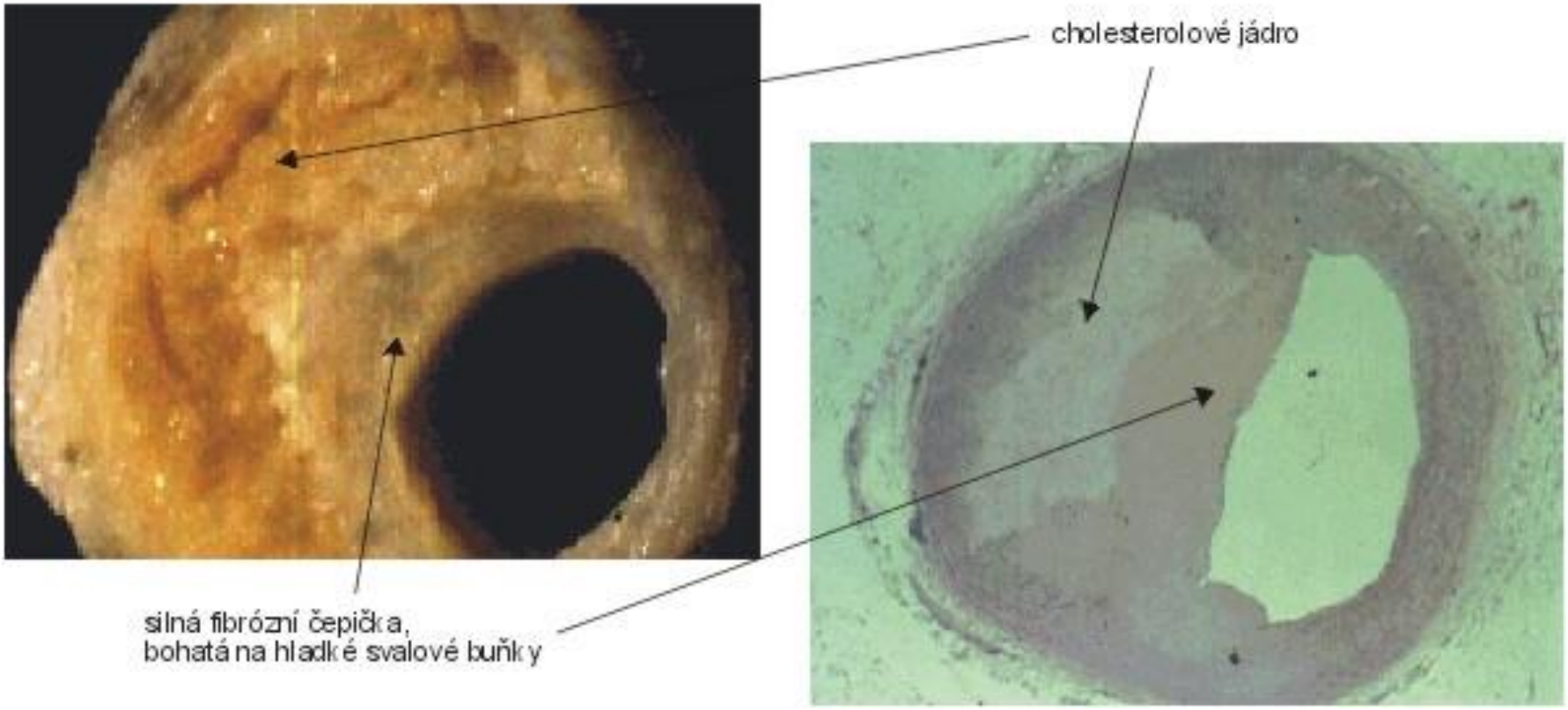
Atherosclerosis



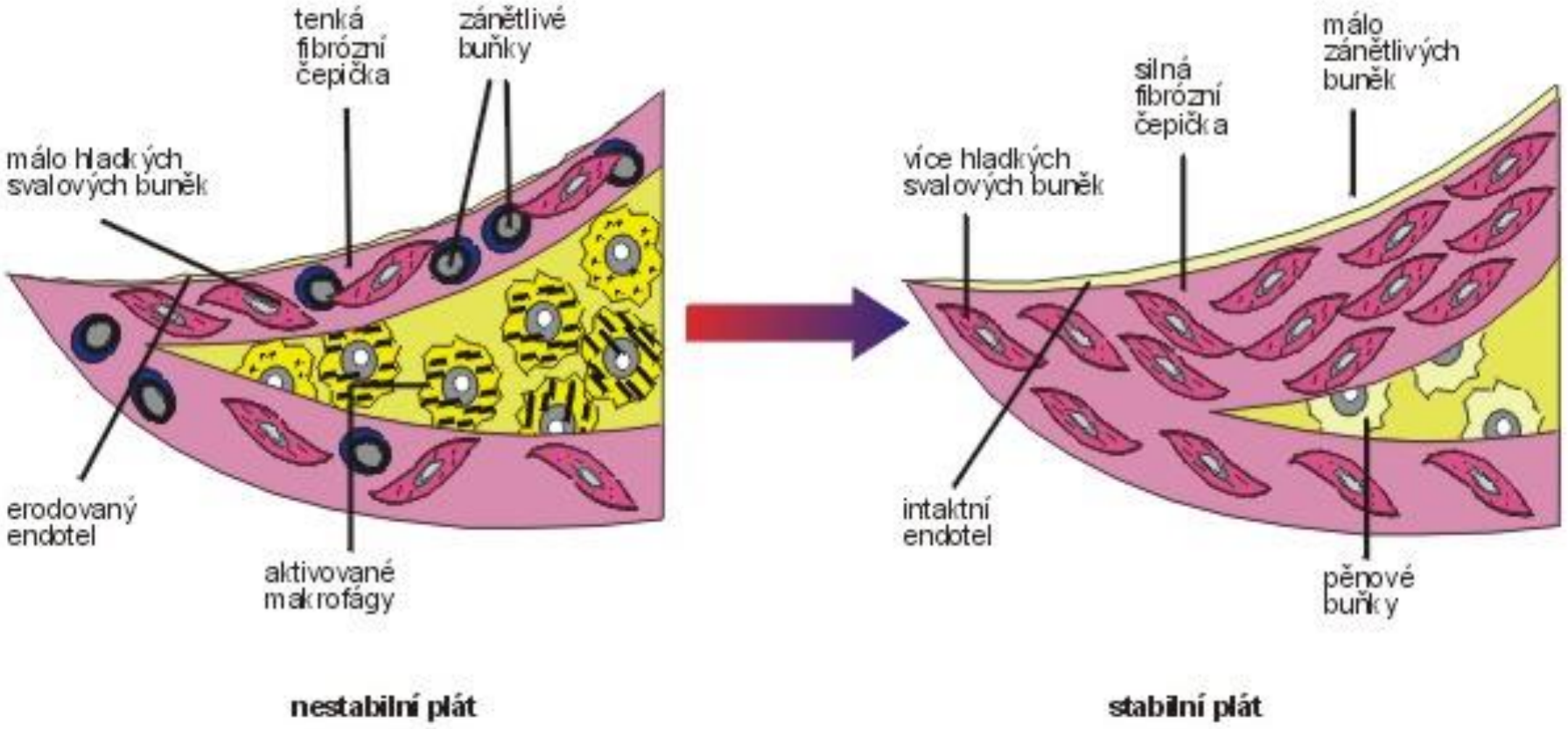
Atherosclerosis - labile plaque



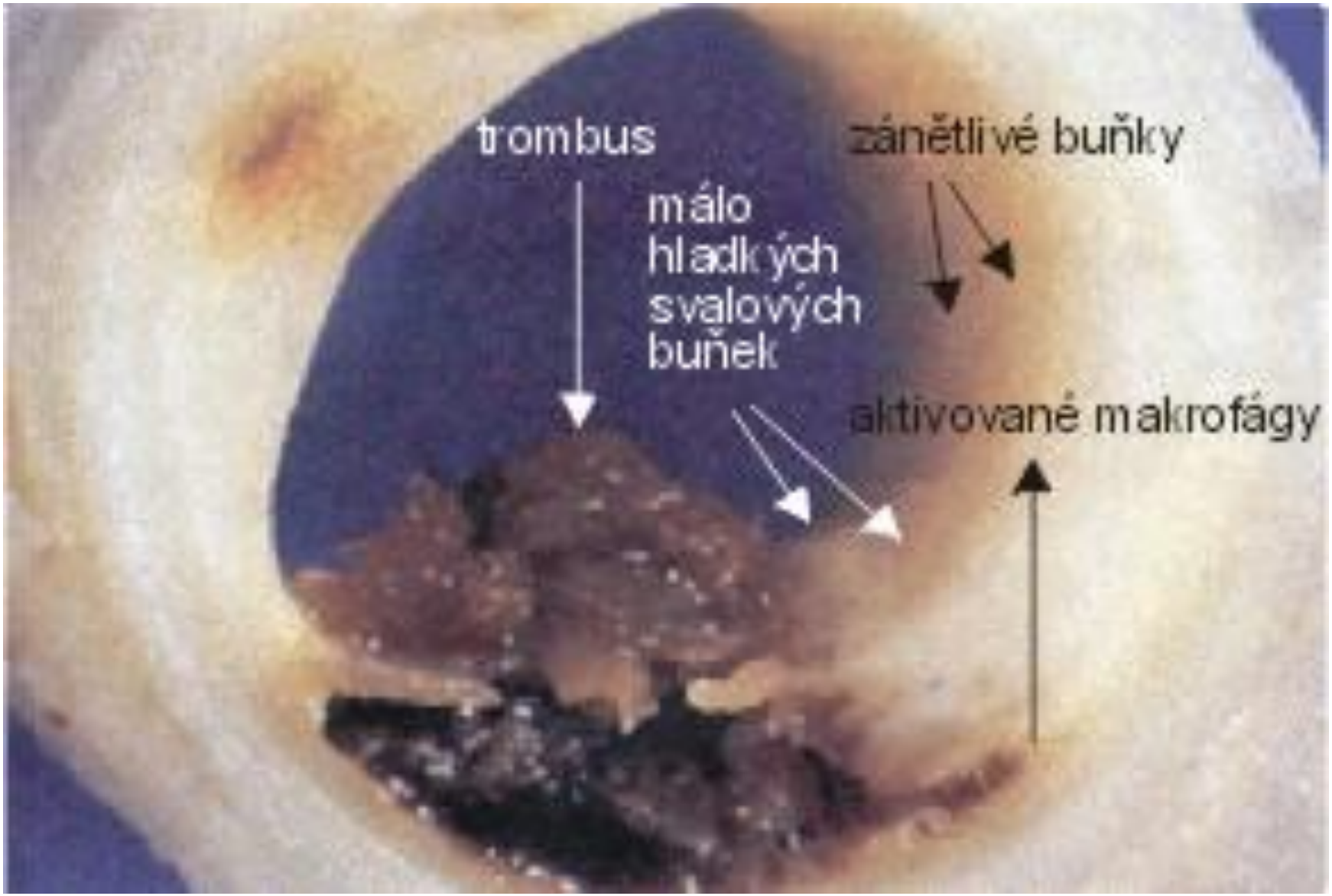
Atherosclerosis – stable plaque



Atherosclerosis



Atherosclerosis – plaque rupture



CAVE

- Atherosclerosis is a lipid-inflammatory process of the intima.
- Retention of apoB lipoproteins is an early key step.
- oxLDL and cholesterol crystals activate innate immunity.
- Macrophages → foam cells → necrotic core.
- SMC and ECM form a fibrotic cap (stabilizes).
- Inflammation weakens the cap (MMP*) → vulnerability.
- Acute events are mainly thrombosis after rupture or erosion.
- LDL-C reduction is the basis of prevention; inflammation explains the residual risk.

***MMP (matrix metalloproteinases) = a family of Zn^{2+}-dependent endopeptidases that cleave components of the extracellular matrix (ECM) (collagen, elastin, proteoglycans) and thereby control tissue remodeling.**