Atherosclerosis, coronary artery disease; Hypertension

MAREK BRENISIN, MD., PHD.,

DEPARTMENT OF PATHOPHYSIOLOGY MF P.J. SAFARIK UNIVERSITY

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Atherosclerosis

Atherosclerosis

- Process of changes of vascular elasticity and diameter by building up fatty acids, cholesterol and similar substances in the vessel wall
- Physiological process with possible pathological consequences
  - A part of metabolism of lipoproteins
  - Cumulative damage over time in case of regulatory failure
- Onset – very early (hypothesised even in intrauterine period)
- Location
  - Large elastic arteries (e.g., aorta, carotid, and iliac arteries) and large and medium-sized muscular arteries (e.g., coronary and popliteal arteries)
  - Turbulent blood flow presence

Atherosclerosis

- Possible pathological consequences
  - Decreased perfusion or obstruction of coronary and brain vessels
  - Deterioration of peripheral arteries -> peripheral vascular disease, critical (lower) limb ischemia
  - Possible contributor to hypertension establishment
    - Decrease of blood perfusion in renal artery -> RAAS activation -> atherosclerosis aggravation -> vitious circle established
- Reason of significant morbidity and mortality
  - Coronary artery disease
  - Acute coronary syndrome
    - Myocardial infarction, unstable angina pectoris, sudden cardiac death, *coronary syndrome X*
  - Ischemic or hemorrhagic stroke
  - Etc.

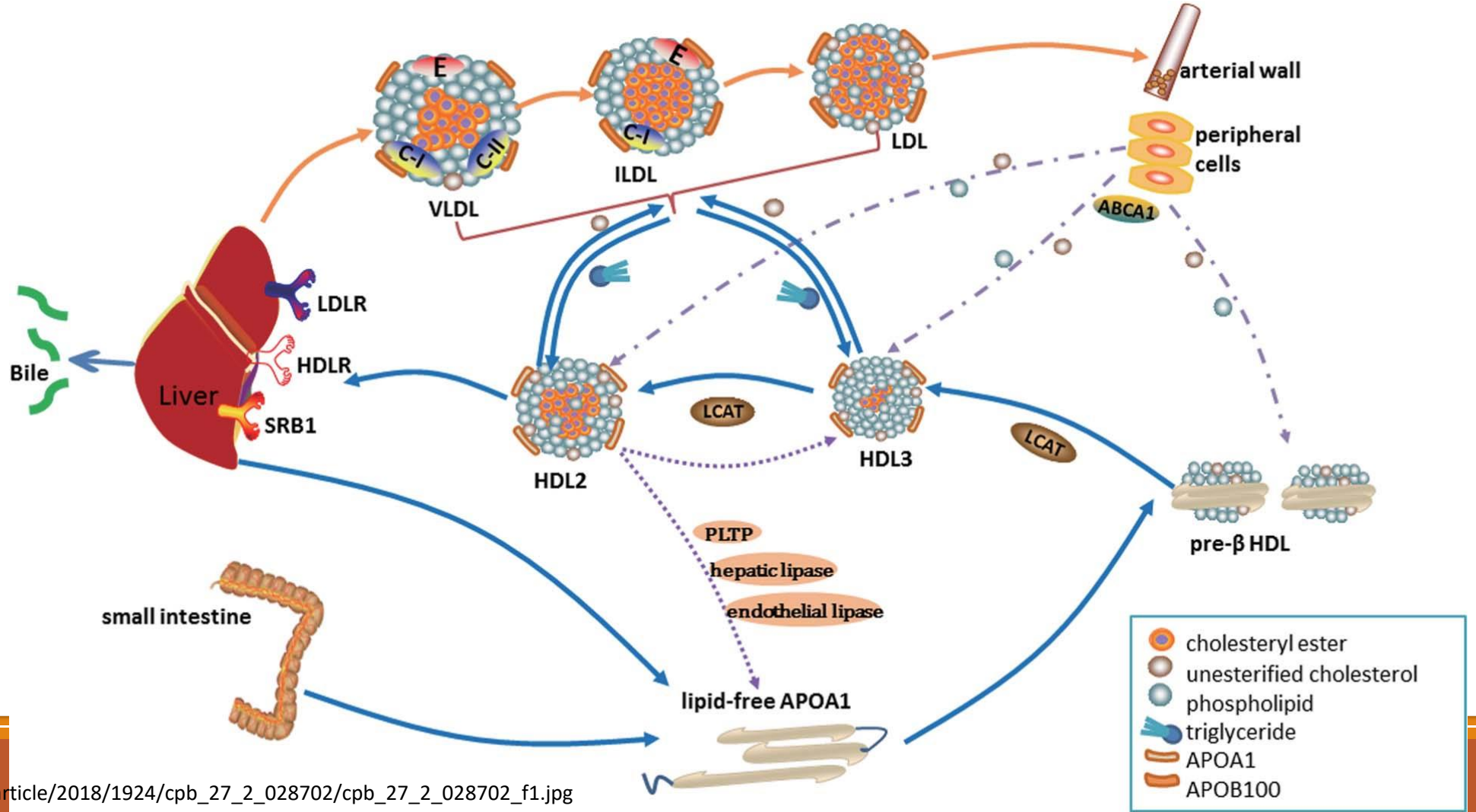
Risk factors – nonmodifiable (?)

1. Genetic abnormalities
   - Familial hypercholesterolemia
     - (AD, 3 possible mutatons -> LDL-R, ApoB-100, PCSK9 – responsible for degradation of LDL-R)
   - Apolipoprotein ε4 presence (ε2 may present both increased and decreased risk, ε3 is rendered as neutral)
2. Family history
   - Polyfactorial process
3. Increasing age
   - Decreased efficiency of reparatory mechanisms -> reversible lesions turn to irreversible
4. Male gender – estradiol in women pose protective effects (until menopause)

Risk factors - modifiable

1. Hyperlipidemia
   - Dyslipoproteinemia is more important -> ↑LDL, ↑ox-LDL, ↓HDL (? ox-HDL)
   - Lipoprotein a as the main factors for atherosclerosis
     - Range <0.2->200 mg/dl (<0.5-500 nmol/l), synthetised in liver -> polymorfisms, isoforms
     - Preferred carrier of oxidised phoshpolipids, also carries cholesterol; clearance remains unknown (LDL-R partially responsible)
2. Hypertension
   - Stronger pulsations enhance endothelial damage
   - Turbulent flow emergence possibility at locations of laminar flow
3. Cigarette smoking and tobacco products used
   - Reactive oxygens species and toxic substances in cigarettes; imperfect combustion, pyrolysis

Cholesterol transport



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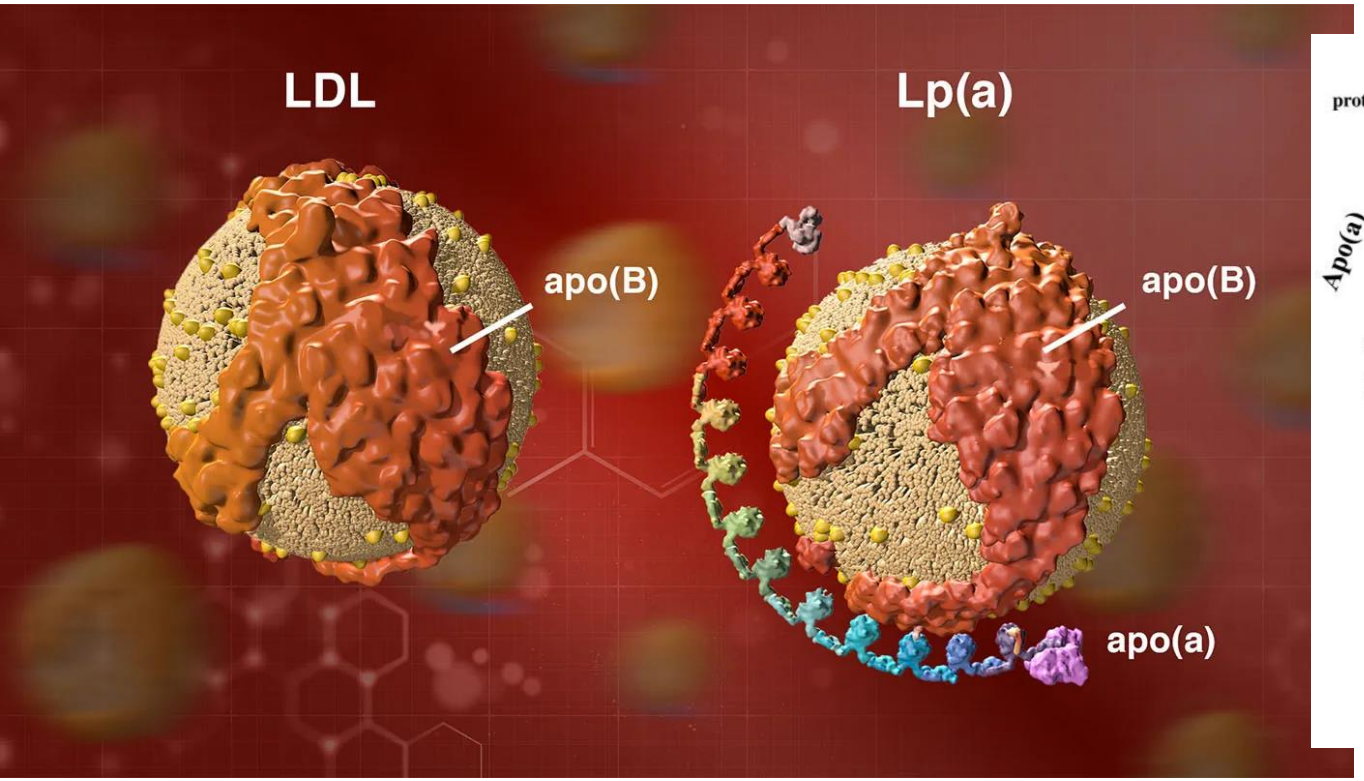
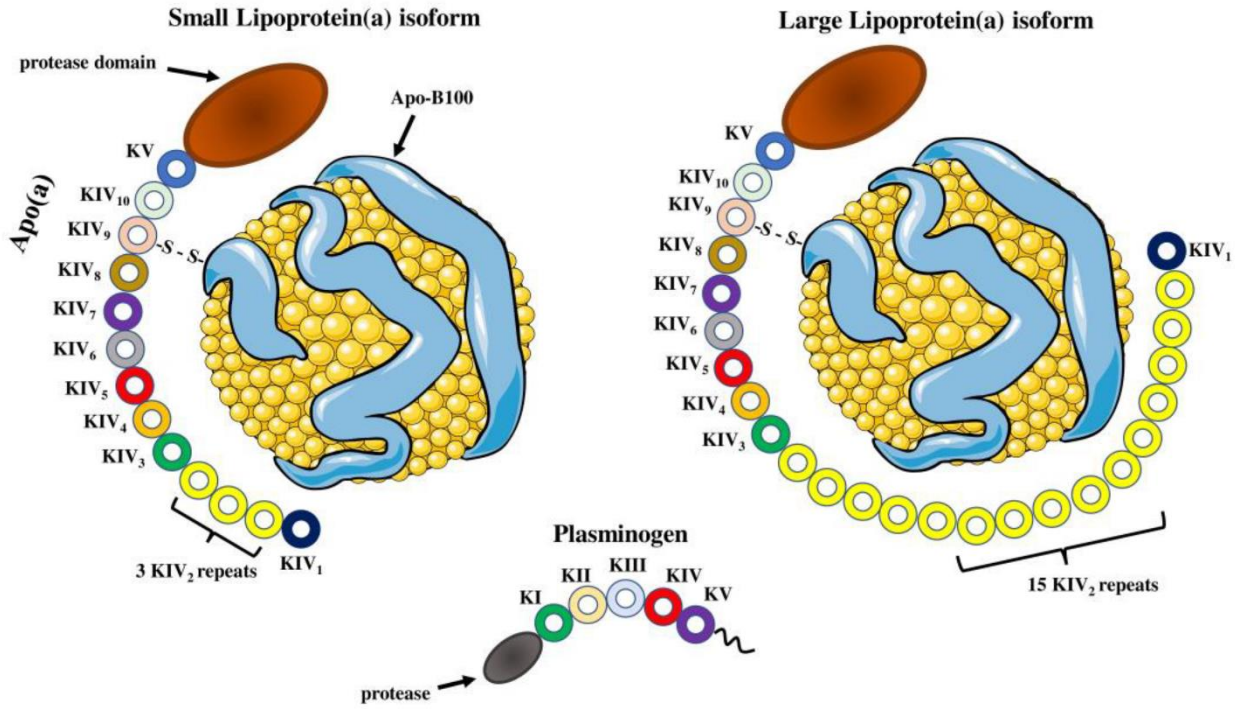
Risk factors - modifiable

4. Diabetes mellitus
   - Glycation of proteins -> Schiff base -> Amadori product -> advanced glycation endproducts (AGEs) -> deposition in blood vessel walls
     - LDL and HDL may be oxidised and glycated as well
     - Only euglycemia prevents extensive glycation
5. Inflammation
   - Low-grade inflammation present at the site of atherosclerosis development
     - Stable vs. unstable plaque -> determined also by intensity of inflammatory reaction





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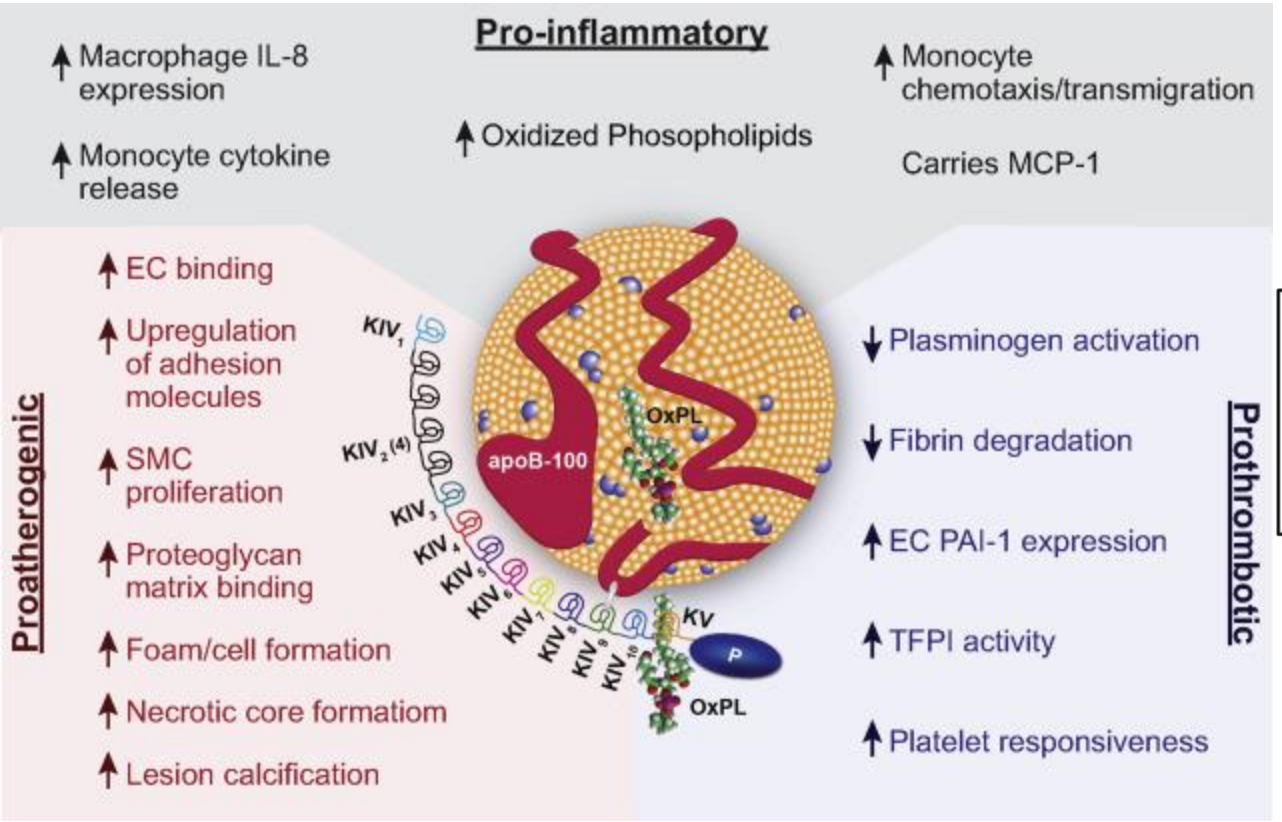

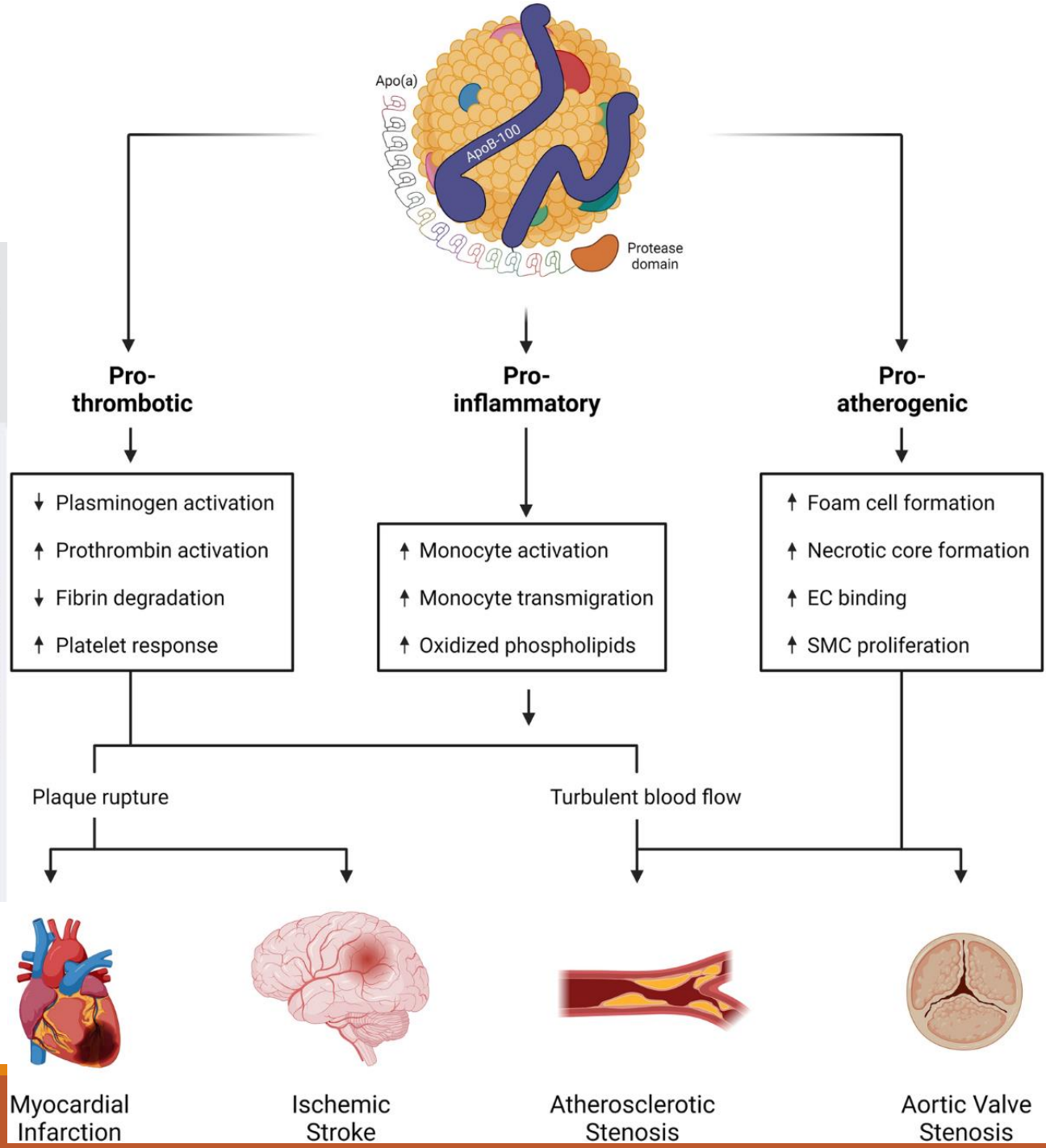

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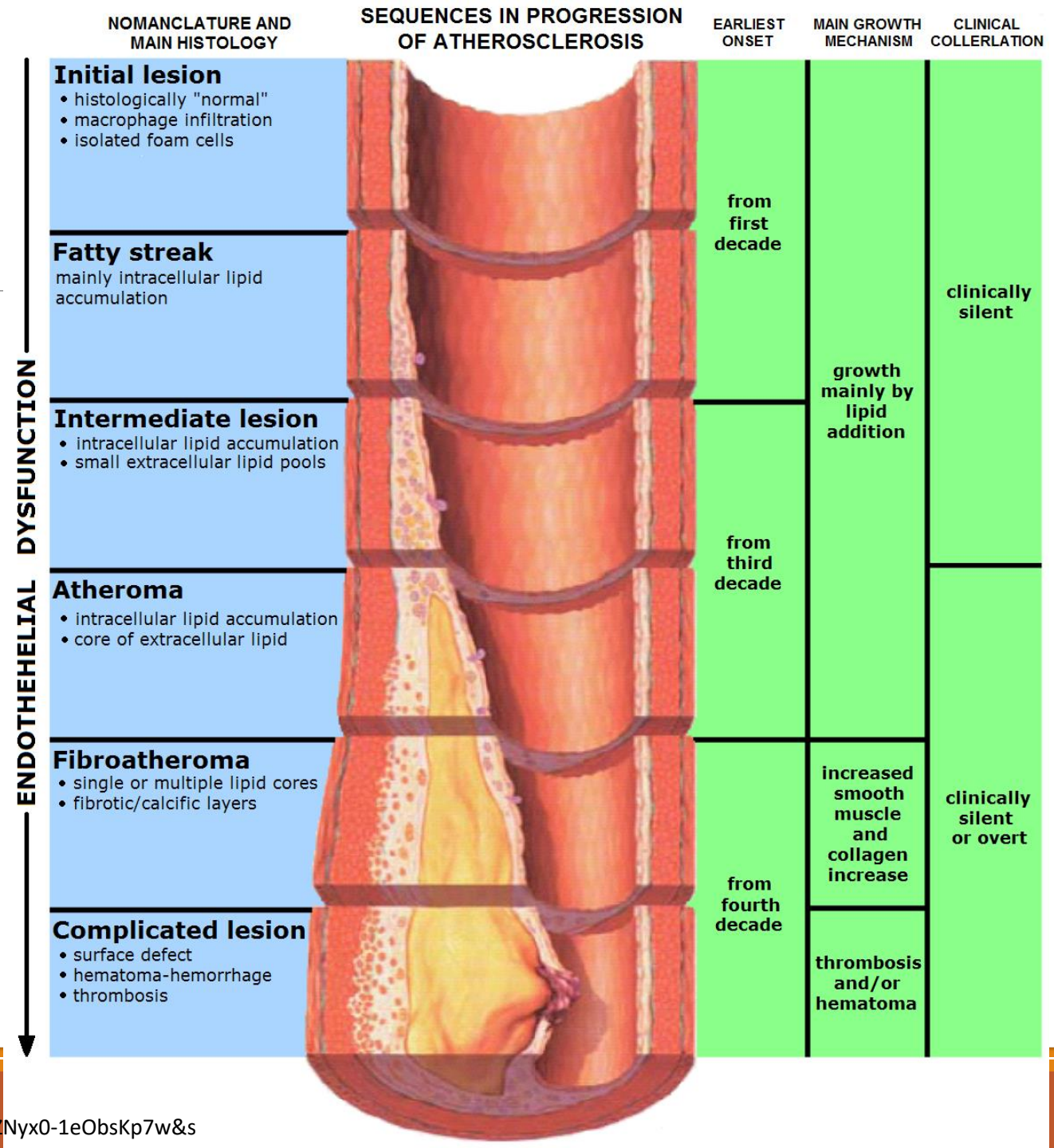
Atherosclerosis overview



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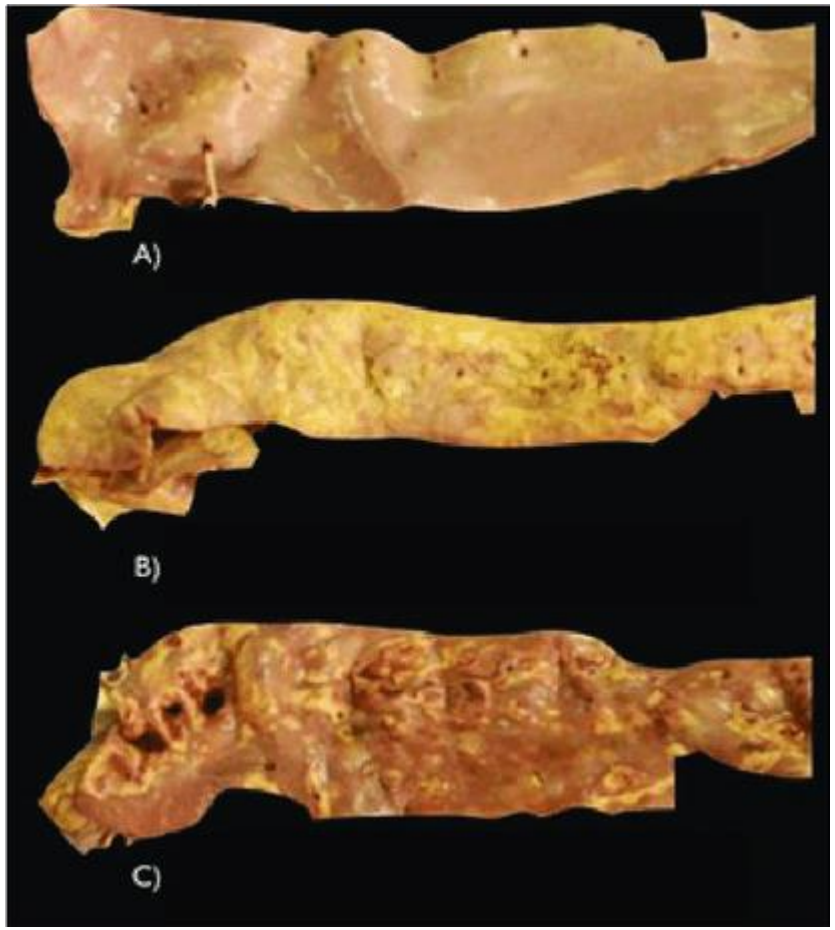
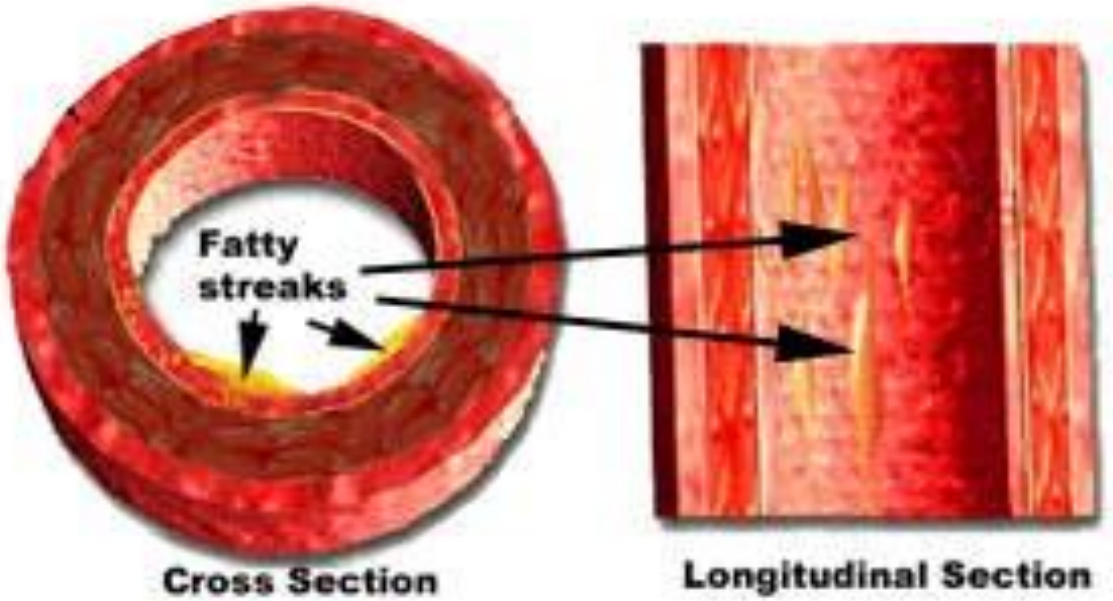
Atherosclerosis mechanism

1. Reversible lesions (0 – 10 years)
   - LDL particles and Lp (a) transporting cholesterol from liver to target tissues
   - Some cholesterol escapes targetted regulation -> subendothelial depositions

   a) Initial lesions emerging
      - Isolated apo-B particles exposure (TG-rich-VLVL and Chol-rich-LDL)
      - Isolated macrophages and foam cells, M2 phenotype preferred
      - Extra cholesterol evacuated by HDL particles

   b) Fatty streaks
      - Intracellular lipid accumulation prevailing





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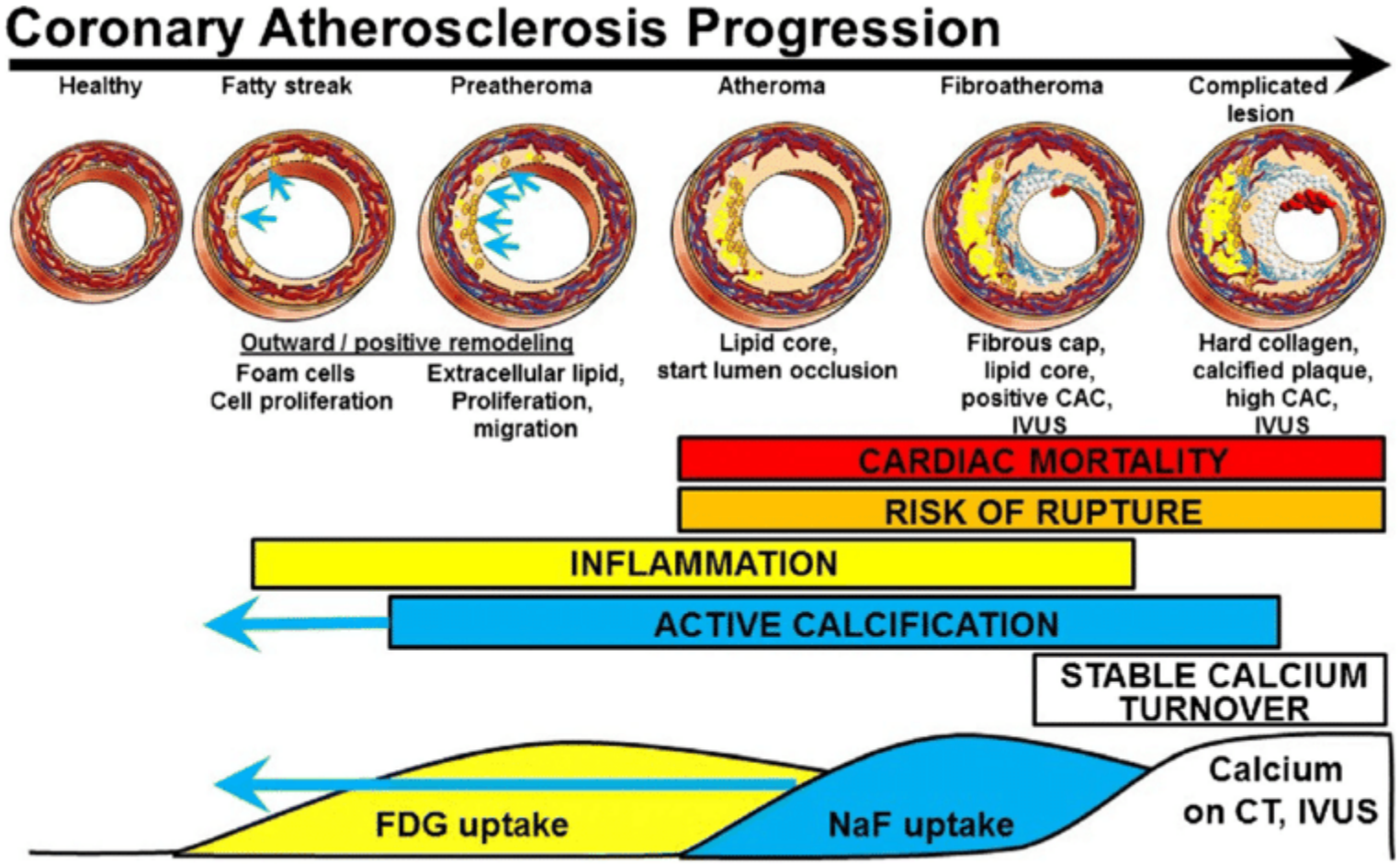
https://www.homepages.ucl.ac.uk/~zchab6a/v2/ssm_yr1_1/ath_1.jpg

Atherosclerosis mechanism

2. Reversible lesions (30+ years of age)
   - Fully reversible when intervened accordingly
   - Current treatment is not precise and often comes late

   a) Intermediate lesions
   - Intracellular lipid accumulation enhanced
   - Small extracellular pools appear -> DANGER!

   b) Atheroma
   - Lipid core(s) formation
   - Immune cells attraction -> DANGER!
   - M1 macrophage type starts to be preferred over M2



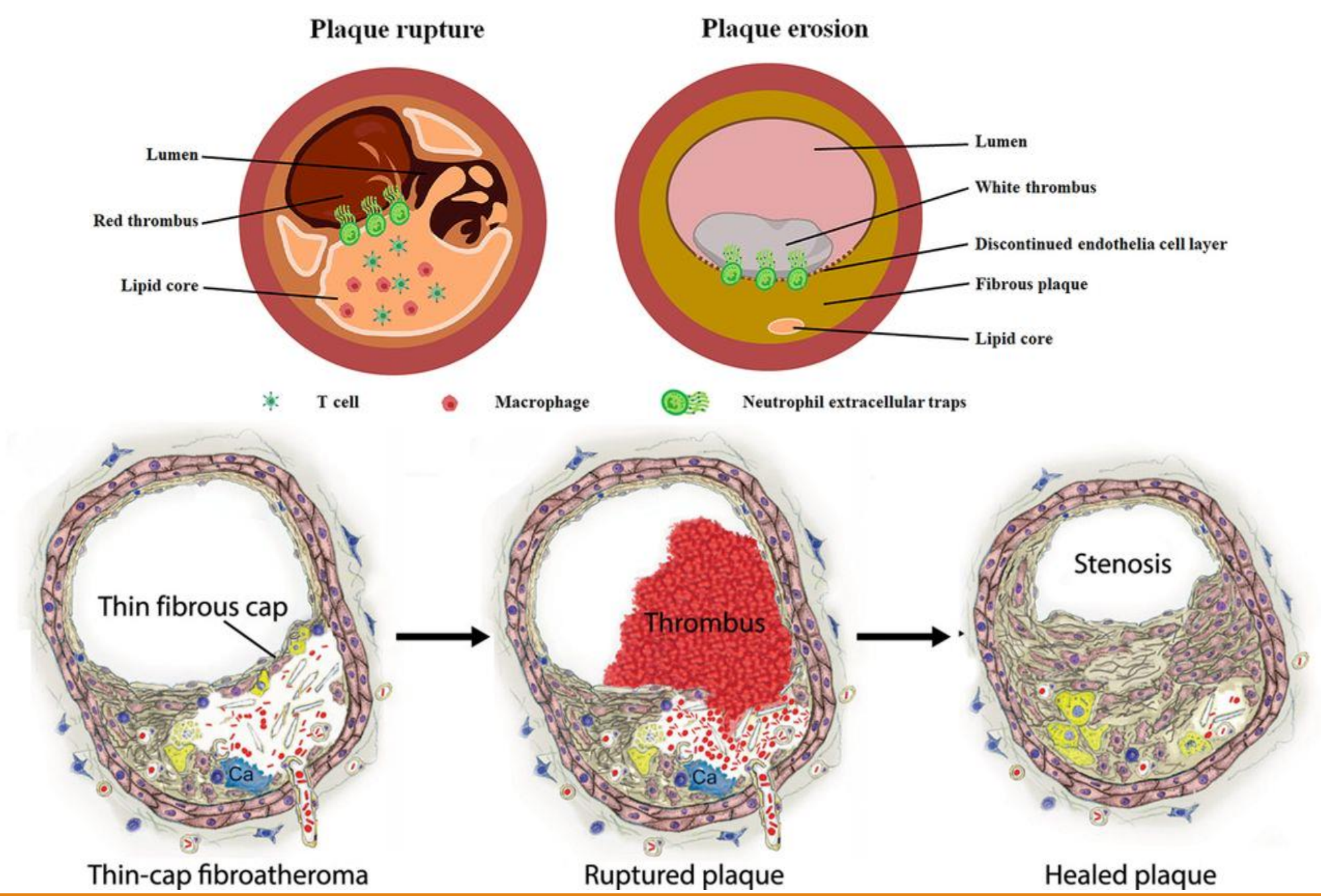
https://www.researchgate.net/publication/341283048/figure/fig1/AS:889813918048258@1589159578573/The-progression-of-a-complicated-atherosclerotic-lesion-Although-it-has-been-established.png

Atherosclerosis mechanism

3. Irreversible (?) lesions (40/50+ years of age)
   - Immune reactions triggered -> „low-grade inflammation“
   - Smooth muscle cells stimulation -> multiplication, migration, extracellular matrix synthesis -> fibrosis
   - Fibrous cap established

   a) Fibroatheroma
   - Fibrosis in attempt to stabilise lesion
   - Lesion may „grow“ into neighbouring lesion even after dyslipidemia correction

   b) Complicated/Advanced lesion
   - More intense inflammation -> fibrous cap thinning -> risk of rupture
   - Pro-thrombogenic surface -> risk of platelets activation
   - Bleeding into core and/or fat embolism



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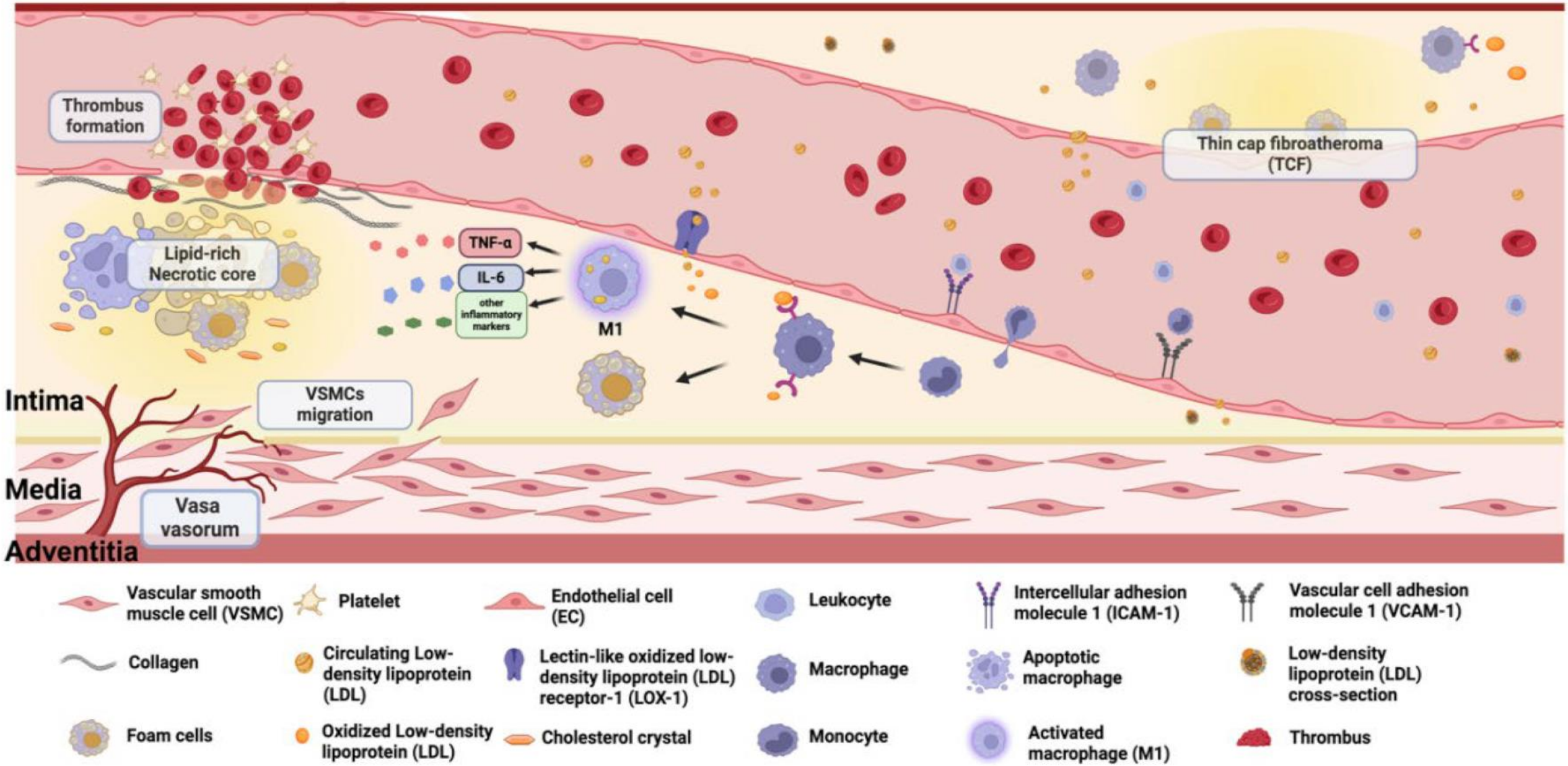

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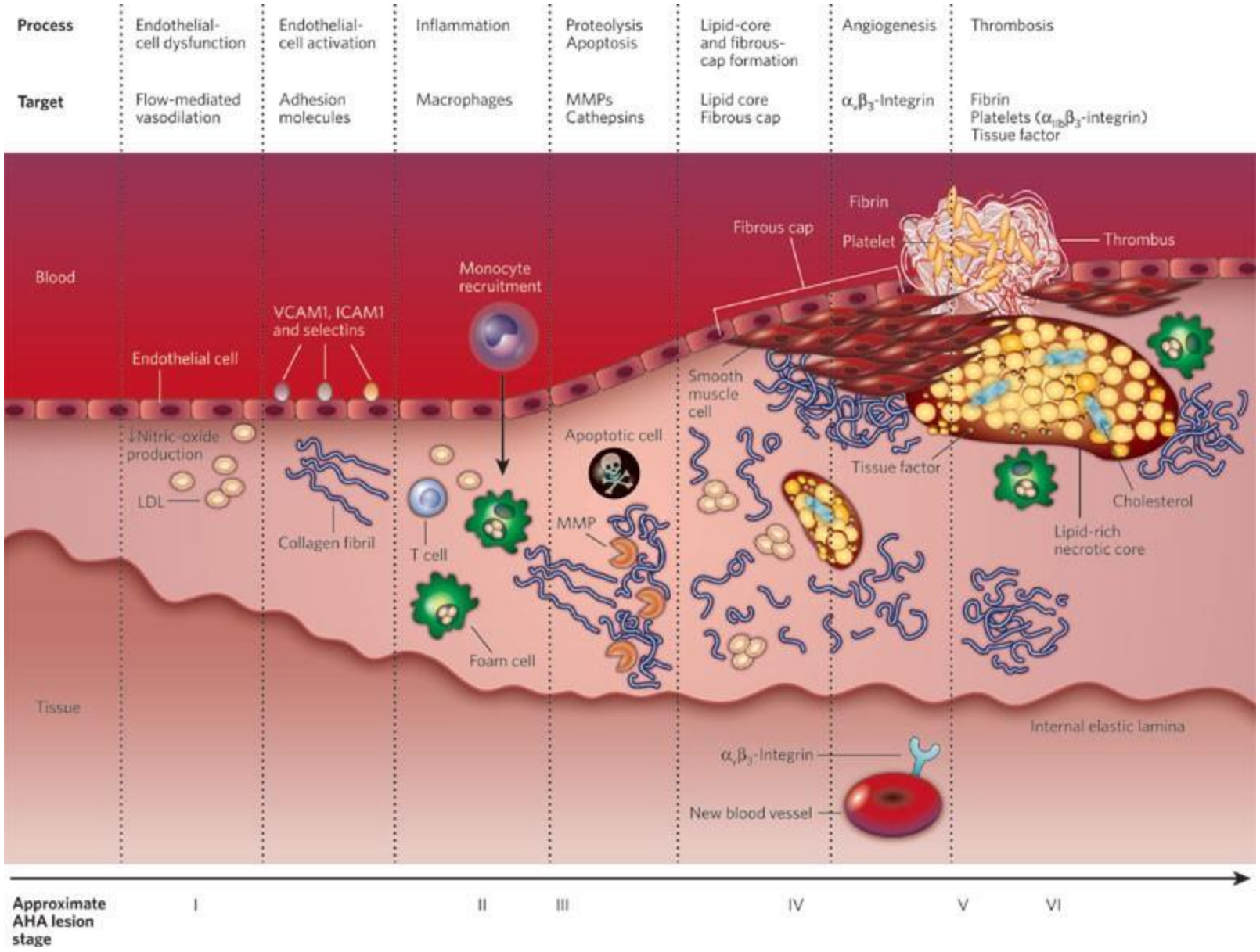

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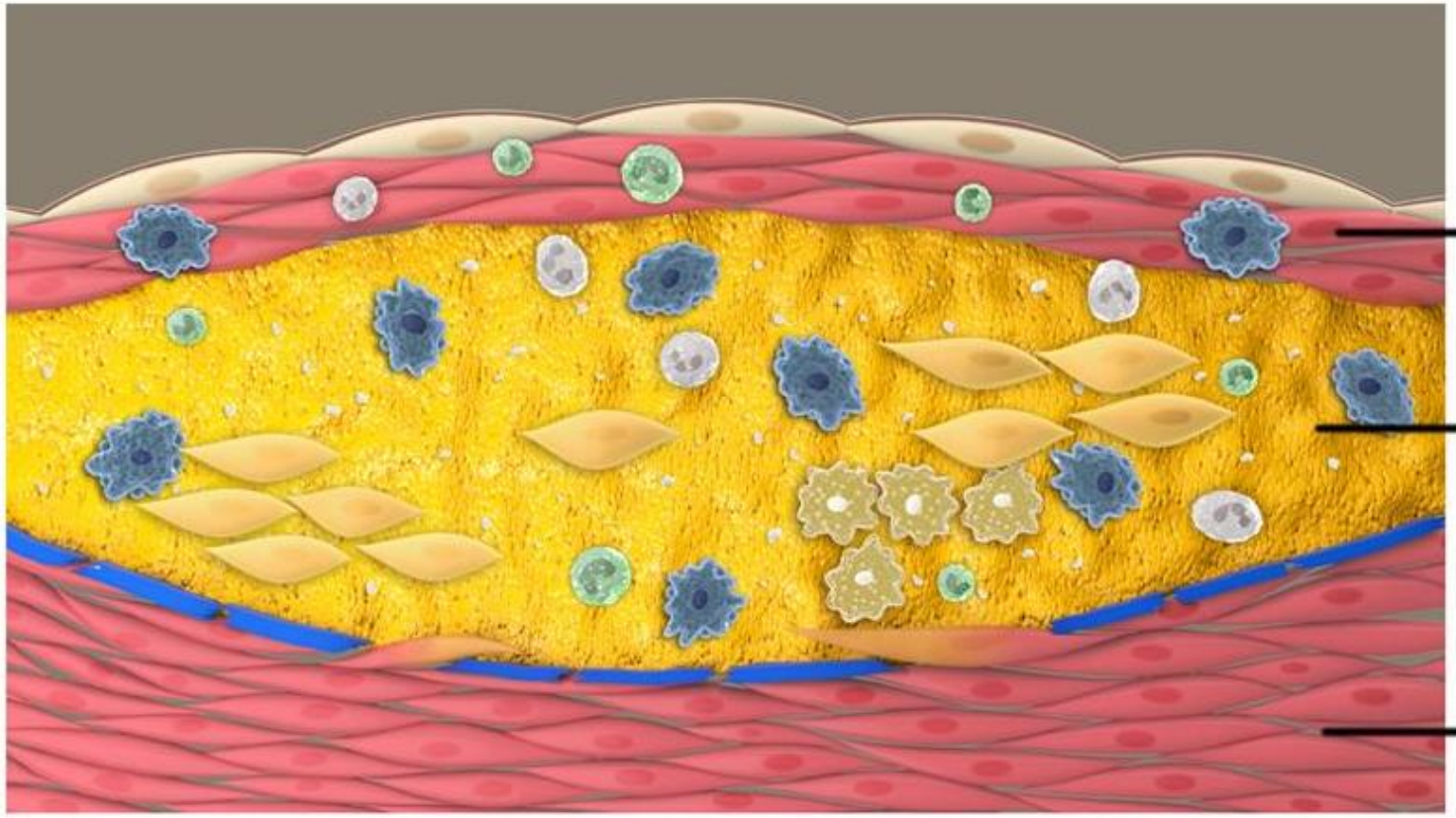
Atherosclerotic plaque



Fibrous Cap
- Smooth muscle cells
- Macrophages
- Lymphocytes
- Collagen

Necrotic Center
- Smooth muscle cells
- Macrophages
- Foam cells
- Lymphocytes
- Cholesterol crystals
- Calcium
- Cell debris

Media
- Smooth muscle cells

https://upload.medbullets.com/topic/108038/images/041218xwstep1cardasplaque_anatomy.jpg

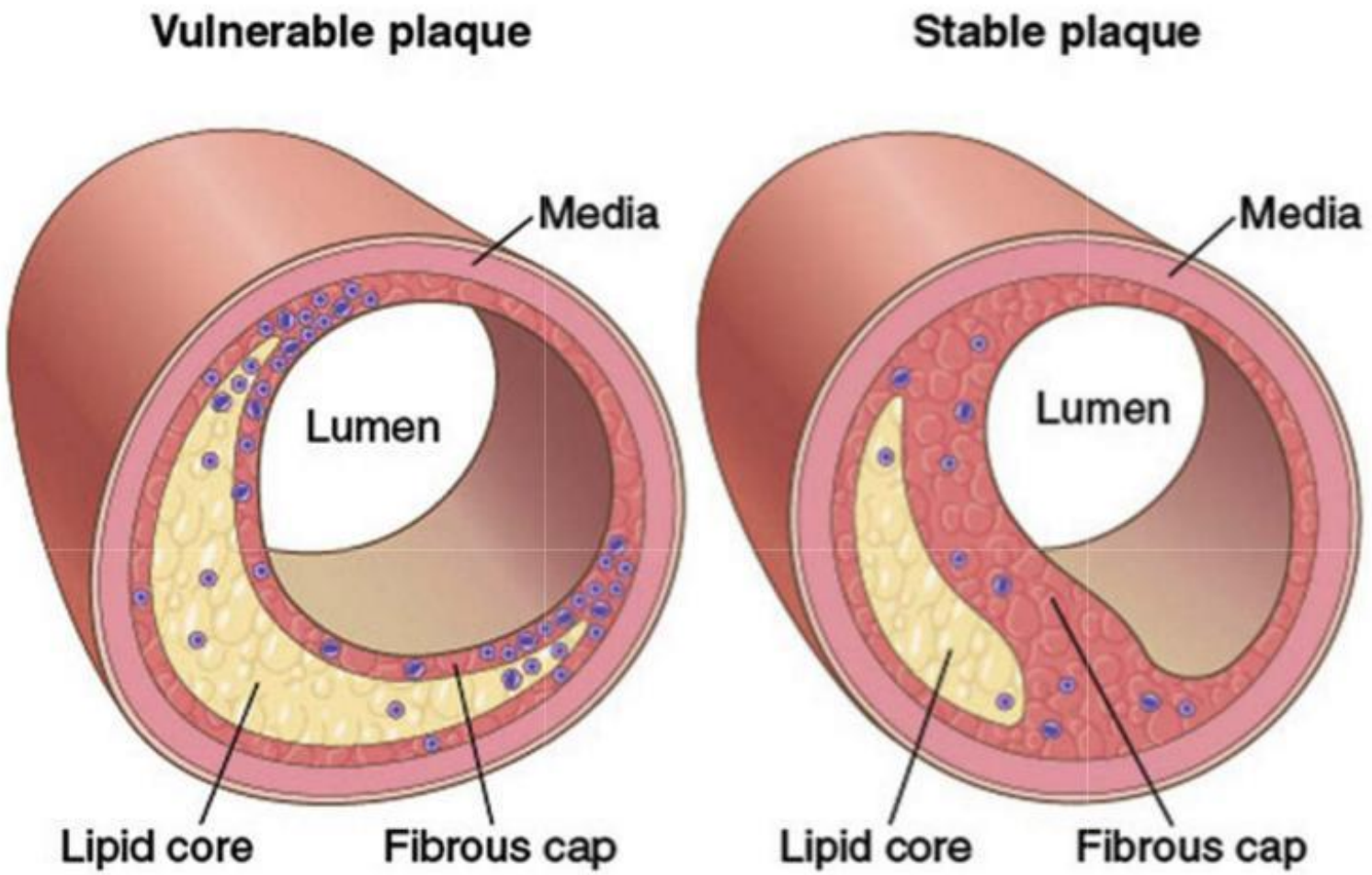
Stable and unstable plaque

STABLE LESION

- Fibrous cap
  - Thick
- Lipid core
  - Small
  - Usually single core
- Immune reaction and inflammation
  - Macrophages emigration
  - „Low-grade“ intensity
  - M2 macrophages preferred

UNSTABLE LESION

- Fibrous cap
  - Thin
- Lipid core
  - Large
  - Multiple cores possible
- Immune reaction and inflammation
  - Macrophages retention
  - Neutrophiles attracted -> NETs formations
  - M1 macrophages phenotype preferred
- Prone to rupture, thrombosis, embolism



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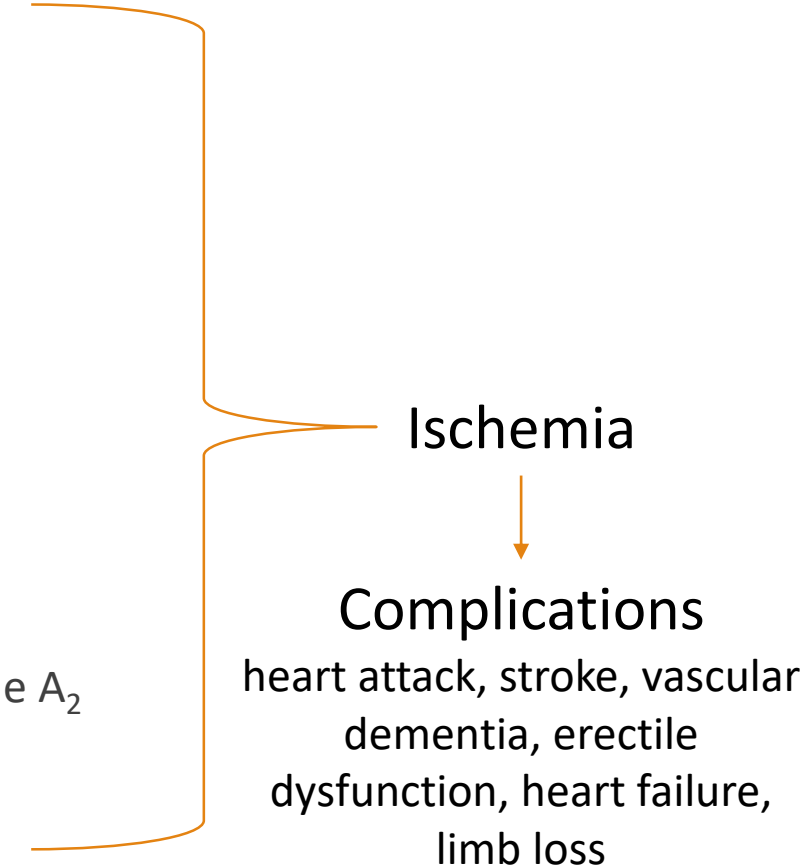
Atherosclerosis possible consequences

1. Stenosis
   - Narrowing of blood vessel lumen
     - 60-70 % decrease -> manifestation during physical activity
     - >90 % decrease -> symptoms during resting conditions
   - Acute vs. chronic
2. Thrombosis
   - Rupture of plaque
   - Plaque erosion -> „white thrombus“
3. Vasoconstriction -> Vasospasm
   - Decrease in NO synthesis
   - Constriction mediators prevail -> endothelin-1, thromboxane A_2
4. Plaque/lesion calcification



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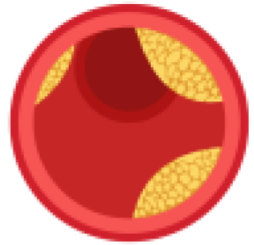
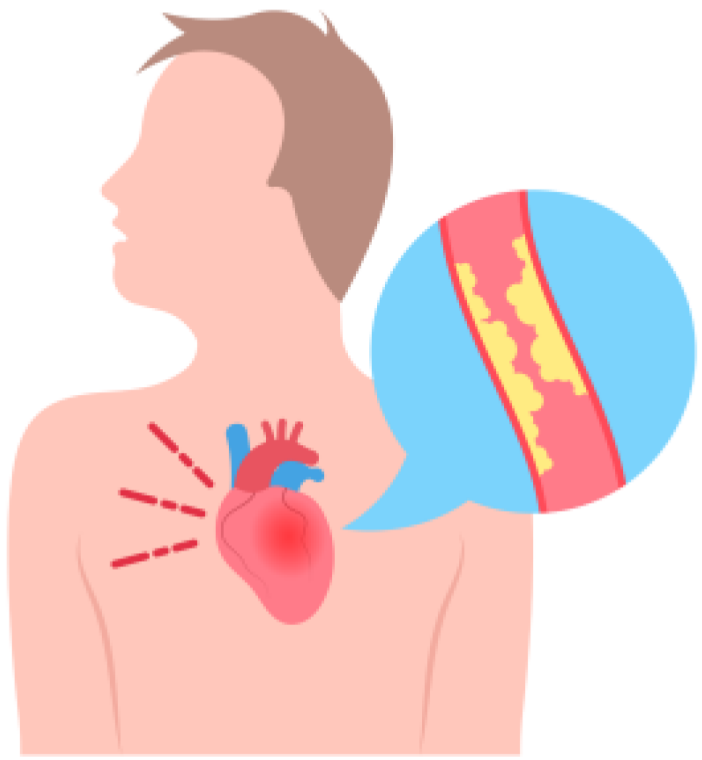
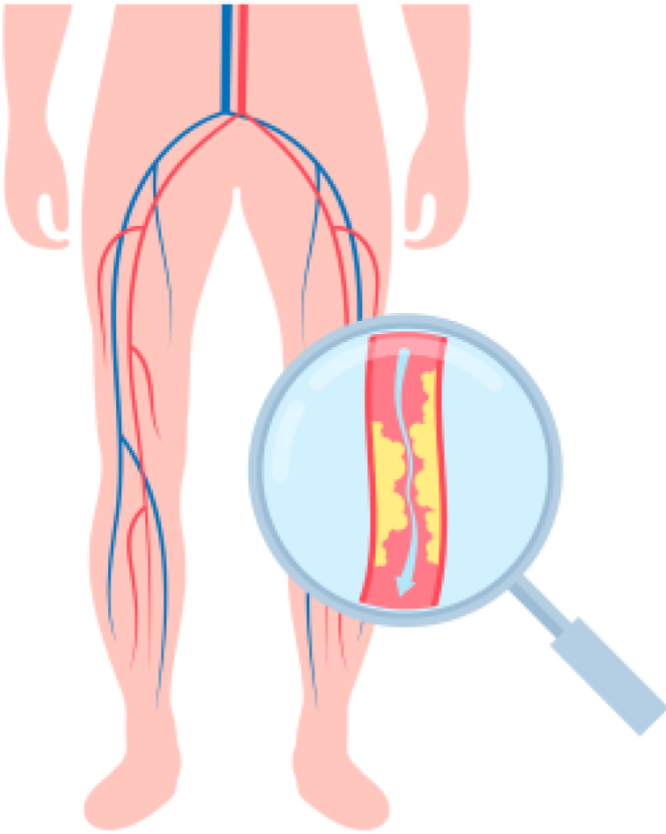
Atherosclerosis







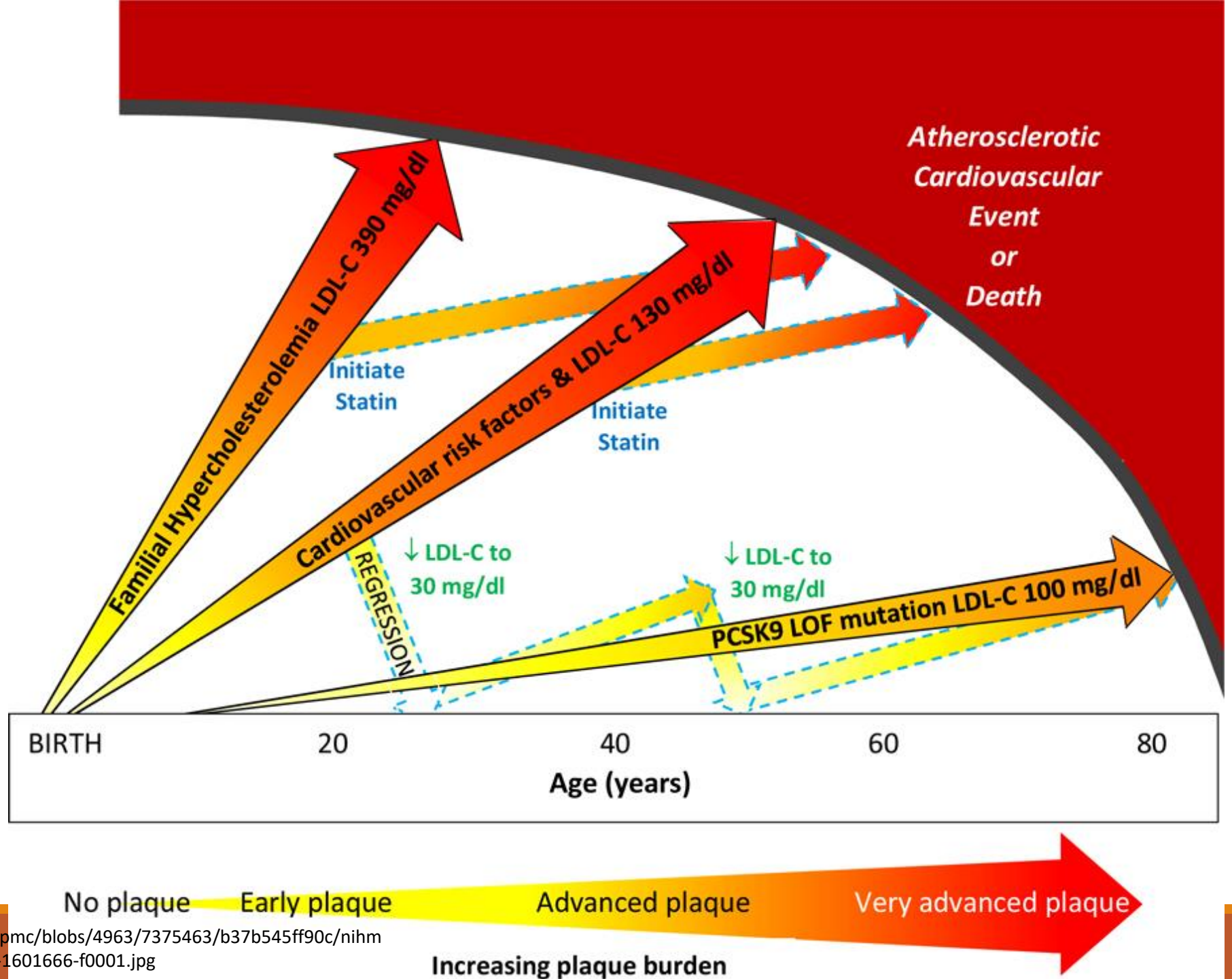
Carotid	Coronary	Lower extremities
STROKE TIA	ACUTE CORONARY SYNDROMES	INTERMITTENT CLAUDICATION

Can atherosclerosis be cured?

- Only reversible lesions can be reverted currently
- Advanced lesions are to be stabilised -> slowing of progression
  - JUPITER trial -> 7.7 % risk of cardiovascular events even with statins treatment in 10 years
  - IMPROVE IT -> 32.7 % risk (ezetimib (PCSK9 inhibitor) + simvastatin)
  - Probable complications of a residual plaque

- PCSK9 inhibitors -> LDL-c decrease in 50–60 %
- Statins – protective effect may last even 20 years (even discontinued) ->“legacy“ effect
- ApoB exposure as the most prominent factor for progress (HDL protective)
- Even advanced lesions may revert -> calcification is the limit?

Suggested reading: Wilkins, JT., Gidding, SS., Robinson, JG. Can Atherosclerosis Be Cured? *Curr Opin Lipidol*, 2020, 30 (6): 477–484 (https://pmc.ncbi.nlm.nih.gov/articles/PMC7375463/#S8)
Goldberg, IJ., Sharma, G., Fisher, EA. Atherosclerosis: Making a U Turn. *Annu Rev Med*, 2020, 71: 191–201 (https://pmc.ncbi.nlm.nih.gov/articles/PMC7112505/)



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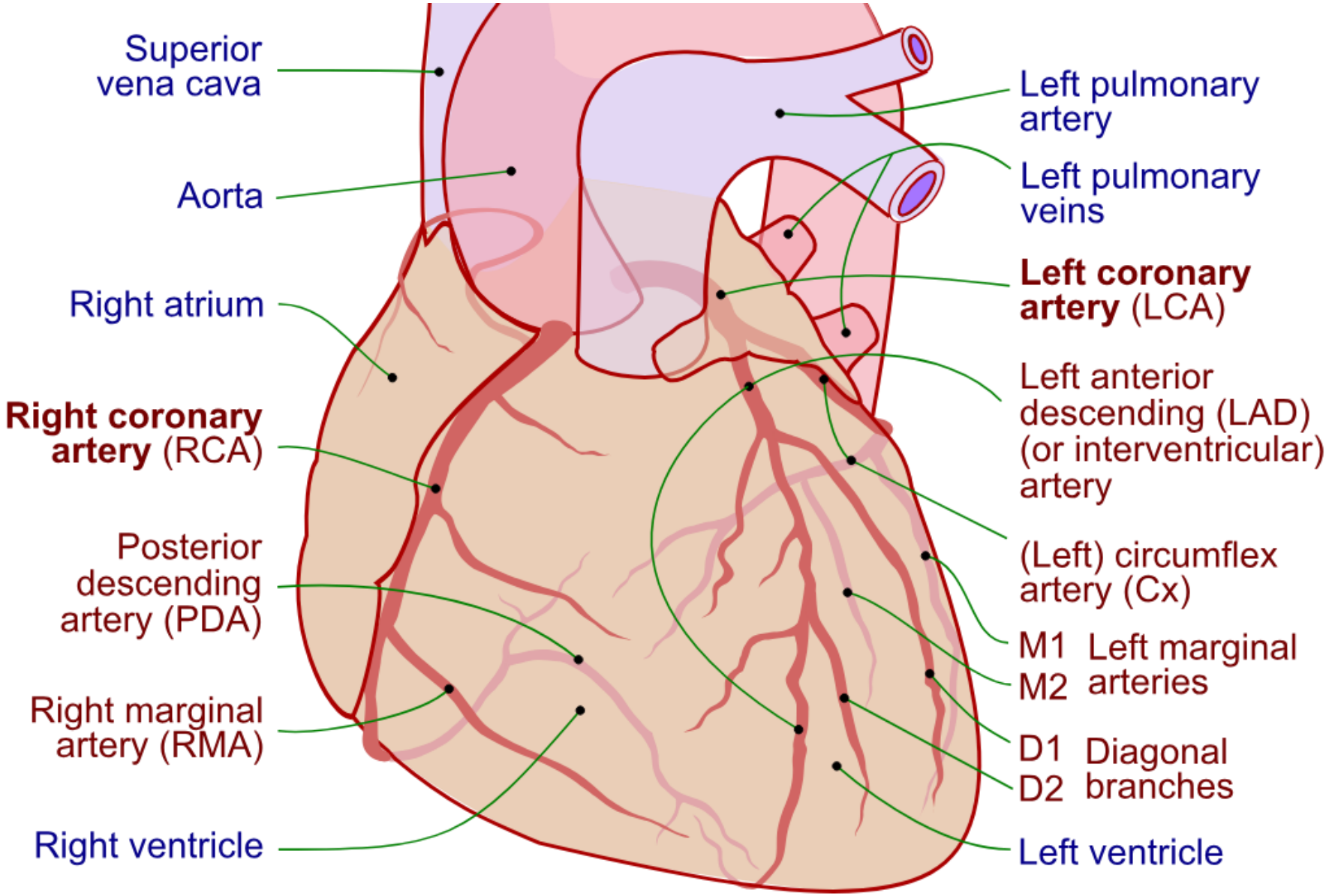
Coronary artery disease

CHRONIC FORMS, ACUTE CORONARY SYNDROME (ACS)

Coronary arteries characteristics

- An end type circulation
  - Minimal amount of anastomoses -> occlusion of an artery leads to tissue ischemia and a possible necrosis
- Aortal sinuses
  - Left posterior sinus -> left coronary artery
  - Anterior aortic sinus -> right coronary artery
- Coronary circulation is filled during diastole (systolic contraction compresses also coronary arteries)

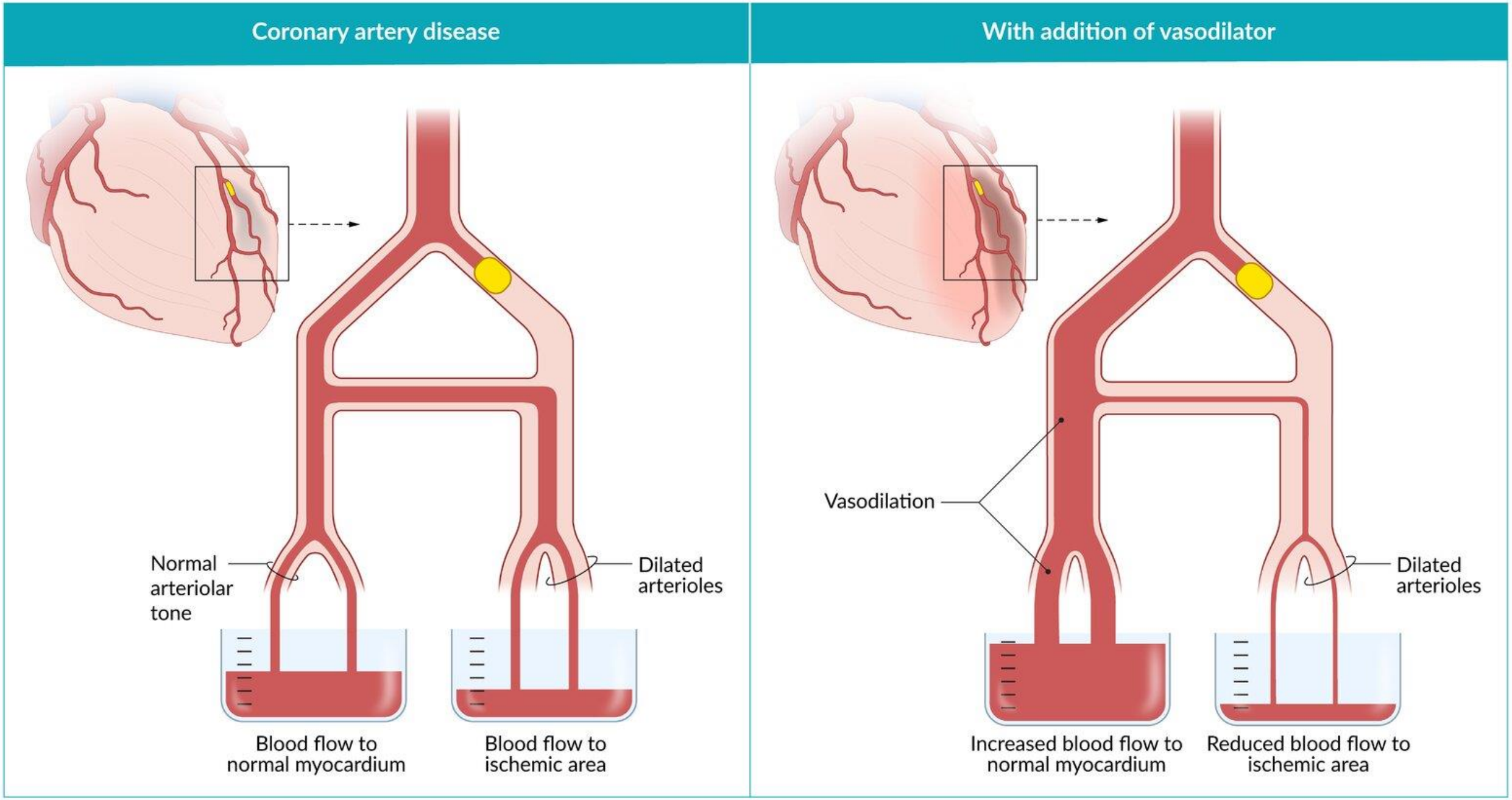


https://upload.wikimedia.org/wikipedia/commons/1/18/Coronary_arteries.svg

Causes and consequences of coronary arteries stenosis

- Causes of coronary arteries stenosis
  - Enhanced atherosclerosis
  - Vasospasm (e.g. Prinzmetal angina pectoris)
- Occlusion/constriction –> vasodilation mediators released (e.g. NO) ->
  - Back-up vessels vasodilatation + increased oxygen demands -> deterioration of oxygen reserves
- Steal phenomenon – blood redirected to dilatated vessels
  - Enhanced ischemia of the affected region

- >60-70 % occlusion – clinically significant during exercise
- >90 % occlusion – symptoms appear even during the resting condition



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Endothelial dysfunction in coronary artery disease

- Atherosclerosis -> endothelial dysfunction
  - ↓NO synthesis -> ↓vasodilation
  - ↓relaxation of smooth muscle cells
- Vasoconstriction -> vasospasm
  - Thromboxane A2, serotonin, endothelin-1
- Steal phenomenon -> blood redirection to unaffected circulation
  - Enhanced during physical activity
- Consequence -> ↓ATP in cardiomyocytes -> early changes (ion dysbalance, contractibility disorders)
  - Irreversible changes after approximately 20 minutes of ischemia/hypoxia

Energy myocardial metabolism during oxygen shortage

- GENERAL CHARACTERISTICS
- Increased amount of mitochondrias
  - Approximately 1/3 of myocardial mass
  - Higher amount of cytochroms than other tissues
- Main source of energy – β-oxidation
  - Fatty acids are the main substrate for oxidative phosphorylation (approx. 40–44 ATPs per one fatty acid)
  - Constant oxygen supply necessary!
- Glucose and glycogene are additional substances for metabolism

- OXYGEN SHORTAGE (FETAL MYOCARDIUM)
- Limited ability to perform anaerobic glycolysis (approx. 2 ATPs per glucose molecule)
  - Result – glycogenolysis, creatin phosphate degradation, lactate accumulation

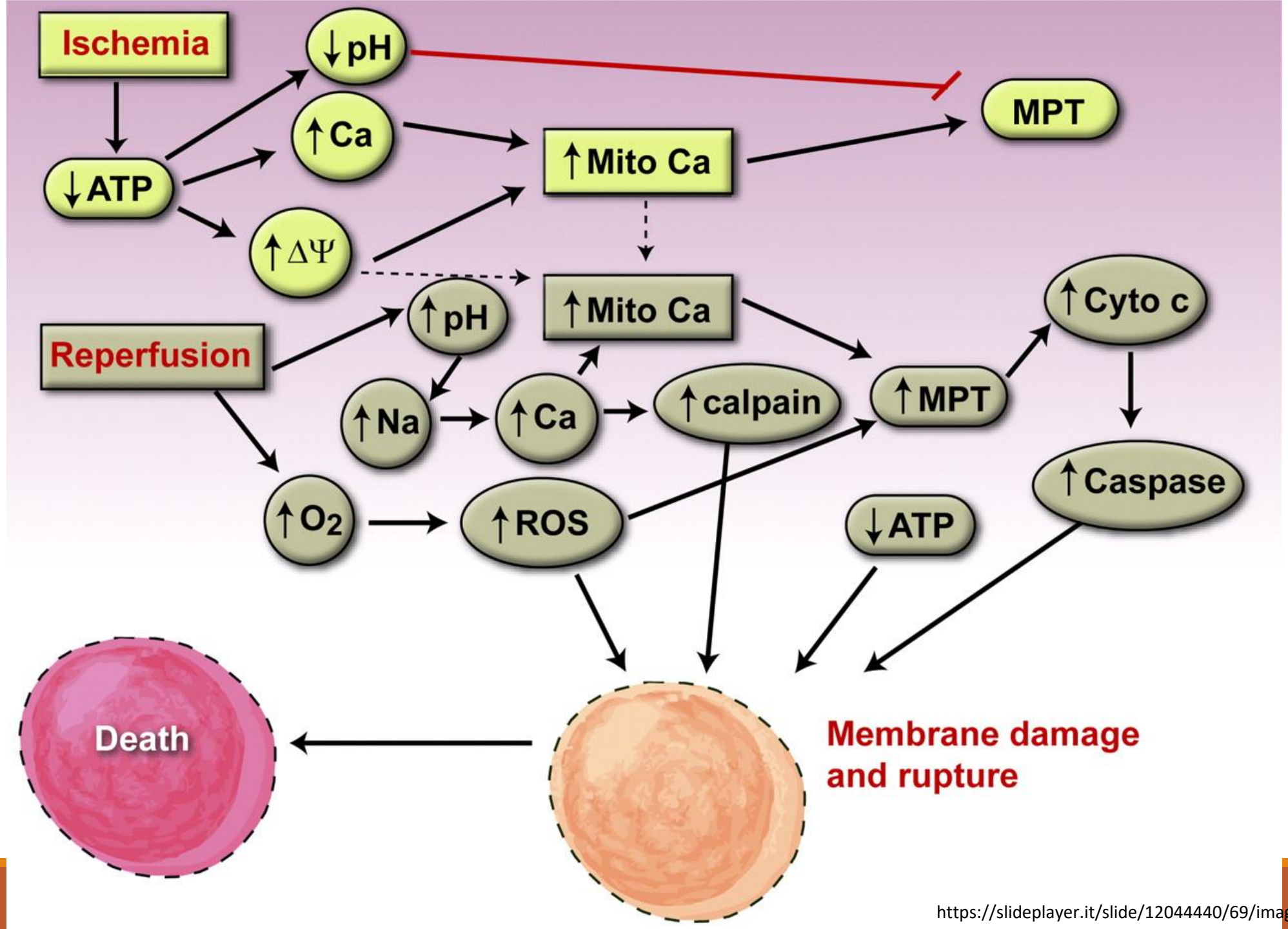
Ischemia and its consequences

- ↓ATP -> early changes in 6-10 seconds
  - Ion pumps dysfunction (Na^+/K^+-ATPase)
    - Intracellular K^+ loss -> microcurrents generation („Pardee wave“), arrhythmia prone
    - Na^+ accumulation in cell -> cellular swelling
  - Intracellular Ca^{2+} overload
    - Ion exchanges to counter Na^+ overload -> Ca^{2+} mobilisation from sarcoplasmic reticulum
    - ↑Ca^{2+} >10 µmol/l -> ryanodine receptors activated -> efflux of Ca^{2+} from sarcoplasmic reticulum to cytosol -> activation of proteases e.g. calpain
    - CAVE! – Ca^{2+}-induced-Ca^{2+}-overload in reperfusion!
  - Contractibility disorders (actin-myosin complex dysfunction)
    - Diastolic relaxation impaired
    - Hypokinesis, akinesis or dyskinesis
    - Decreased response per Frank-Starling mechanism („increased end-diastolic volume -> stronger contraction“ mechanism broken)

Ischemia and its consequences

- Anaerobic metabolism
  - Anaerobic glycolysis -> 2 ATPs generated
  - Pyruvate -> lactate -> intracellular acidosis (protective against cell death types)
  - ↑lactate, adenosin, serotonin -> anginous pain
    - C7 – Th4 irritation -> retrosternal pain may start to „irradiate“
- Von Hippel-Lindau (VHL) and hypoxia inducible factor (Hif) response
  - Abundance of oxygen -> modification of VHL protein -> blockade of Hif-1α -> „EVERYTHING IS OKAY!“
  - ↓oxygen -> VHL not modified -> Hif-1α and Hif-1β dimerisation -> HRE triggered
    - VEGF produces -> collateral vessels formation (mild and/or chronic ischemia)
    - Xanthine dehydrogenase to xanthine oxidase -> ROS generated druing reperfusion

HRE – hypoxia responsible elements



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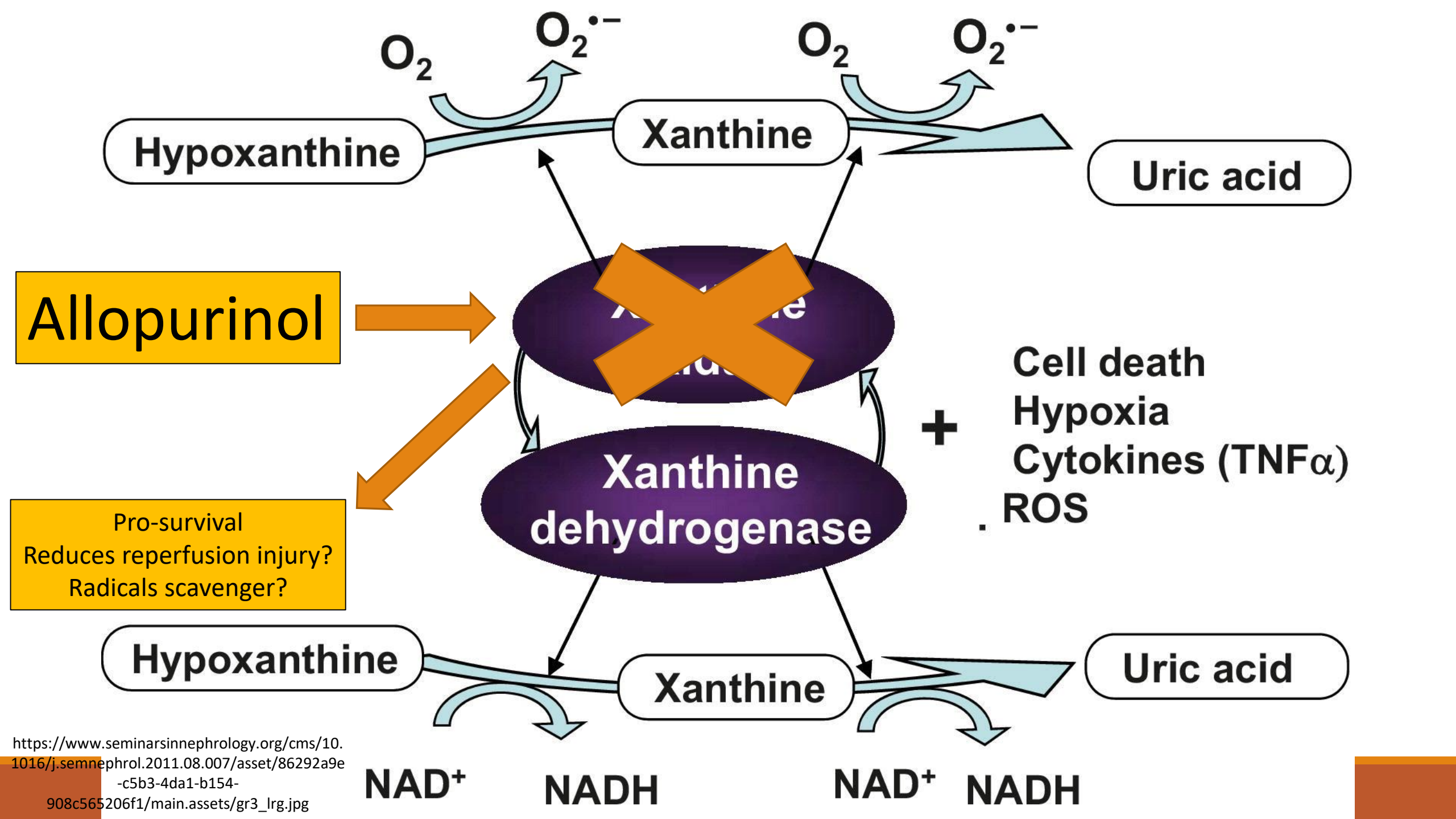

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General consequences of myocardial ischemia

- Decreased ejection fraction
  - Lower pulse volume
  - Increased end-diastolic pressure in ventricle
    - Increased venous pressure – body, lungs

Susceptibility to arrhythmias

- Danger of ventricular fibrillation (15 mins to defibrillate or cardiac arrest)

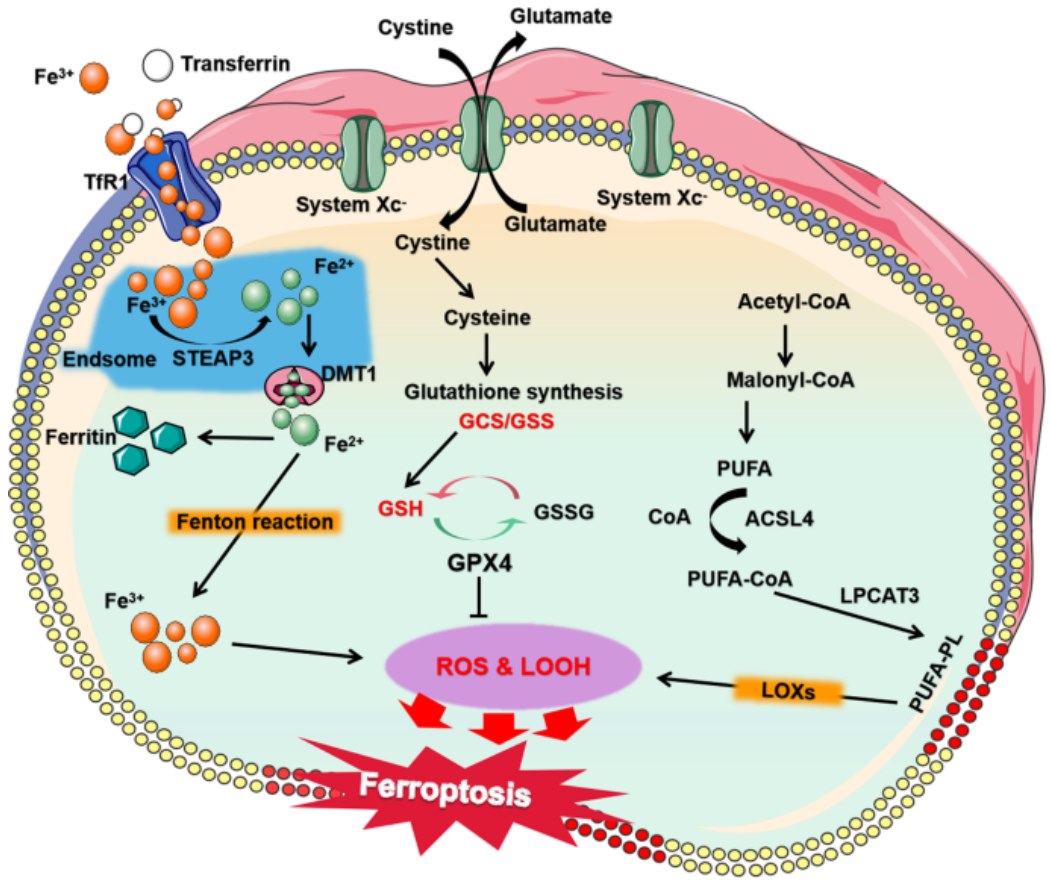
- Cardiogenic shock threat – more than 40 % of myocard disabled

General consequences of myocardial ischemia

- Diastolic pressure increased in the left ventricle
  - Pulmonal hyperemia, deterioration of ventilation, dyspnoe, rumbles
- Stronger contractibility of the left ventricle
  - Another hear beat auscultable (S4) – „atrial gallop“
- Papillary muscles dysfunction
  - Transient or permanent mitral regurgitation -> possible volume overload -> eccentric hypertrophy imminent -> permanent systolic dysfunction

Ferroptosis in cardiac injury

- Cell death type manifested by Fe^{2+} overload or glutathion peroxidase 4 inactivation
- Marked by
  - ROS generation via Fenton reaction
  - Membrane lipid peroxidation
  - Dense mitochondrias without cristae
- Primary type of cell death for cardiomyocytes in ischemic/reperfusion injury
- Ferroptotic cardiomyocytes produce
  - Pro-M2 cytokines -> macrophages to M2 cells
  - Pro-angiogenic factors e.g. VEGF
- Ferroptosis suppression improves cardiac injury consequences, though mechanisms remain uknown



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Myocardial changes according to the length of ischemia

1. Adaptation – preconditioning
2. „Stunned“ myocardium
3. „Hibernating“ myocardium
4. No-reflow phenomenon
5. Acute myocardial infarction -> acute coronary syndrome

Adaptation – „preconditioning“

- Short hypoxia enable better survivability of longer ischemia when followed by reperfusion
  - 10–40 minutes of ischemia
- Classification
  - Early (2–3 hours) – cell death prevention
  - Late (3–4 days) – significant for clinical outcome
    - Cells may undergo stunning or hibernation
- Goals
  - ATP concentration is maintained longer – prevents arrhythmias
  - Ca^{2+} overload prevention and ROS generation decreased
- Metabolical changes
- Capillary adaptation – dense network of collaterals

„Stunned“ myocardium

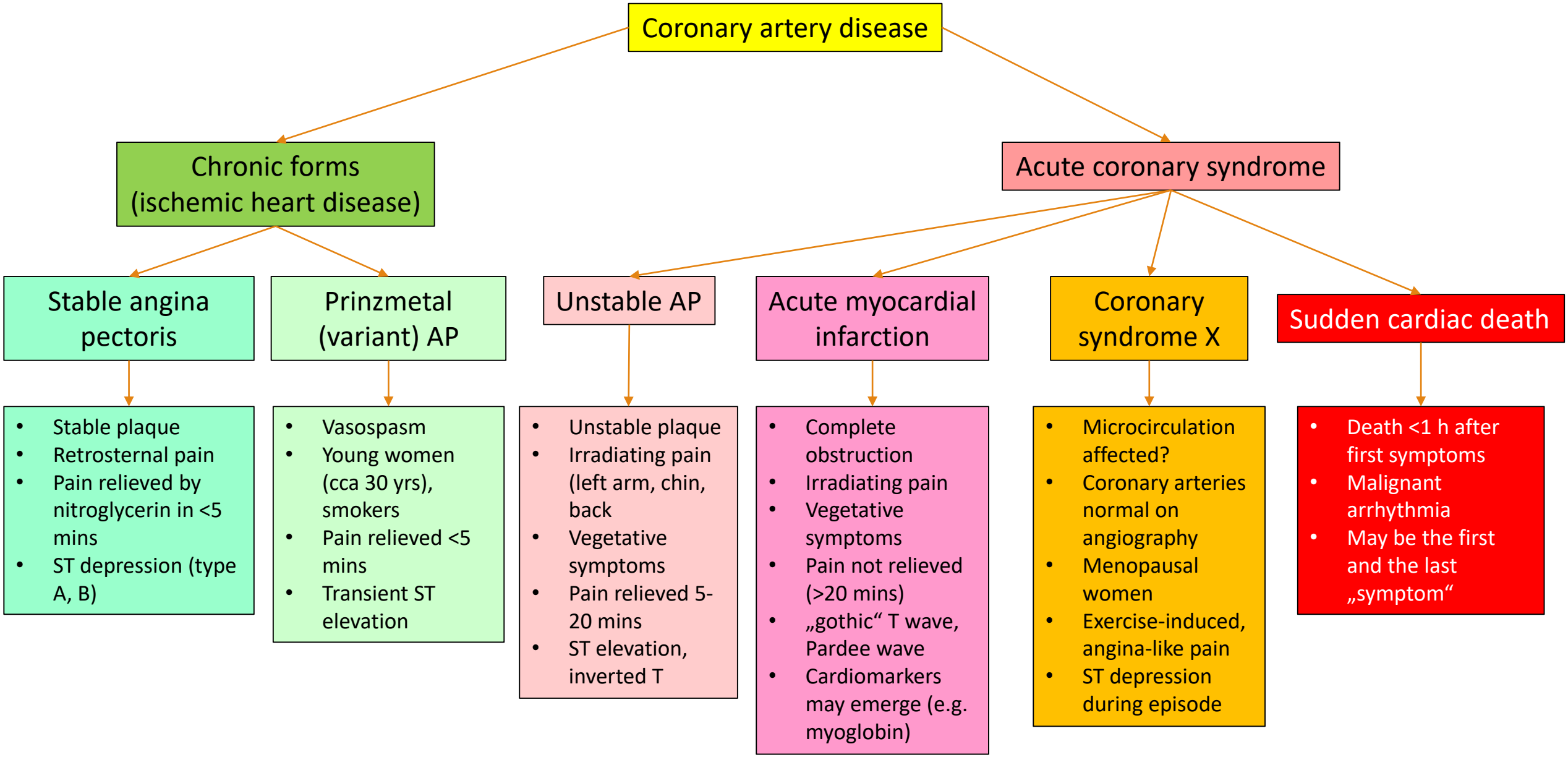
- After transient hypoxia, perfusion restored – fully reversible changes
- Decrease of ATP, Ca^{2+} overload (mediated by Ca^{2+}-ATPase/SERCA and RyR2)
  - Conductibility and contractility changes
- Temporary disorder of ATP utilisation after reperfusion (may last days)
- Fully reversible
- After reperfusion – Ca^{2+} concentration get lower
  - CAVE! – Ca^{2+}-índuced-Ca^{2+} overload (Ca^{2+} paradox) during reperfusion possible

„Hibernating“ myocardium

- After chronic hypoxia – moderate or repeated non-lethal ischemia
  - Decreased mRNA expression, damage to contractile and cytoskeletal proteins
  - ↓myocardial phosphates, ↓myofibrils response to Ca^{2+}
  - Anaerobic metabolism preferred
- Lowered contractibility and diastolic relaxation
  - Gets better after by-pass – partial recovery possible
- Structural changes – patophysiology unclear
  - Cumulative hypoxia, reperfusion injury – Exercise? Stress?

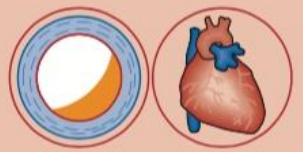
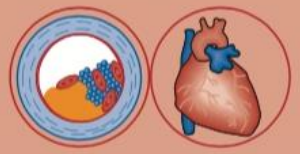
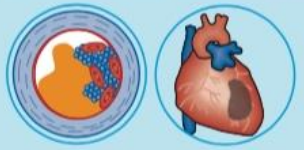
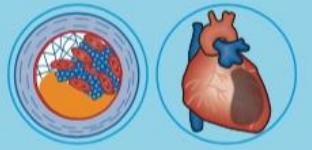
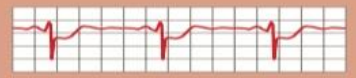
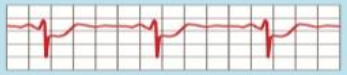
No-reflow phenomenon

- Rare condition occuring after ischemia during reperfusion period
- Incomplete and uneven reperfusion of microcirculation despite re-opening of coronary artery
- Frequency – cca 0.6-3.2 % of percutaneous coronary interventions
- Pathomechanism
  - Cumulative effect of endothelial injury, leukocyte plugging and mechanical compression
    - Endothelial injury intensified by acute inflammatory response, ROS generation, intracellular Ca^{2+} overload
    - Myocytes swelling -> mechanical compression of microcirculation
- Observed in subendocardial layer -> may progress to subepicardium
- Compromised tissue perfusion -> „stabilisation“ of necrosis
  - Necrosis has a tendency to „grow“ – combination of cell debris and factors from cytoplasm + impaired perfusion


Coronary artery disease
Chronic forms (ischemic heart disease)
Acute coronary syndrome
Stable angina pectoris
Prinzmetal (variant) AP
Unstable AP
Acute myocardial infarction
Coronary syndrome X
Sudden cardiac death
• Stable plaque
• Retrosternal pain
• Pain relieved by nitroglycerin in <5 mins
• ST depression (type A, B)
• Vasospasm
• Young women (cca 30 yrs), smokers
• Pain relieved <5 mins
• Transient ST elevation
• Unstable plaque
• Irradiating pain (left arm, chin, back
• Vegetative symptoms
• Pain relieved 5-20 mins
• ST elevation, inverted T
• Complete obstruction
• Irradiating pain
• Vegetative symptoms
• Pain not relieved (>20 mins)
• „gothic“ T wave, Pardee wave
• Cardiomarkers may emerge (e.g. myoglobin)
• Microcirculation affected?
• Coronary arteries normal on angiography
• Menopausal women
• Exercise-induced, angina-like pain
• ST depression during episode
• Death <1 h after first symptoms
• Malignant arrhythmia
• May be the first and the last „symptom“

The British Journal of Primary Care Nursing

BACK TO BASICS: RECOGNISING DIFFERENT TYPES OF CORONARY ARTERY DISEASE 1

KEY FACTORS	STABLE DISEASE	UNSTABLE DISEASE (including acute coronary syndrome, unstable angina and myocardial infarction)		
WHAT TYPE OF CORONARY ARTERY DISEASE?	Stable angina 	Unstable angina 	Type 1: Non-ST elevation MI 	Type 1: ST elevation MI 
Pathophysiology	• Stable atheromatous plaque narrows the lumen • Oxygen demand exceeds supply during exertion or emotion	• Plaque becomes **unstable and ruptures** • Bleeding & thrombus causes **partial occlusion** • Clot/plaque micro-emboli block smaller arteries downstream	• Thrombus causes **intermittent occlusion** • Blood and oxygen supply reduced	• Thrombus causes **complete occlusion**
Myocyte damage and blood markers	• No myocyte damage • Blood troponin (Tn) levels normal	• Minimal myocyte damage • Tn usually normal but may be slightly raised	• Myocytes deprived of oxygen for more than 20 minutes die off, releasing Tn into the blood. Tn reaches a peak level at 12h and stays elevated for up to 14 days	
Symptoms	Angina - constricting central chest pain/ discomfort brought on by physical exertion & relieved quickly by rest or GTN	Angina at rest or on minimal exertion, is prolonged or only short-lived relief with GTN	Prolonged heavy central chest pain, which may spread to the throat, jaw, arms and back. Associated with pallor and sweating, breathlessness, nausea and vomiting and not relieved by rest or GTN	
ECG	 • Normal at rest • ST depression on exertion	 • Normal or non-specific changes • ST depression, T wave inversion	• Normal or abnormal  • ST segment depression and T wave inversion • No ST segment elevation	• Abnormal • ST segment elevation or development of new LBBB 
A normal ECG does not exclude myocardial infarction				
What do I do?	• Refer to RACPC or cardiology OP for further assessment • Identify risk factors: HBP, DM, high cholesterol, smoking, family history	• Admit to hospital via 999 • Perform 12-lead ECG and fax ahead – but do not let this delay transfer to hospital • Give aspirin 300 mg stat. Consider GTN, morphine + anti-emetic and monitored oxygen (aim for O_2 sats 94-98%)		
Specialist treatment	Further tests such as CT or catheter coronary angiography, stress testing or nuclear perfusion scans confirm the diagnosis and establish those who might benefit from revascularisation	• Those at high risk have angiography within 96 hrs +/-revascularisation by PCI +/- stenting • Those at low risk are treated conservatively		Key priority is to unblock the artery within 12 hours by: Primary PCI or thrombolysis with clot-busting drugs
5 types of myocardial infarction	• Type 1: MI associated with plaque rupture (STEMI & NSTEMI) • Type 2: MI secondary to other conditions *eg* hypotension, anaemia, arrhythmia, infection	• Type 3: MI with ECG changes but troponin levels not done • Type 4: MI during PCI • Type 5: MI during coronary bypass surgery		

https://www.issuesandanswers.org/wp-content/uploads/2020/02/88e646fa0b7c4b8b84105421119029fb.jpg

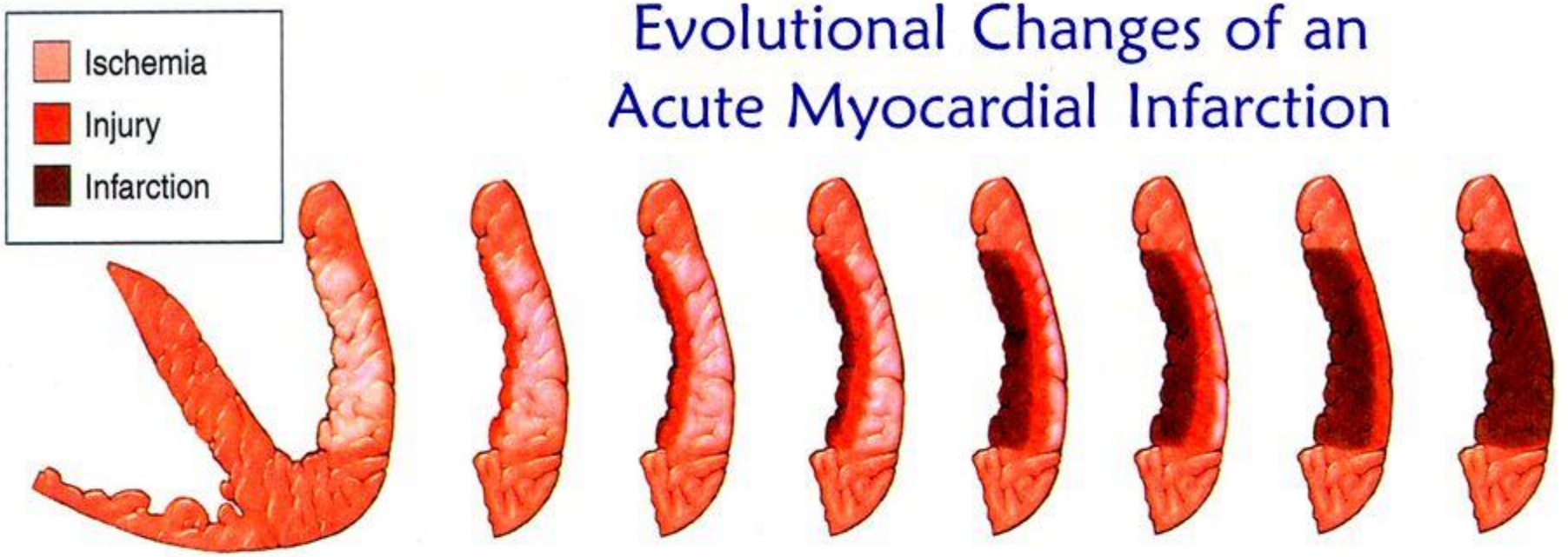
Acute myocardial infarction

- When perfusion interruption lasts longer than 20-40 minutes
  - Contractibility changes occur after 2 mins!
  - Apoptosis/Necrosis of cardiomyocytes – lack of oxygen, acidosis, waste metabolits

- Time course and macroscopic changes
  - 0-1 hrs – affected area is pale, slightly cyanotic
  - 4-12 hrs – swelling occurs
  - 4 hrs – neutrophile infiltration – reactive oxygen species damage
  - 18-36 hrs – purpure colours, coagulation necrosis
  - 48 hrs – gray colour
  - 8-10 days – resorption, scar formation begins
  - 2-3 months – scar complete (susceptible to rupture!)

A. Changes in Anatomy

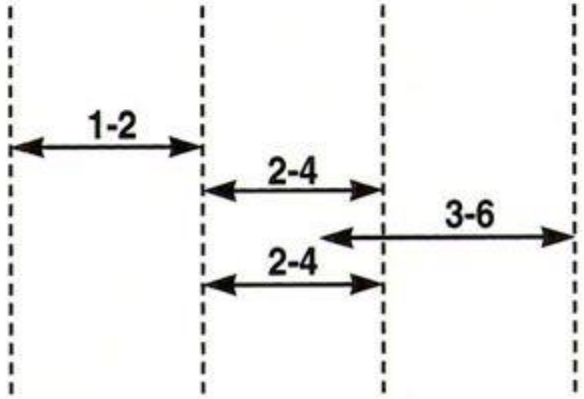
Evolutional Changes of an Acute Myocardial Infarction



Time after onset	Onset	<20-40 min	30 min	1 hour	2 hours	4 hours	6 hours	24 hours
Extent of infarction		0%	10%	30%	50%	70%	90%	100%

B. When Serum Markers Are First Detectable (Hours)

- Myoglobin
- Troponins
- CK-MB
- CK-MB isoforms

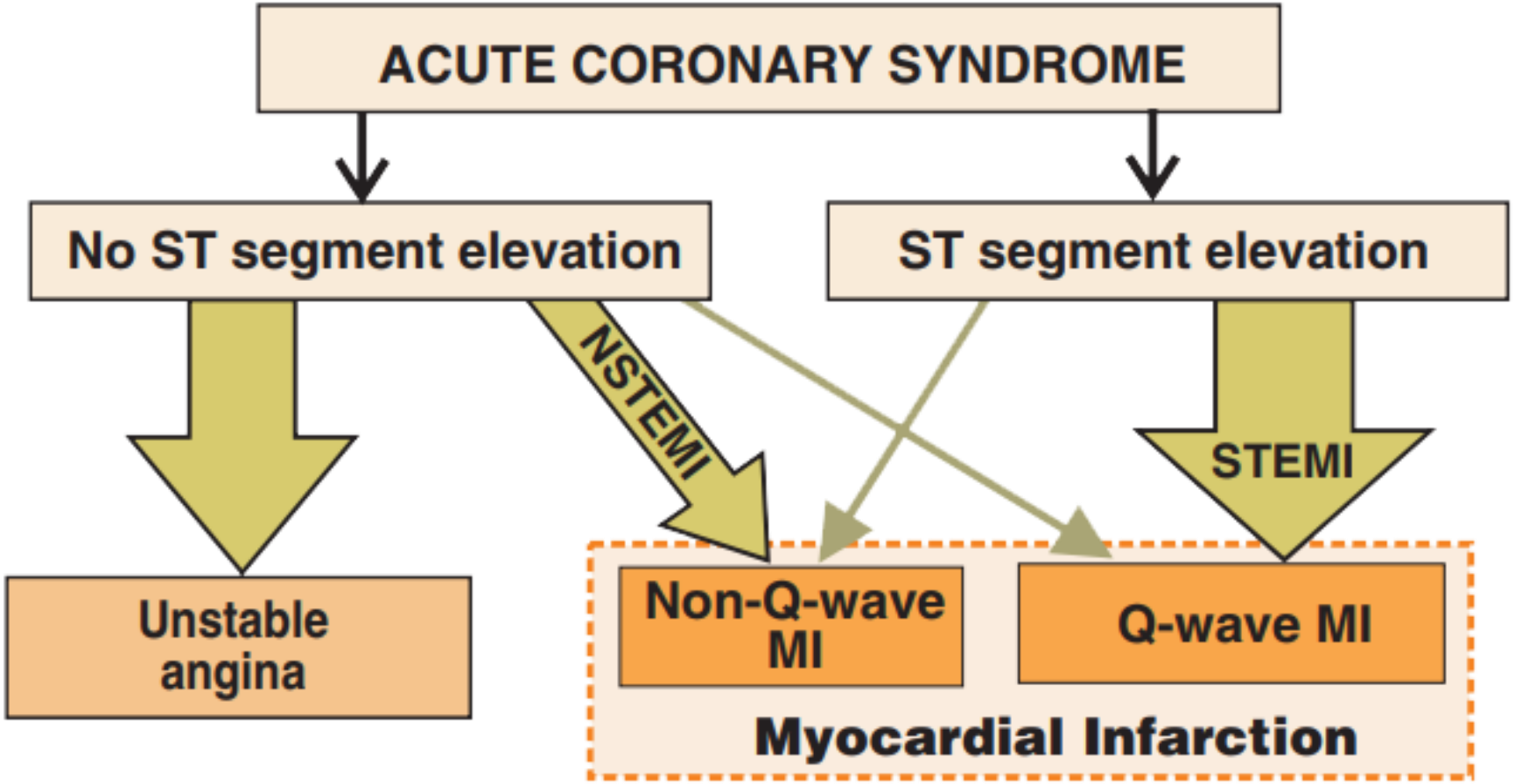


Predicted mechanism of ischemic injury leading to damage of myocardium

Lead change – intracellular Ca^{2+} increase

- Lack of ATP – Ca^{2+} changes -> enzyme activation – organells or cytoplasmatic membrane damaged
- Lactate + acidosis – Na^{+}/H^{+} and Na^{+}/Ca^{2+} pump affected – increase of Ca^{2+}
- K^{+} depletion – repolarisation affected
- Lowered metabolism of fatty acids – lack of ATP

Result is apoptosis or necrosis



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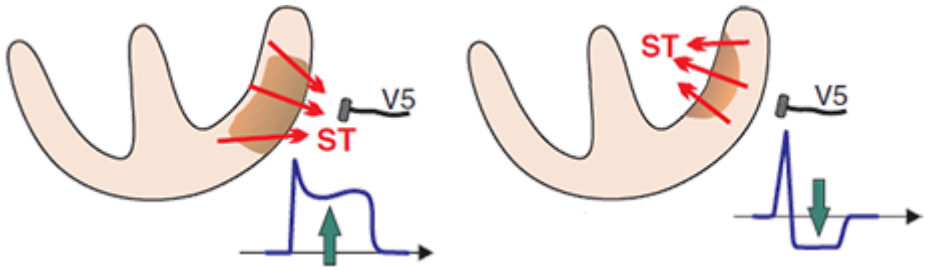
Parameter	ST elevations	ST depressions	
Mechanism	Occlusion	Stenosis	
Location	Subepicardial	Subendocardial	
Condition	STEMI	NSTEMI	Unstable AP
Necrosis	Yes	Yes	No
Necrosis type	Transmural	Subendocardial	N/A
Troponins release	Yes, after 3-8 hours	Yes, after 3-8 hours	No
Pathological Q	Yes	No	No



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https://www.ecgbook.com/ekg-kniha/obr/700AKS/NSTEMI-infarction.png

ECG changes during myocardial infarction

Early potential – permanent depolarisation - electric currents affecting healthy myocardium

- Denivelisation of the whole segment (except Q-T)

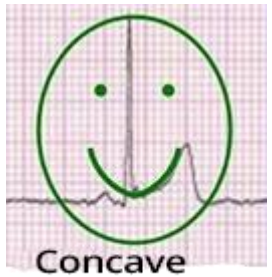
„Electric heart window“

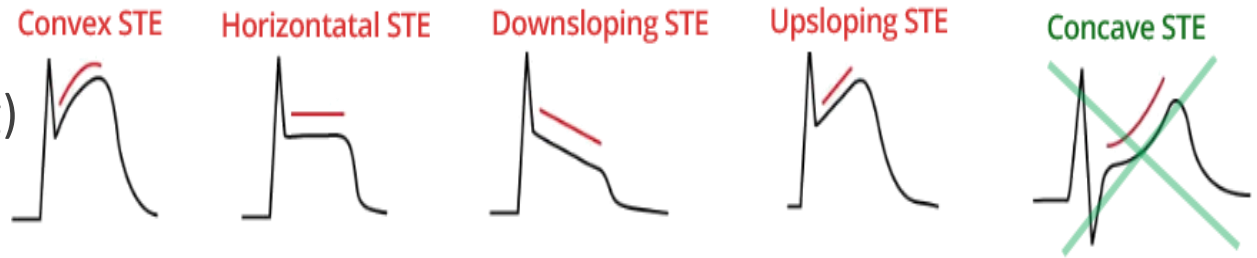
- Electrode sees „through“ the damaged area
- Q changes - >0.04 s, deeper than ¼ of R spike, or QS complex (no R) – changes are permanent!
- Depolarisation changes – Q spike pathological!

ECG alterations during MI

ST ELEVATIONS

- Need to be present in at least 2 leads
- Typical for acute and subacute STEMI
- Types
  - Convex (frowny)
  - Horizontal
  - Rarely descending or ascending
- STEMI never creating concave (smiling) elevations





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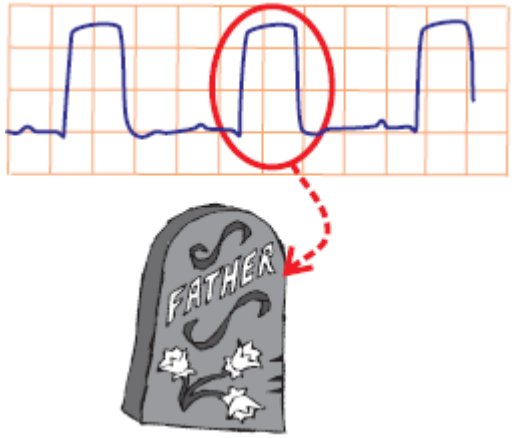
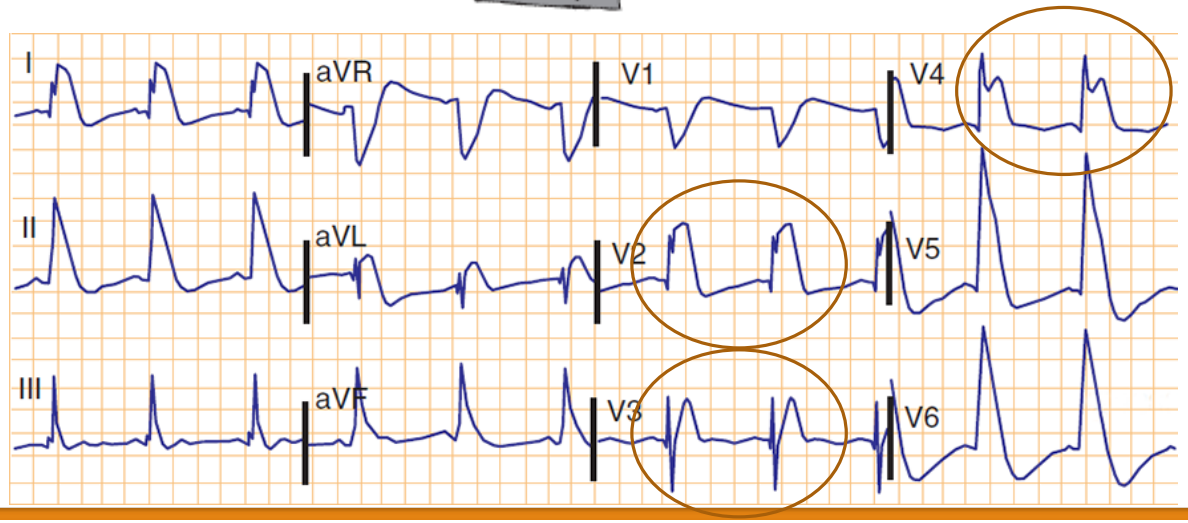
https://www.ecgbook.com/ekg-kniha/obr/700STEMI/characteristics-ischemic-ST-elevations.png

ECG alterations during MI

PARDEE WAVE

- Very high elevation of ST segment
- „Tombstoning“ -> connecting R and T waves
- Due to proximal obstruction -> huge MI area
- Signalizing poor prognosis
  - „Tombstoning STEMI“
- Typical in acute stage





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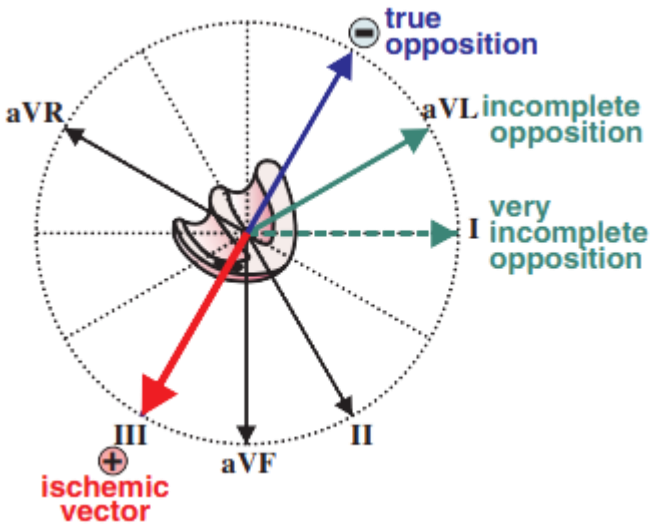


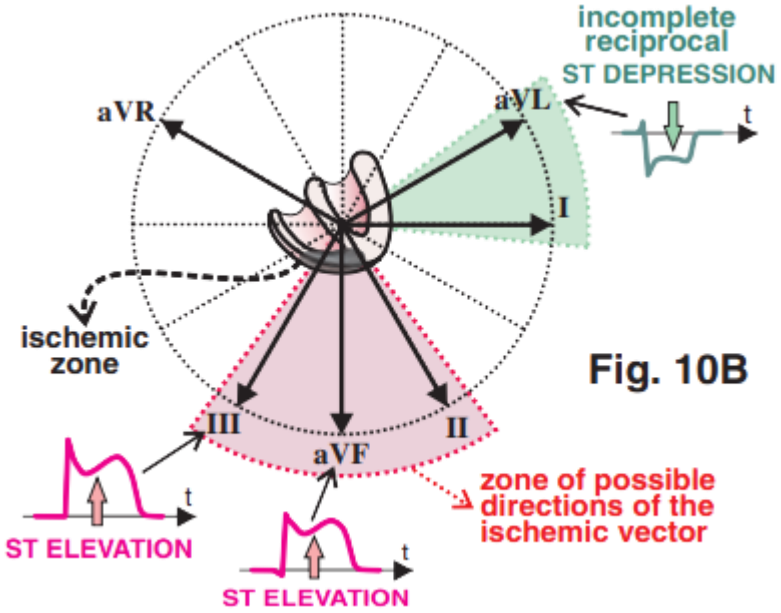
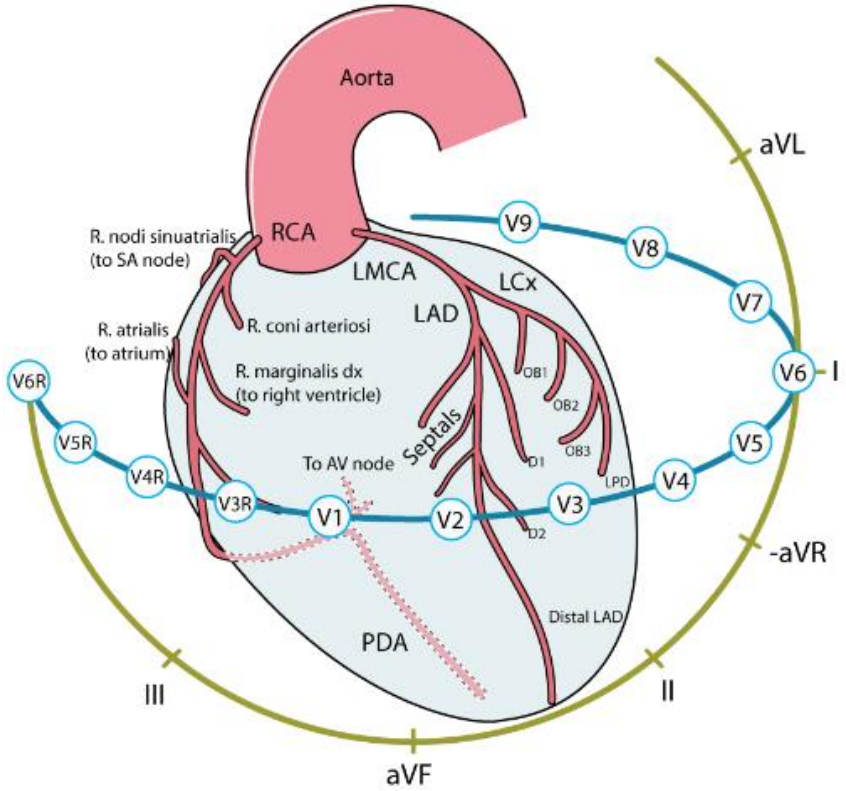


Fig. 10B



RCA = Right coronary artery
PDA = Posterior descending artery

LMCA = Left main coronary artery
LAD = Left anterior descending artery
D = Diagonal branches (D1, D2)
Septals = Septal branches
LCx = left circumflex artery
OB = Obtuse marginals (OB1, OB2, OB3)
LPD = Left posterior descending artery

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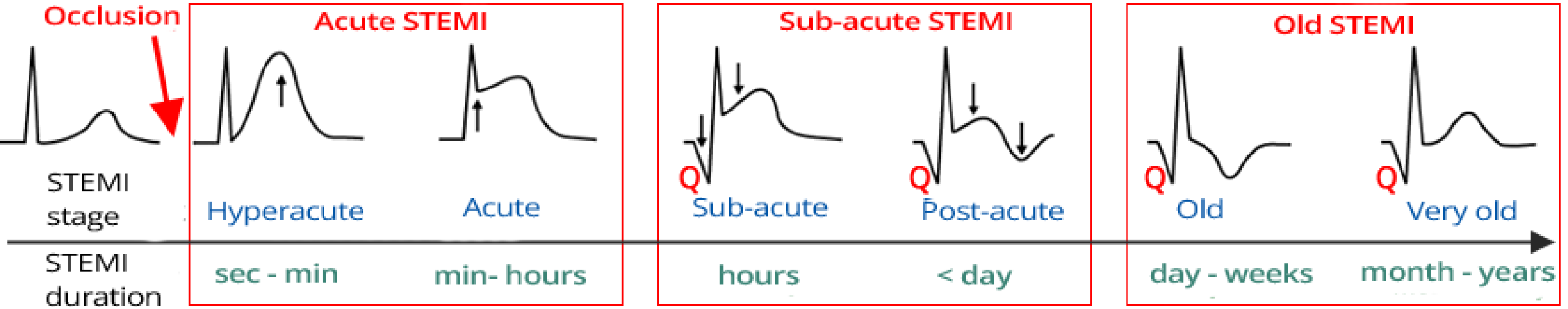
https://www.ecgbook.com/ekg-kniha/obr/700STEMI/STEMI-reciprocal-ST-depression.png
https://www.ecgbook.com/ekg-kniha/obr/700STEMI/heart-artery-supply-ECG-lead.png

Time course of MI



https://www.ecgbook.com/ekg-kniha/obr/700STEMI/ECG-STEMI-infarction-evolution.png

Cardiac consequences

- End-diastolic pressure increase
  - Fourth heart-beat (auscultation, atrial gallop)
- Systolic murmur
  - Rupture of interventricular septum
  - Mitral, aortic regurgitation
- Formation of thrombus -> systemic (or paradoxal) embolisation
- Paradoxal movement of affected area (hypokinesis, akinesis, dyskinesis)
- Ventricle remodelling
  - Ventricle wall aneurysm formation
  - Fibrosis of myocardium -> sympathetic NS (β-receptors)

Systemic consequences

- Organs hypoperfusion
  - Fatigue, psychic changes, tiredness
- End-diastolic pressure increase -> backwards propagation
  - Lung hyperemia – juxtacapillary receptors irritated – fast, shallow breathing
  - Systemic hyperemia – rarely seen in MI
- Pain – C7-Th4 – irradiation to left arm
- Pain + hypotension –> autonomous nervous system irritated
  - Nausea, sweating, tachycardia, cold and sweaty skin
  - Peripheral resistance increased + increased contractibility – circulus vitiosus
- TNF-α and IL-1β from macrophages -> tissue resorption
  - Subfebrilities, ↑sedimentation, leukocytosis (stress reaction, G-CSF)

Diagnostic markers from damaged myocardium

- Initial stress reaction (mins)
  - Cortisol increased, glycemia increased, sedimentation increased, leucocytosis
- Cardiomarkers – elevation may not reflect the size of damage! (circulation around the area, etc.)
- Specific markers
  - Troponin (TnT)
    - Myocardium specific
    - Released during infarction (necrosis), not during ischemia
    - Course – rise 2-4 hrs -> peak 12-24 hours -> disappear after 7-10 days

Diagnostic markers from damaged myocardium – non-specific

Myoglobin (non-specific)

- Hrs – 24 hrs – eliminated by kidneys

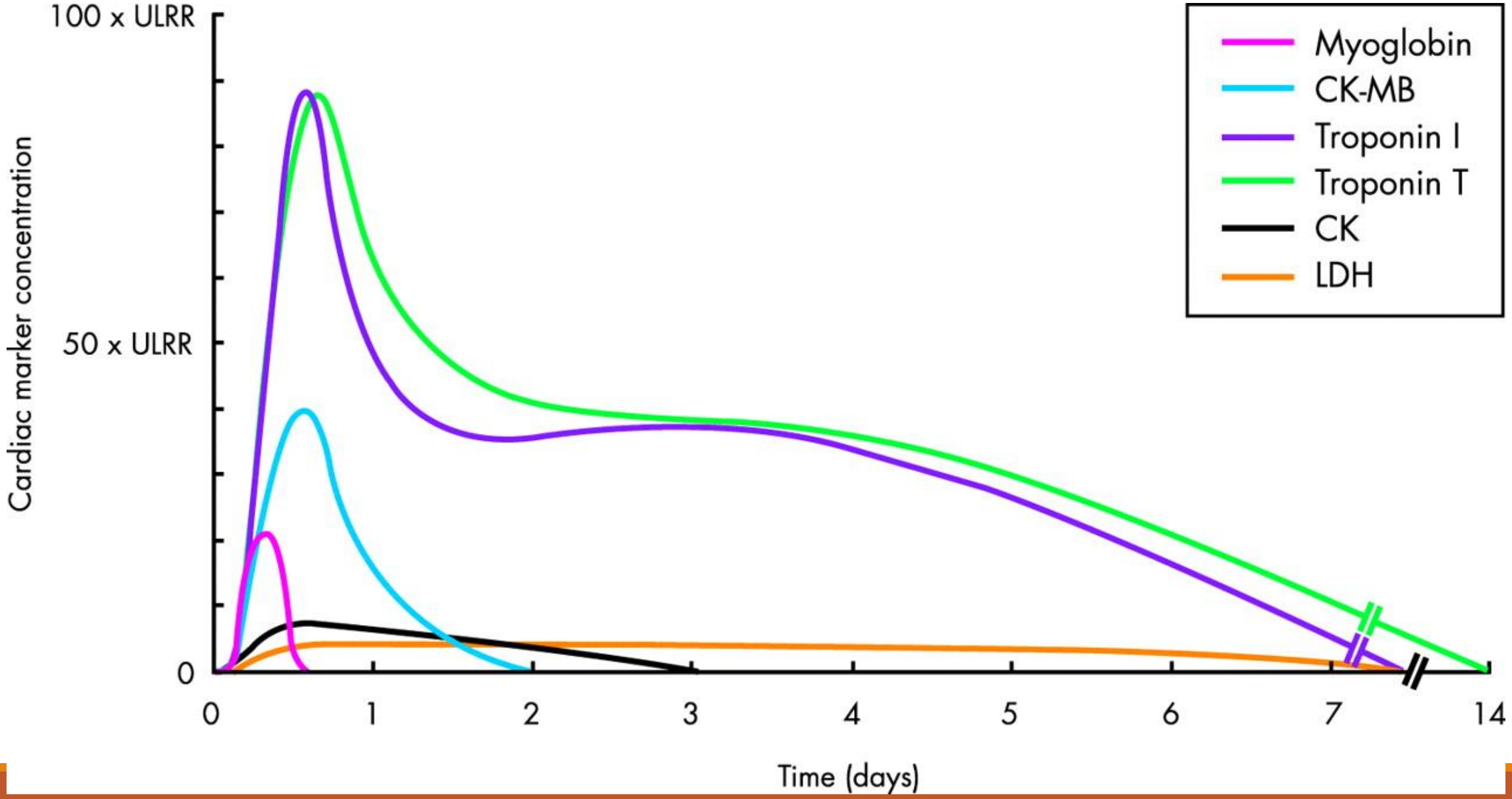
Lactate-dehydrogenase (LDH, non-specific)

- Slow increase, lasts 7-10 days
- Also present during myocarditis, lung embolism, hemolytic anemia, malignant tumours, megaloblastic anemia, etc.

Aspartate-aminotransferase (AST, non-specific)

- 4-8 hrs – 16-48 hrs maximum – 3-6 days returns to normal
- Also present during hepatopathy, congestive hepatopathy, right-heart failure

- Creatinkinase – non-specific – elevates in 4-8 hours, 48-72 hrs return to normal values (skeletal muscle also increases CK)
  - Isoenzyme CK-MB is more specific



https://heart.bmj.com/content/heartjnl/90/1/99/F1.large.jpg

Marker	Normal Value	Time to rise in the blood (hours)	When detectable in the blood (Hours)	Peak	Days to become normal
Creatine Kinase	22 to 198 U/L	5 to 8	6 to 8	24 to 36 hours	3 to 4 days
CK -MB	0 to 3 ng/mL or 0 to 3 µg/L	5 to 15	4 to 6	12 to 24 hours	2 to 3 days
Troponin I	<0.35 ng/mL or <0.35 µg/L	4 to 6	3 to 8	10 to 24 hours	3 to 10 days
Troponin T	<0.2 ng/mL*	3 to 4	3 to 8	10 to 24 hours	5 to 10 days
Myoglobin	<55 ng/mL	1 to 3	1 to 3	6 to 9 hours	1 day
AST (SGOT)	Adult male 5 to 40 U/L*	3 to 5	6 to 8	24 to 48 hours	4 to 6 days
LDH	140 to 280 U/L*	2 to 4	8 to 12	2 to 4 days	8 to 14 days

Troponin-T = >1.0 ng/mL indicates current myocardial injury.
SGOT Slightly lower in the female.
LDH = 300 to 800 U/L indicates myocardial infarction.

https://www.researchgate.net/profile/Mustafa-Mohammed-9/publication/362431545/figure/tbl2/AS:1184932420436057@1659521312448/Types-of-cardiac-markers-72.png

Cardiac remodelling

- Drop in blood pressure

1. Renin-angiotensin II-aldosteron system (RAAS) activated
   - Growth of cardiomyocytes enhanced - mainly via angiotensin II receptors
     - Gq/11-1,2-diacylglycerol -> protein kinase C -> MAPK, JNKs, JAK, STAT cascades activated
     - Gq/11-inositol 1,4,5-triphophate –> calcium–calcineurin-dependent activation of MAPK
     - G12/13 -> activation of Rho A-Rho kinase
     - JAK/STAT -> activation of matrix metalloproteinases
2. Activation of sympathetic nervous system -> release of catecholamines -> β2-, α1-receptors stimulated
   - Increased contractility, frequency -> increased oxygen demands
   - Ventricular dilation and fibrosis possible

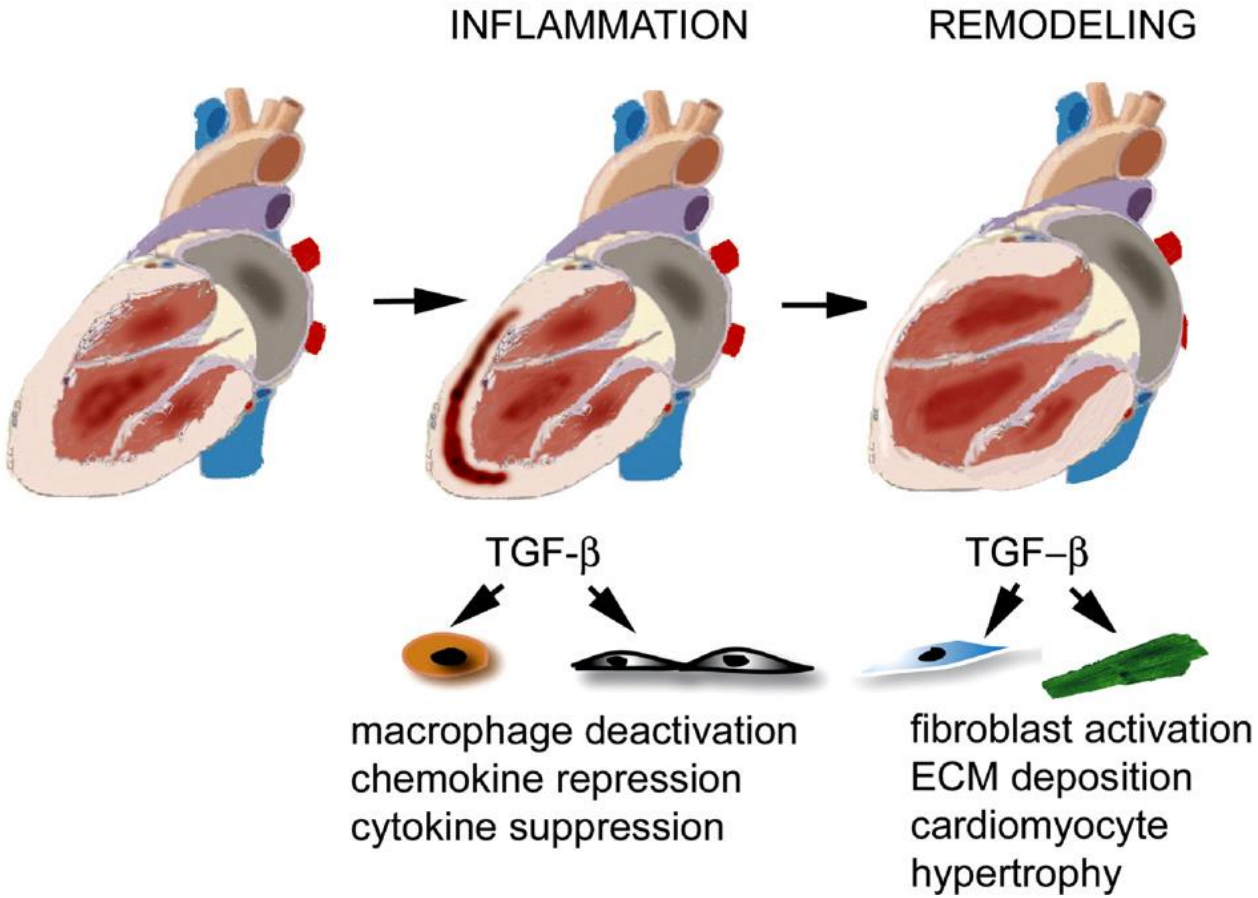
MAPK – mitogen activated protein kinase, JNKs –c-Jun N-terminal kinases, JAK – Janus kinases, STAT – activators of transcription

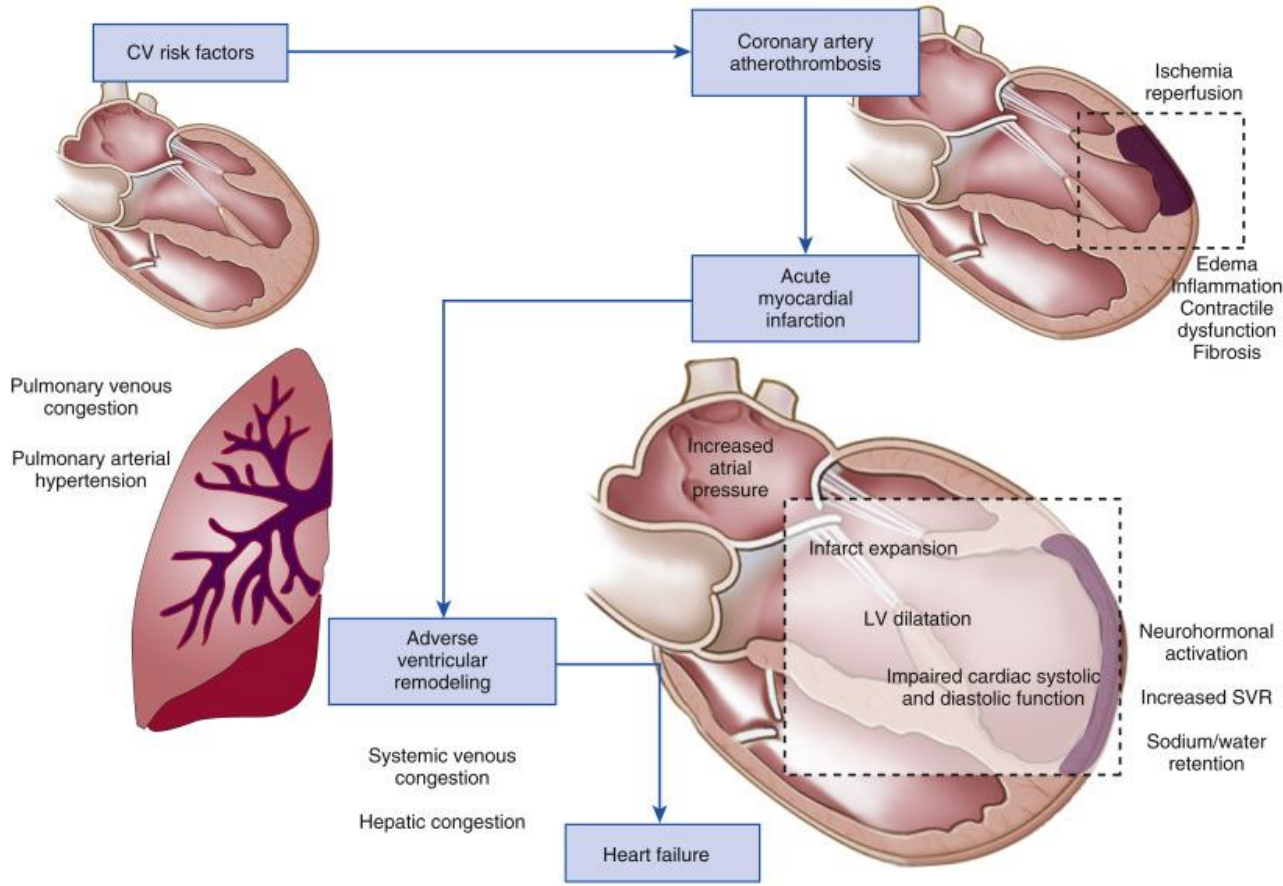
Cardiac remodelling

- Functional and structural remodelation –> cell hypertrophy
- Mechanical stress
  - Endothelin I and angiotensin II released
  - Antiport Na^+/H^+ activated
- Pressure is mediated viac integrins and cytoskeleton –> enzymes activation
- Posttranslation protein modification –> cardiomyocytes hypertrophy, fibroblasts multiplication
- Subendocardial angiogenesis not properly activated!
  - Hypertrophy compensation with limited effect -> subendocardial hypoxia possible

Cardiac remodelling

- Qualitative and quantitative collagen changes
  - Rigidity, diastolic dysfunction, dilatation cardiomyopathy
- Metabolic rate shift to glucose
  - Normal 65 % fatty acids, 30 % glucose -> switch to glucose
  - Lowered carnitin, acetyl-CoA-synthetase, carnitine-palmitoyl-transferase, less VLDL receptors, lipoprotein lipase ceased
  - Pyruvate-dehydrogenase phosphorylation – activation of glycolysis
  - Not compensated – progress to heart failure
  - ATP preferably delivered to $Ca2^{+}$ pumps – adaptation
- Mimic fetal myocardium (glucose preferred) – congenital metabolic diseases of fatty acids are associated with cardiomyopathies





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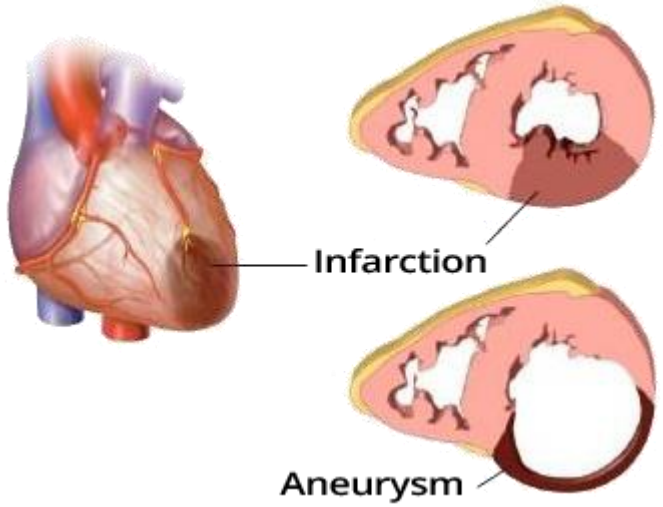
https://i0.wp.com/thoracickey.com/wp-content/uploads/2019/08/f36-01-9780323359436.jpg?w=960

Persistent ST elevations and aneurysm formation

- ST elevations should disappear within 2 weeks
- Persistent ST elevations -> necrotic wall expansion -> aneurysm formation
  - 60 % after anterior STEMI
  - 5 % after inferior STEMI
- ST elevations
  - Do not change (no dynamics)
  - Duration of >2 weeks
  - No reciprocal ST depressions (opposing leads)



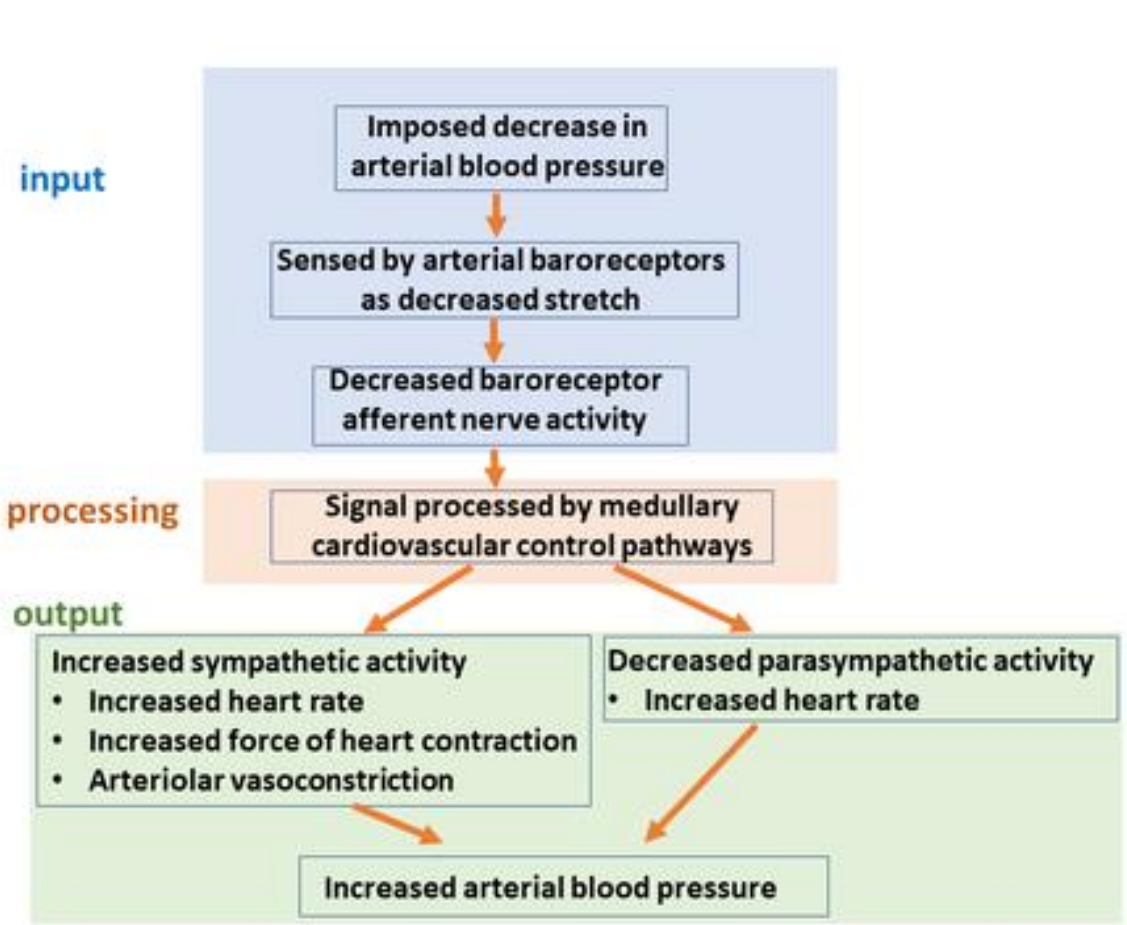
https://www.ecgbook.com/ekg-kniha/obr/700STEMI/STEMI-aneurysm-ST-slevation.png

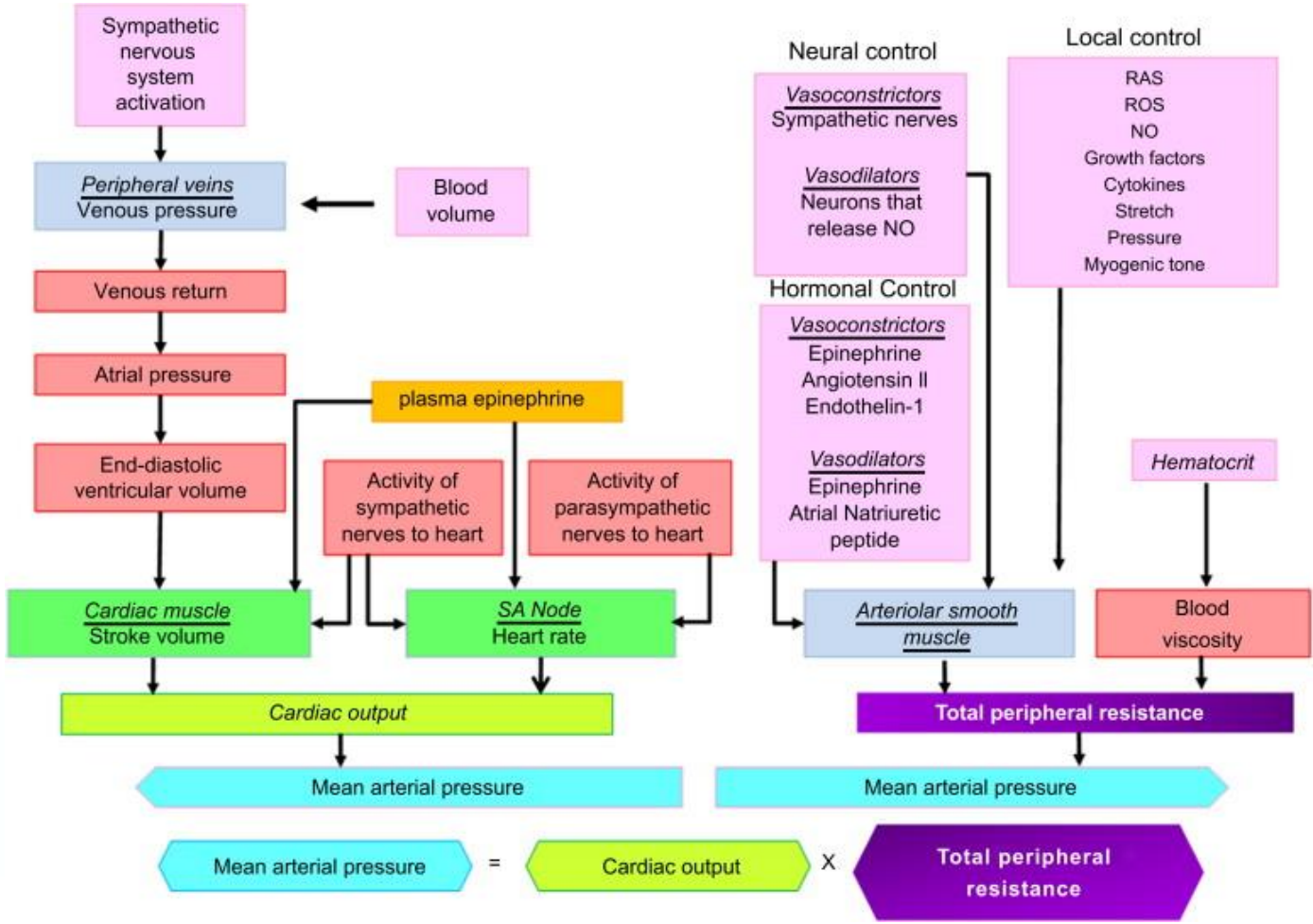
Hypertension

SYSTEMIC, PULMONARY

Physiological mechanims of blood pressure regulation

- Increase of systolic and/or diastolic blood pressure in systemic/lung circulation may occur due to (P = Q x R)
  - Increased blood flow (Q)
  - Increase resistance of blood vessels (R)
  - Both mechanisms engaged (QxR)
- Vasomotoric centre in oblongate medulla
  - High-pressure baroreceptors -> carotid sinuses, aortic arch
  - Low-pressure baroreceptors -> atria, ventricles, pulmonary vessels
  - Baroreceptors react to short-term changes only -> reset within days -> possible adaptation (hypertension prone)





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https://ars.els-cdn.com/content/image/3-s2.0-B9780124052062000144-f14-01-9780124052062.jpg

Factors influencing blood pressure (BP)

SYSTOLIC BLOOD PRESSURE (SBP)

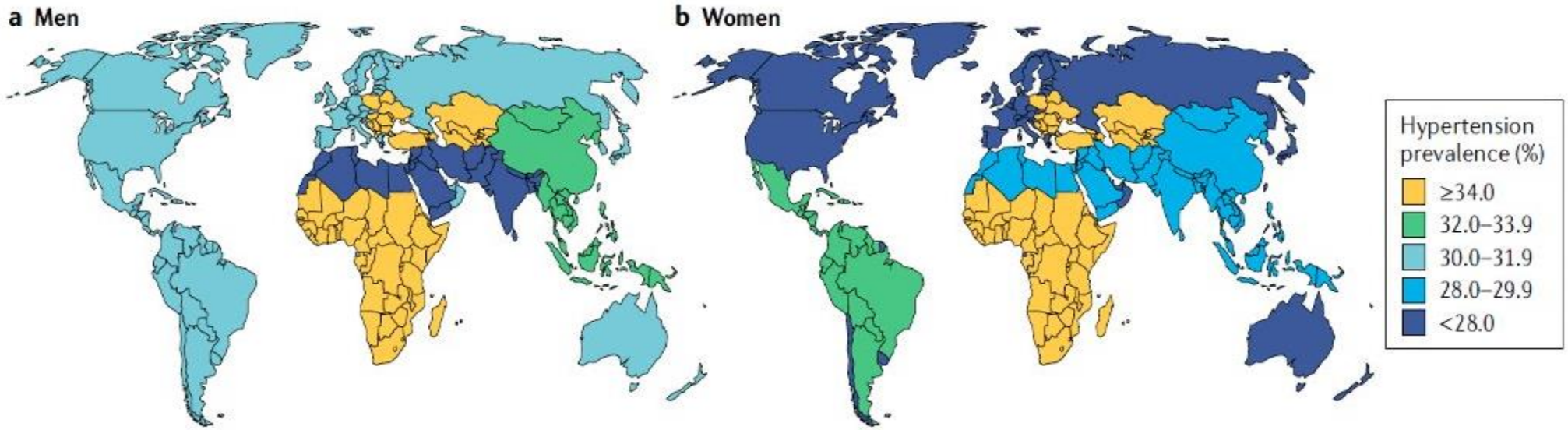
- Venous return and ventricles preload
- Myocardial contractility
- Pulse volume – amount of blood expulsed into vessels during one systolic contraction
- Expulsion velocity of blood
- Compliance of large arteries
- Arterial resistance – de facto diastolic blood pressure
- Peripheral resistance working against blood flowing from large arteries

DIASTOLIC BLOOD PRESSURE (DBP)

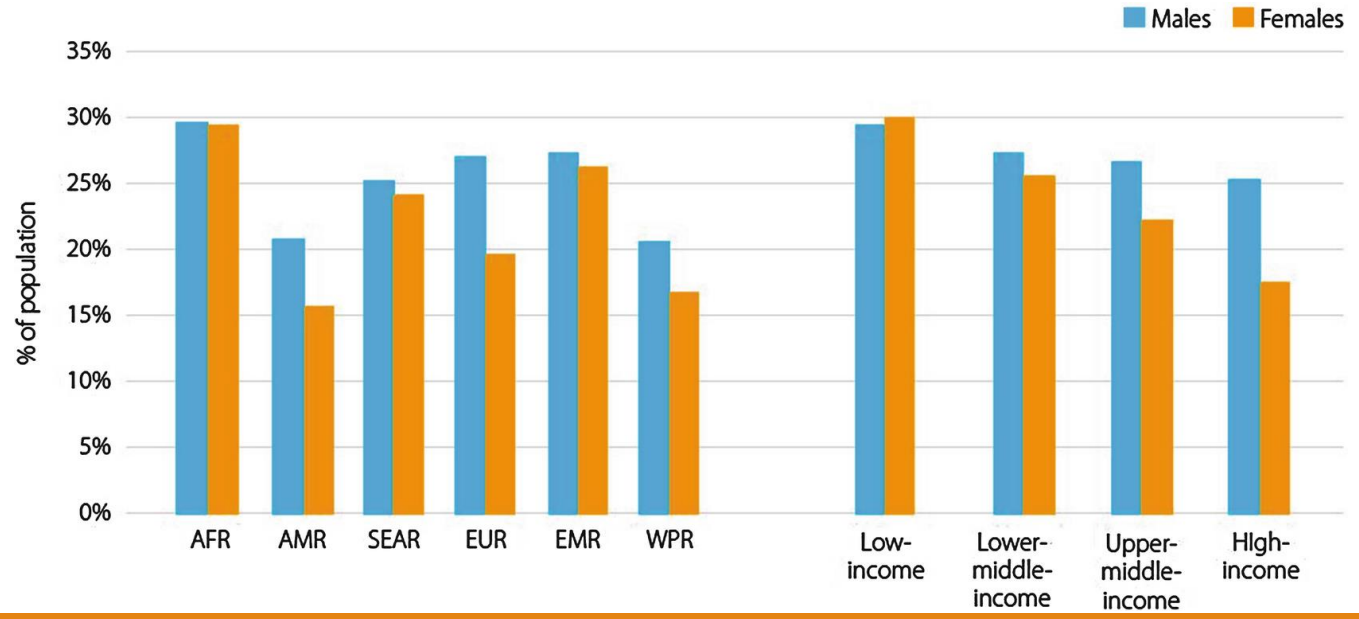
- Systolic BP
- Peripheral resistance working against blood flowing from large arteries
- Time period between two systoles

Hypertension – definition and characteristics

- Definition
  - ESH 2024 – sBP >140 mmHg and/or dBP >90 mmHg (isolated systolic hypertension when sBP elevated only)
    - „Pre-hypertension“ cancelled -> optimal BP (<120/80 mmHg) and „normal“ BP (120-130/80-90 mmHg)
  - AHA 2020 – sBP >130 mmHg and/or dBP >80 mmHg
- Classification
  - Systemic arterial vs pulmonary hypertension
  - Primary (essential) vs. secondary (known cause)
- Epidemiology
  - Prevalence – 1.3 billion worldwide (2023)
    - 46 % patients unaware, 42 % patients diagnosed and treated
    - Only 21 % patiens with controlled hypertension



Mills et al. Nat Rev Nephrol. 2020 Apr;16(4):223-237



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Physiology summary and transition to pathology

- Conditions leading to arterial hypertension (HT)
  - „Hypercirculation“ associated conditions
  - Conditions connected with increased peripheral resistance

- Amplitude between systolic and diastolic BP may change leading to increase to one or both BP

- BP arises due to dysregulation of functional relationship between amount of circulating blood and resistance to blood flow
  - Cardiac output vs. peripheral resistance

Guideline Similarities	2017 ACC/AHA	2023 ESH
Accurate Blood Pressure Measurement	Office-based BP measurements and use of validated, cuffed devices and home/ambulatory BP monitoring are recommended prior to diagnosing hypertension.	
Cardiovascular Risk Calculator for Treatment Thresholds	Pooled Cohort Equation and SCORE2/SCORE2-OP provide estimates for 10-year risk of fatal and non-fatal cardiovascular events and should be used to guide treatment decisions.	
Initial Pharmacotherapy Recommendations	Initial therapeutic choices include ACE inhibitors, angiotensin-receptor blockers, thiazide or thiazide-like diuretics, and calcium channel blockers. Single pill combination therapy is a first-line strategy for many patients.	

Guideline Differences	2017 ACC/AHA	2023 ESH
Hypertension Definition	≥ 130/80	≥ 140/90
Normal BP Ranges (mmHg)	Normal: < 120/80 Elevated: 120-129/<80	Optimal: < 120/80 Normal: 120-129/80-84 High-Normal: 130-139/85-89
Hypertensive BP Ranges (mmHg)	Hypertension Stage 1: 130-139/80-89 Hypertension Stage 2: ≥ 140/90	Hypertension Grade 1: 140-159/90-99 Hypertension Grade 2: 160-179/100-109 Hypertension Grade 3: ≥ 180/110
BP Targets for Treatment		
18 – 64 years (mmHg)	< 130/80	< 130/80
65-79 years (mmHg)	< 130/80	< 140/80*
≥ 80 years (mmHg)	< 130/80	140-150/<80
Pharmacotherapy	Initial therapy with beta-blockers reserved for specific conditions including ischemic heart disease or heart failure	Beta blockers included as first-line therapy for hypertension.

** Target < 130/80 if tolerated*

ACC/AHA 2020

Blood Pressure Category	Systolic mm Hg (upper number)		Diastolic mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 - 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (Hypertension) Stage 1	130 - 139	or	80 - 89
HIGH BLOOD PRESSURE (Hypertension) Stage 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

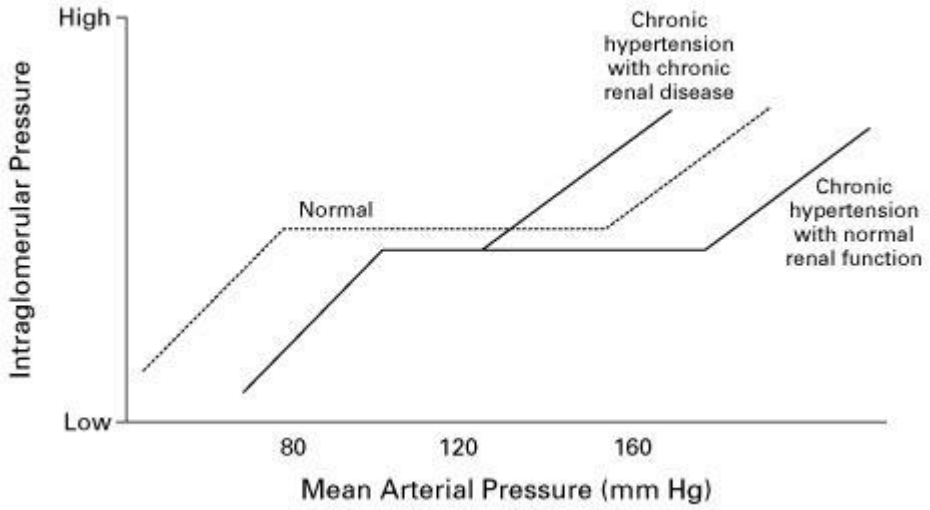
https://www.acc.org/-/media/Non-Clinical/Images/Latest-in-Cardiology/Articles/2024/02/PREV-EA-Vemu-Table1.png
https://blog.ohiohealth.com/wp-content/uploads/2022/02/Blood-Pressure-Guidelines-Update_Infographic-2022.jpg

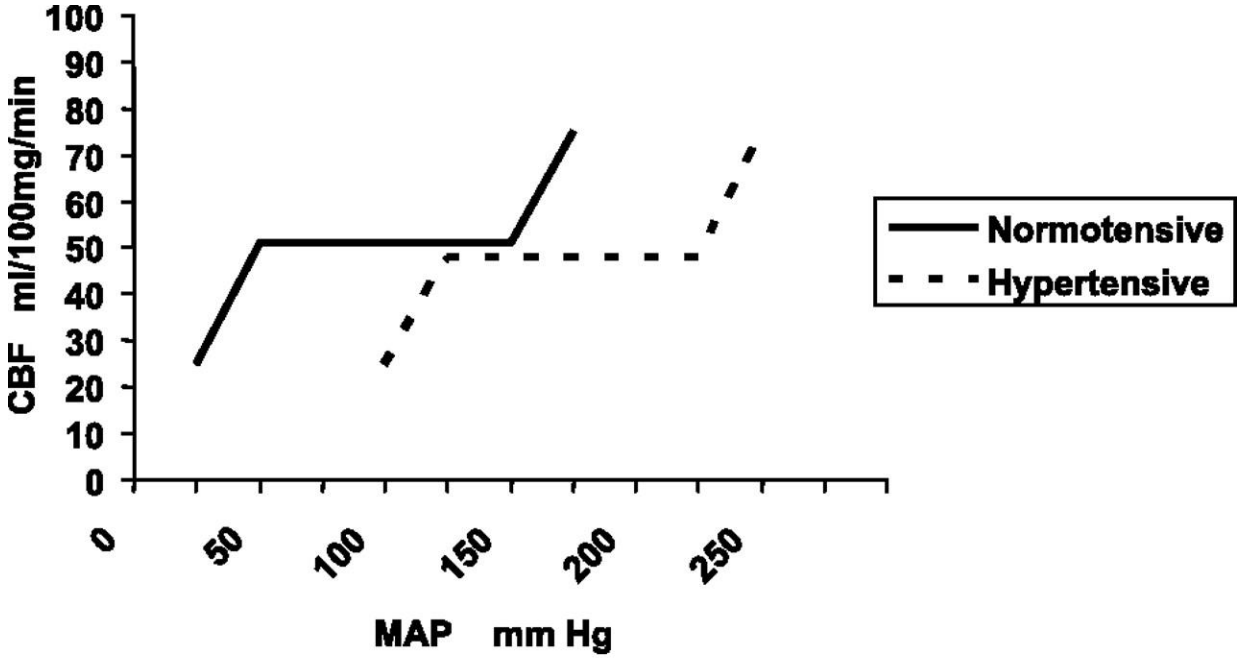
Systemic arterial HT

- Definition – applies from ESH 2024 or ACC/AHA 2020
  - Europe – sBP >140 mHg and/or dBP >90 mmHg
- Only arterial circulation affected
- Organs affected
  - Heart
  - Kidney
  - Brain
  - Arteries
- Classification
  - 95 % - essential (primary)
  - 5 % - known conditions (secondary)

Hypotheses of essential BP development

1. „Hypertension by volume increase “
   - Primary change -> circulating volume elevates
   - Result – hypercirculatory state -> peripheral resistance arises
2. Circulation compensating primary kidney malfunction
   - Lowered excretion of sodium and water -> increase in BP -> pressure diuresis -> homeostasis achieved (damages kidney over a time!)
3. *Increased sympathetic activity*
   - *Vasoconstriction -> hypertension*
   - *Lack of proof*
     - *Sympathetic hyperactivity conditions as heart failure, liver cirrhosis are rarely accompanied by HT*





CBF=cerebral blood flow; MAP=mean arterial pressure

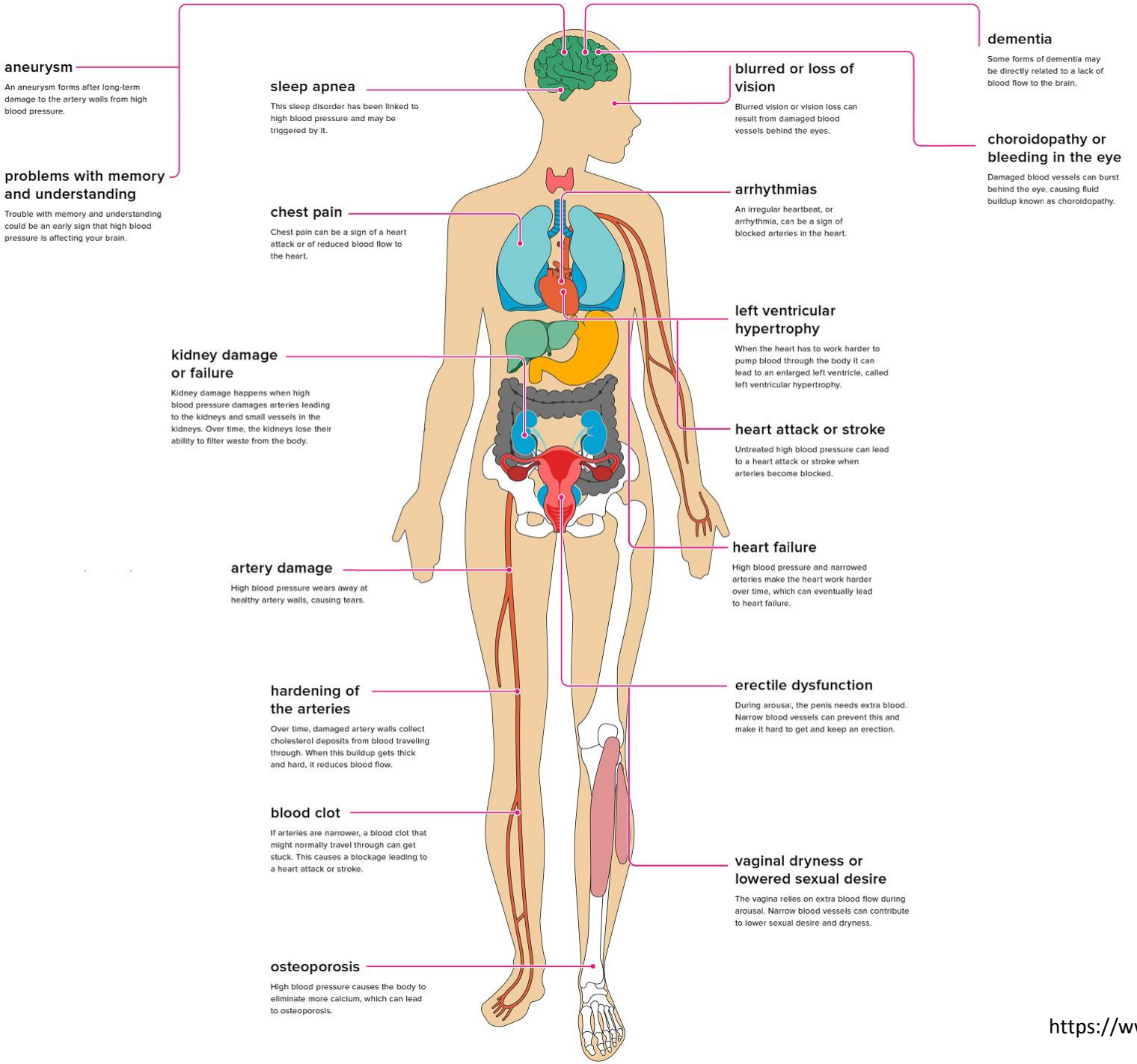
http://www.nejm.org/na101/home/literatum/publisher/mms/journals/content/nejm/2002/nejm_2002.347.issue-16/nejmra020676/production/images/img_medium/nejmra020676_f1.jpeg
http://hyper.ahajournals.org/content/hypertensionaha/49/5/977/F1.large.jpg

Essential HT

- Dyscrepancy between circulating volume and peripheral vessels resistance
- Dysregulation between perfusion of organs and peripheral resistance
  - Kidney (RAAS) and brain mostly
    - Angiotensin II increases peripheral resistance
    - Aldosterone -> Na^+ retention -> hypervolemia
- During HT there is no hyperperfusion of organs
  - After crossing certain limit (higher in HT than normal) -> reaction of peripheral circulation in adjusting of blood flow
- „Stabilisation of HT“ -> ↓BP -> ↓organ perfusion (kidney, brain) -> tendency to return back hypertension conditions
- Arterial HT as a health burden and a risk factor for cardiovascular diseases

Essential HT

- Increase in cardiac output + hypercirculation conditions
- Chronic increase of tissue perfusion -> vasoconstriction of peripheral vessels -> increase in peripheral resistance
- Consequences
  - Endothelial damage (strengthened pulsations) -> atherosclerosis acceleration
  - Afterload increase -> concentric hypertrophy of left heart ventricle
  - Increase in heart work -> increased oxygen consumption by myocard
  - Risk of circulation disruption and arterial bleeding – epistaxis, stroke, „ruptured vessels on sclera“, retinal bleeding etc.
  - Hyperfiltration in kidney -> glomeruli fibrotisation -> chronic kidney failure (hypertension nephropathy)



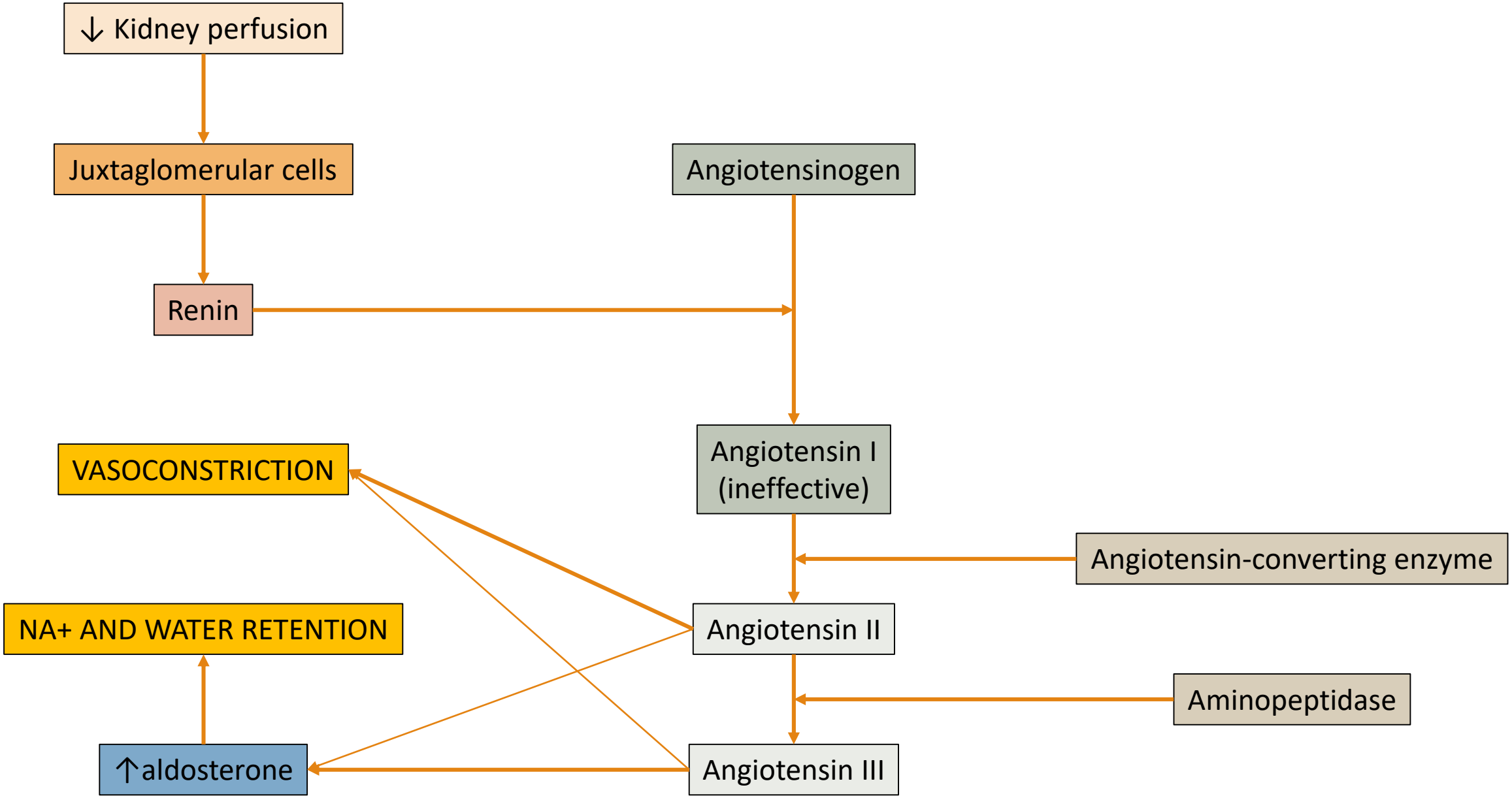
https://www.healthline.com/hlcmsresource/images/Effects_Hypertension/Hypertension_Effects_Pinterest_crop.jpg

Secondary systemic arterial HT

Pathomechanism	Examples
Prevailing peripheral resistance increase	Pheochromocytoma Unilateral a. renalis stenosis
Prevailing increase of blood volume and hypercirculation	Primary hyperaldosteronism (Conn sy.) Surgical removal of kidney (renoprive HT) Cushing sy. (hypercorticism) Acromegaly Polycytemia vera Estrogen administration
HT caused by both peripheral resistance and circulating volume increase	End-stage renal insufficiency – last stage Bilateral ischemia of kidney Pregnancy induced hypertension (?)

Secondary HT caused by peripheral resistance increase

- Pheochromocytoma
  - Origin – suprarenal medulla/sympathetic ganglions
  - Catecholamines produced – norepinephrine mainly -> alfa1-adrenergic receptors
  - Paroxysmal/persistent HT with BP fluctuations -> may reach 300/150 mmHg during paroxysm
- Unilateral a. renalis stenosis (renovascular HT)
  - Perfusion decrease behind the stenosis -> juxtaglomerular cells irritated -> renin production -> RAAS activation
  - Hypervolemia -> preload increase -> increased cardiac output


↓ Kidney perfusion
Juxtaglomerular cells
Renin
Angiotensinogen
Angiotensin I
(ineffective)
Angiotensin-converting enzyme
Angiotensin II
Aminopeptidase
Angiotensin III
VASOCONSTRICTION
NA+ AND WATER RETENTION
↑aldosterone

Secondary HT caused by increase of blood volume and hypercirculation

- Conn sy. (primary hyperaldosteronism)
  - Increased natrium retention -> increased blood volume
- Renoprive HT
  - Accumulation of bodily fluids -> blood volume increase
- Cushing sy.
  - Increased cardiac output suspected

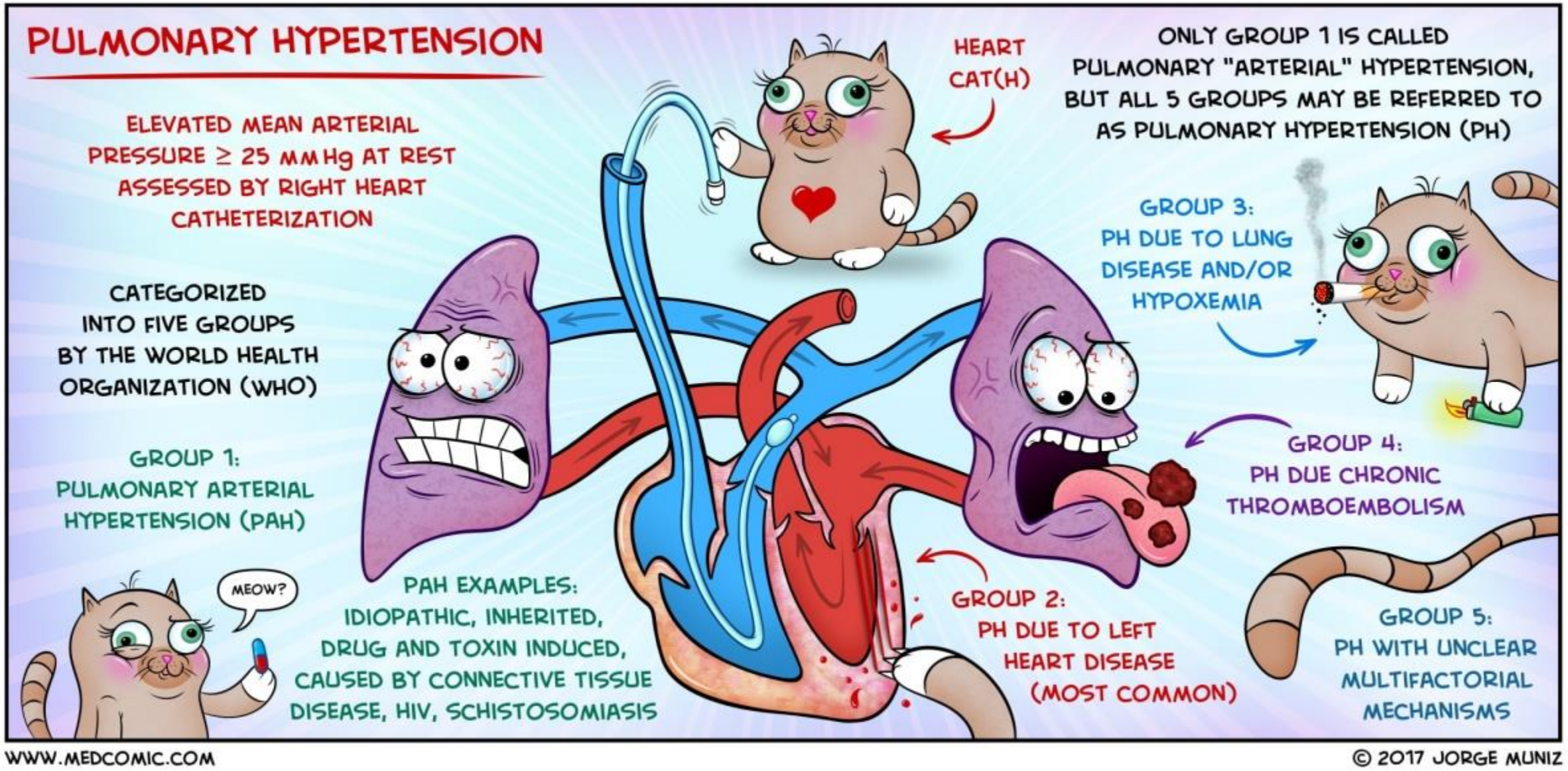
Secondary HT caused by both peripheral resistance and circulating volume increase

- Bilateral ischemia of kidney and ESRI
  - Fluid retention -> vasoconsctriction as a reactive change
  - Dehydratation/dialysis -> renin production intensified -> worsening of HT
  - Volume HT changes to resistance HT

- Pregnancy induced hypertension (5-14 % pregnant!)
  - Maldevelopment of placenta
    - Lack of aa. Spirales proper transformation and/or malinvasion to decidual layer
    - Placental circulation remains as high-resistance circulation (normal is a decrease in resistance)
    - Proteinuria, edemas my occur as well (preeclampsia – edemas + Ht+ proteinuria = EPH gestosis)
    - Maternal metabolism affected (adipokines, cytokines, immune system involved)
    - Increased risk of complications without a treatment

Pulmonary arterial HT

- Physiological BP in pulmonary artery – 8-20 mmHg
- Pulmonary HT
  - BP >25 mmHg resting; >30 mmHg during physical activity
- Often has an acute manifestation
  - Systemic is more chronic
- Significant influence of pulmonary veins
  - In systemic HT venous part is almost only slightly affecting BP
- Classification (see next slide)



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Pulmonary HT forms

1. Hyperkinetic pulmonary HT
   - L->R shunt -> increased amount of blood flowing
   - Pulmonary arterioles remodelation – thicker muscular layer
   - Correction of cardial mistake has to happen sooner then fixation of HT occurs
2. Postcapillary pulmonary HT
   - Primary – increase of pressure in left atrium (left-sided heart failure – backward, mitral stenosis and insufficiency, cardiomyopathies)
   - Chronic – cor pulmonale chronicum (right ventricle hypertrophy)

Pulmonary HT forms

1. Reactive pulmonary HT
   - Lung circulation hypoxia -> arterioles vasocontriction
   - Hypoventilation states – chronic bronchitis, emphysema
   - Mountain sickness
2. Obliteration and obstruction pulmonary HT
   - Idiopatic
   - Dysregulation of pulmonary arterioles composition - BMP (bone morphogenic proteins) cytokines mutation – familiar/sporadic
     - Progressive, irreversible, at physical activity, later resting dyspnoe, right-sided heart failure
   - Pulmonary parenchyme reduction – surgery including
   - Repeated thrombembolism to lungs
     - Right ventricle myokardium may arise BP in a. pulmonalis to 40-100 Torr at once, without preceding hypertrophy, risk of blood pooling in right ventricle and heart failure

marek.brenisin@upjs.sk
https://patfyz.medic.upjs.sk/ehome.htm