PP of circulatory system – part I: AS-driven coronary artery disease (CAD) and its consequences

Coronary artery/coronary heart disease (CAD/CHD) as a consequence of AS

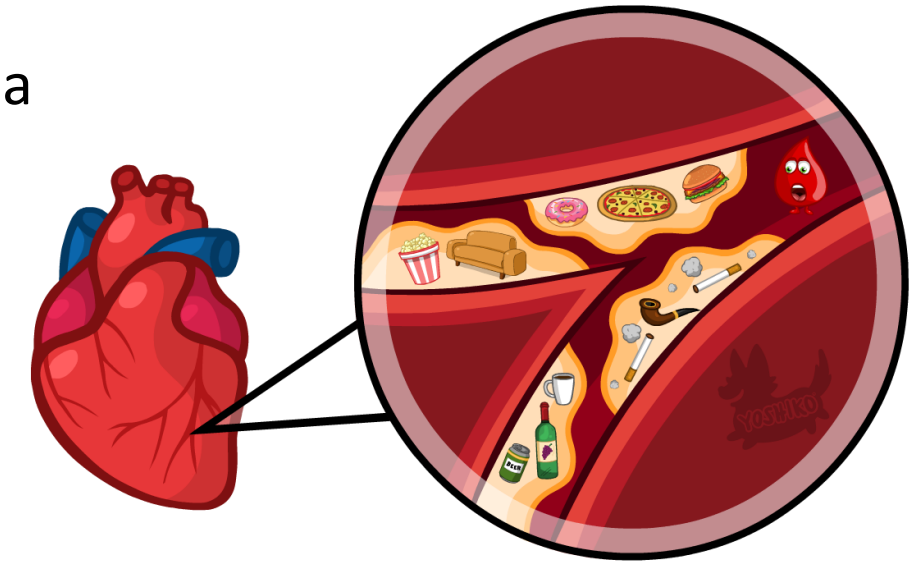
- summary of AS etiopathogenesis

Myocardial ischemia – compensation

Ischaemic heart disease – clinical forms

- chronic – angina pectoris
- acute coronary syndromes

Ischemic cardiomyopathy as the most prevalent cause of heart failure



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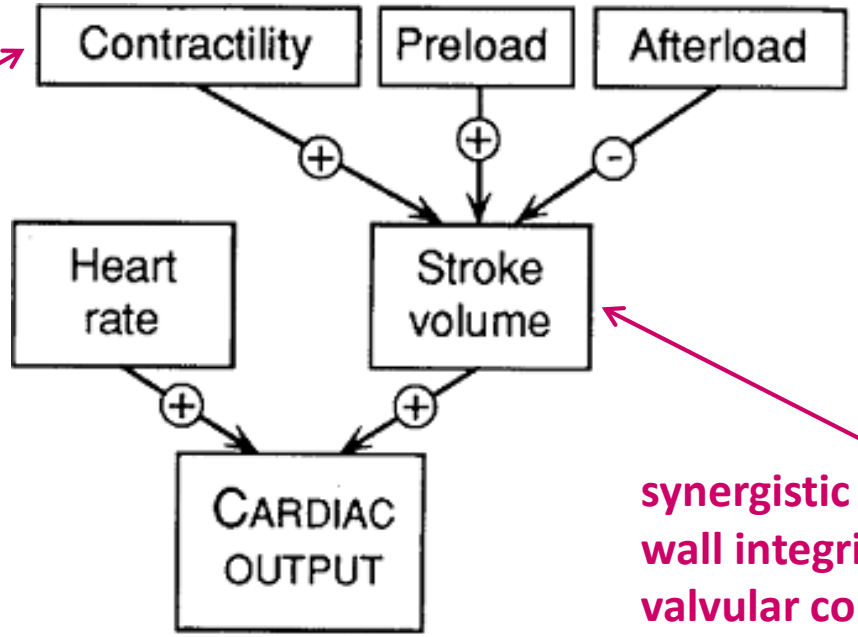
Heart needs a lot of energy (= ATP) to continually perform as a pump (~7,500 L/day, ~ 40 mil beats/year)

venous return (i.e. circulating volume)

systemic vascular resistance (i.e. blood pressure or valve obstruction)



sympathetic nervous system

parasympathetic nervous system

synergistic LV contraction
wall integrity
valvular competence

- quantitatively
  - heart rate ~70/min
  - SV ~70ml
  - CO 70 × 70 = 4,900 ml/min ~ 5 L/min at rest
  - **CO ~ 20 - 25L/min during exercise!!!!**
- influenced by
  - autonomic nervous system activity
  - hormones
  - age
  - gender
  - genetics
  - drugs
  - fitness
  - anatomy/size of the heart

SV × f = CO → 70mL × 70 bpm = ~ 5 L/min

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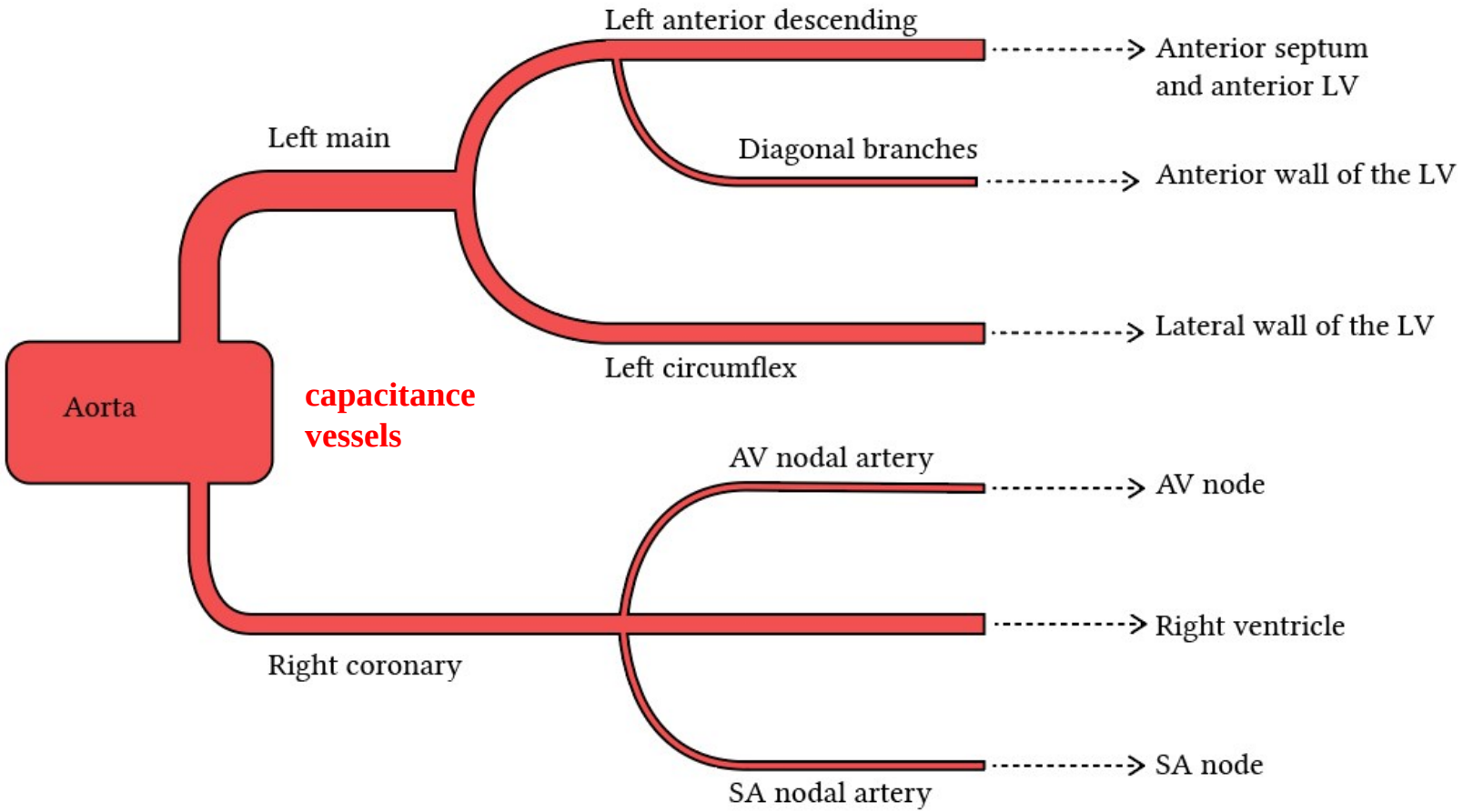
Coronary vascular anatomy



- Coronary arteries arise from the sinuses of Valsalva at the aortic root
  - Left main: divides into left anterior descending and left circumflex, supplies most of the septum and LV
  - Right coronary: supplies the RV, the sinoatrial node
- Coronary sinus: drains into the RA, venous blood oxygen saturation here is ~ 30%

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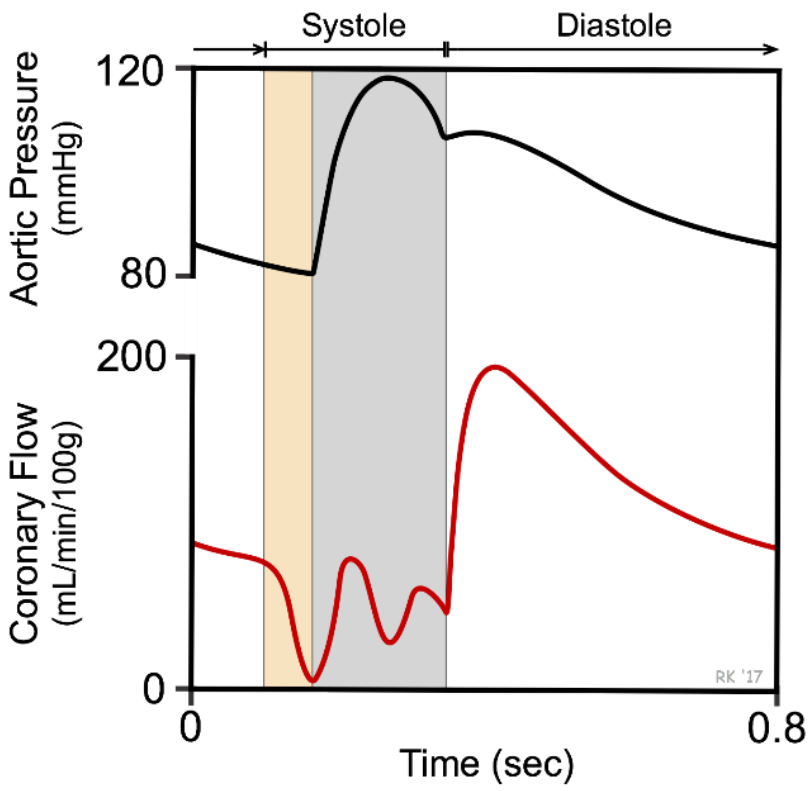
Coronary blood flow



- 5% of cardiac output, or 50-120ml/100g of myocardial mass
- **75% of the left main flow and 50% of RCA flow occurs in diastole**
  - in systole, LV blood flow is reduced due to the high chamber pressure during contraction
  - for the RV, the systolic chamber pressure is lower, and blood flow is less affected
- Thus, diastolic time is more important for LV perfusion, and it can be **compromised by tachycardia**
- Coronary blood flow is automatically regulated to meet metabolic demand
  - **myocardial oxygen extraction ratio** is already very high (**60-75%**).
    - thus, the myocardium cannot increase its oxygen extraction efficiency to meet increased metabolic demand
  - coronary arterial blood flow has to increase to match myocardial oxygen demand, and the oxygen extraction ratio remains stable
    - with exercise, coronary blood flow can increase several-fold
- **Mechanisms** of coronary blood flow **autoregulation**
  - myogenic autoregulation (intrinsic arterial smooth muscle property)
  - metabolic substrates and by-products are thought to act as vasoactive mediators in the coronary circulation
    - multiple agents are considered important, including **adenosine, O2, CO2, lactate, pH, and potassium ions**
    - ATP-sensitive potassium channels also open in response to decreased ATP, resulting in smooth muscle membrane hyperpolarisation and thus relaxation
  - autonomic nervous system
    - α1-adrenergic receptor activation stimulates vasoconstriction
    - β-adrenergic receptor activation produces vasodilation
    - Muscarinic receptor stimulation produces coronary vasodilation
  - various pharmacological agents with coronary vasoactive properties include:
    - vasodilators (adenosine, GTN, dipyridamole)
    - vasoconstrictors (vasopressin, COX inhibitors

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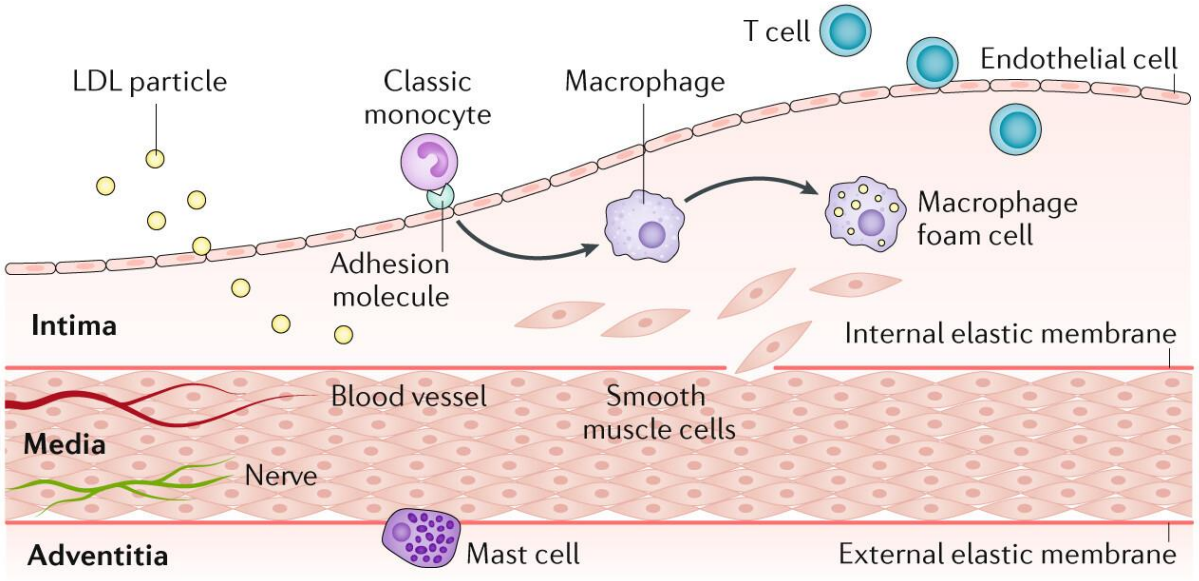
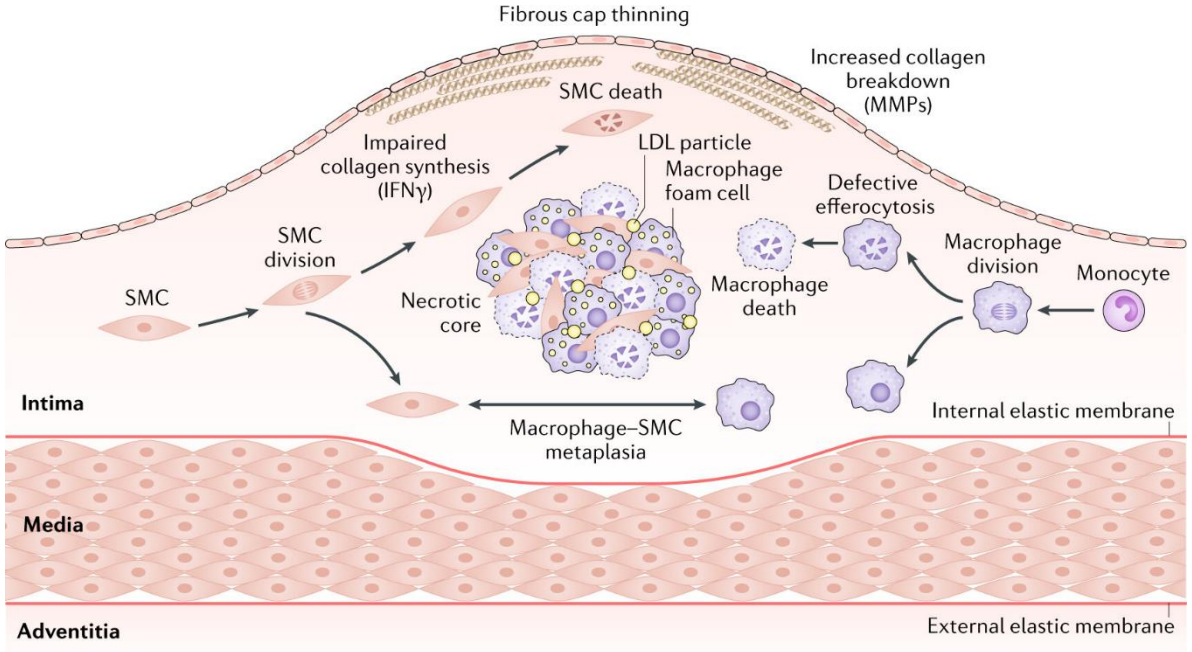
Summary of AS etiopathogenesis – stages



Initiation and progression of atherosclerosis. The normal artery wall has a tri- laminar structure. The outermost layer, the adventitia, contains nerve endings, mast cells, and vasa vasorum, microvessels that nourish the outer layer of the media. The tunica media consists of quiescent smooth muscle cells and a well-organized extracellular matrix comprising elastin, collagen and other macromolecules. The atherosclerotic plaque forms in the innermost layer, the intima. In the early stage of lesion initiation, low- density lipoprotein (LDL) particles accumulate in the intima, where protected from plasma antioxidants, they can undergo oxidative and other modifications that can render them pro- inflammatory and immunogenic. Classic monocytes that exhibit a pro- inflammatory palette of functions then enter the intima. Monocytes circulate in the bloodstream and can bind to adhesion molecules expressed by activated endothelial cells. Chemoattractant cytokines, known as chemokines, can promote the migration of the bound monocytes into the artery wall. Once in the intima, monocytes can mature into macrophages, and attain characteristics associated with the reparative or less pro- inflammatory monocyte/ macrophage population. These cells express scavenger receptors that permit them to bind lipoprotein particles and become foam cells. T lymphocytes, although numerically less abundant than monocytes, also enter the intima, and regulate functions of the innate immune cells as well as the endothelial and smooth muscle cells. Smooth muscle cells in the tunica media can migrate into the intima in response to mediators elaborated by the accumulating leukocytes. The smooth muscle cell chemoattractant platelet- derived growth factor arising from macrophages and deposited by activated platelets at sites of endothelial breaches or intraplaque haemorrhage probably participates in this directed migration of medial smooth muscle cells into the intima.



The progression of atherosclerotic lesions: cellular birth and death. During the evolution of the atherosclerotic plaque, the resident and recruited smooth muscle cells (SMCs) produce extracellular matrix molecules (such as interstitial collagen and elastin, as well as proteoglycans and glycosaminoglycans) that contribute to the thickening of the intimal layer. However, T cell mediators such as IFNγ can impair the ability of the SMC to synthesize interstitial collagen and thereby dampen the ability of these cells to repair and maintain the fibrous cap that overlies the necrotic core. Furthermore, activated macrophages show increased production of enzymes of the matrix metalloproteinases (MMPs) family that degrade the interstitial collagen that lends strength to the fibrous cap. Thinning and structural weakening of the fibrous cap increases the susceptibility of the plaque to rupture. SMCs and macrophages in the evolving lesion can divide. SMCs and the mononuclear phagocytes can also interchange through a process of metaplasia. As the lesion advances, SMCs and macrophages can undergo cell death including by apoptosis. The debris from dead and dying cells accumulates, forming the necrotic, lipid-rich core of the atheroma. Impaired efferocytosis (clearance of dead cells) can contribute to the formation of the necrotic core. LDL, low-density lipoprotein.

(cit. Libby, P., Buring, J.E., Badimon, L. et al. Atherosclerosis. Nat Rev Dis Primers 5, 56 (2019). https://doi.org/10.1038/s41572-019-0106-z)

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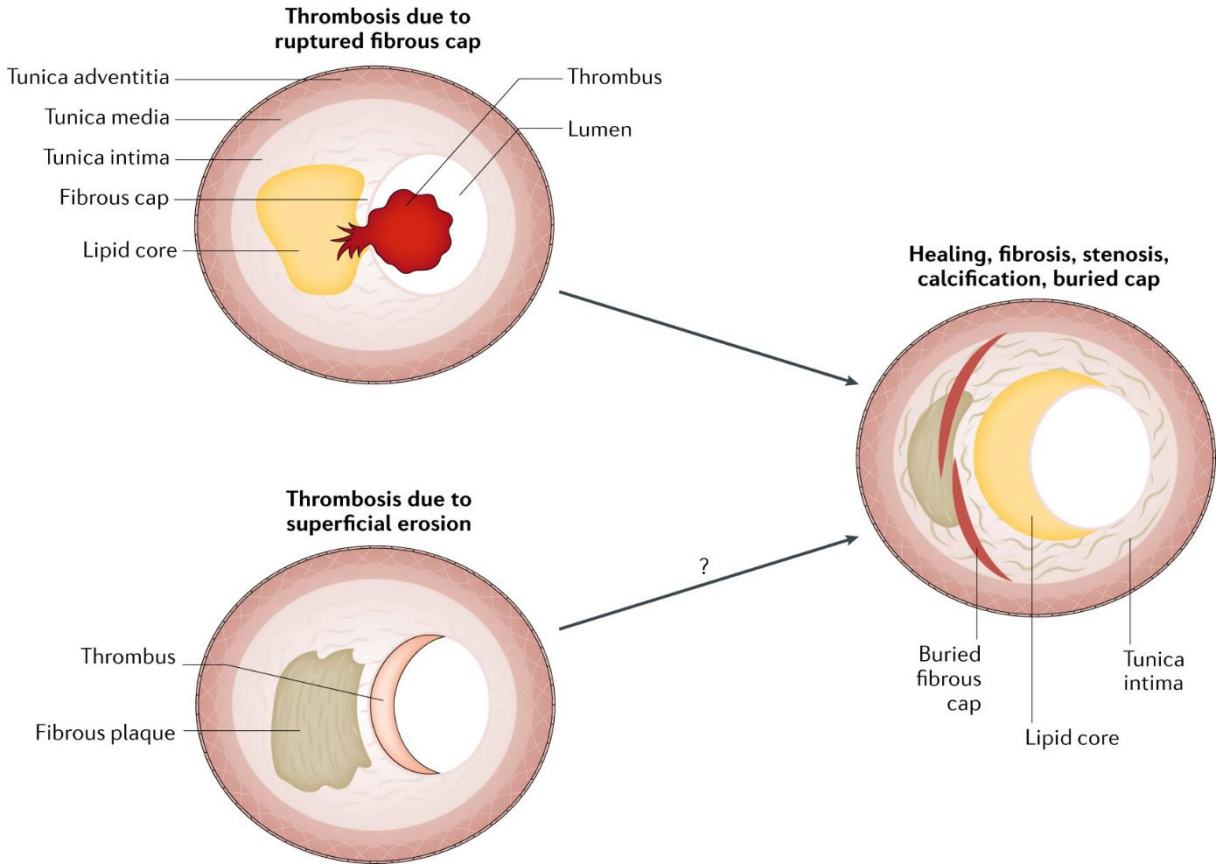
Summary of AS etiopathogenesis – stages



Atheroma complication: disruption and healing.The fracture of the fibrous cap of the atherosclerotic plaque permits blood coagulation components to access to the core of the plaque. Pro-coagulant substances such as tissue factor can trigger thrombosis, which can cause occlusion of the vessel and lead to an acute ischaemic event. Many mural thrombi may not totally occlude the vessel or may undergo lysis due to endogenous fibrinolytic defences. The resorbing thrombus, a source of transforming growth factor-β (TGFβ) and platelet-derived growth factor elaborated by activated platelets, can stimulate smooth muscle cell migration and extracellular matrix production. These processes lead to increased lesion volume and eventual encroachment upon the arterial lumen. Pathological studies of advanced human atherosclerotic plaques showed ‘buried caps’ that provide evidence for prior rupture and healing. Plaques that lack a well-defined lipid core and have abundant rather than sparse extracellular matrix can provoke coronary thrombi due to a process known as superficial erosion. The clots associated with superficial erosion have characteristics of platelet-rich ‘white’ thrombi; by contrast, ‘red’ thrombi are rich in fibrin and trapped erythrocytes and associate with plaque rupture

(cit. Libby, P., Buring, J.E., Badimon, L. et al. Atherosclerosis. Nat Rev Dis Primers 5, 56 (2019). https://doi.org/10.1038/s41572-019-0106-z)

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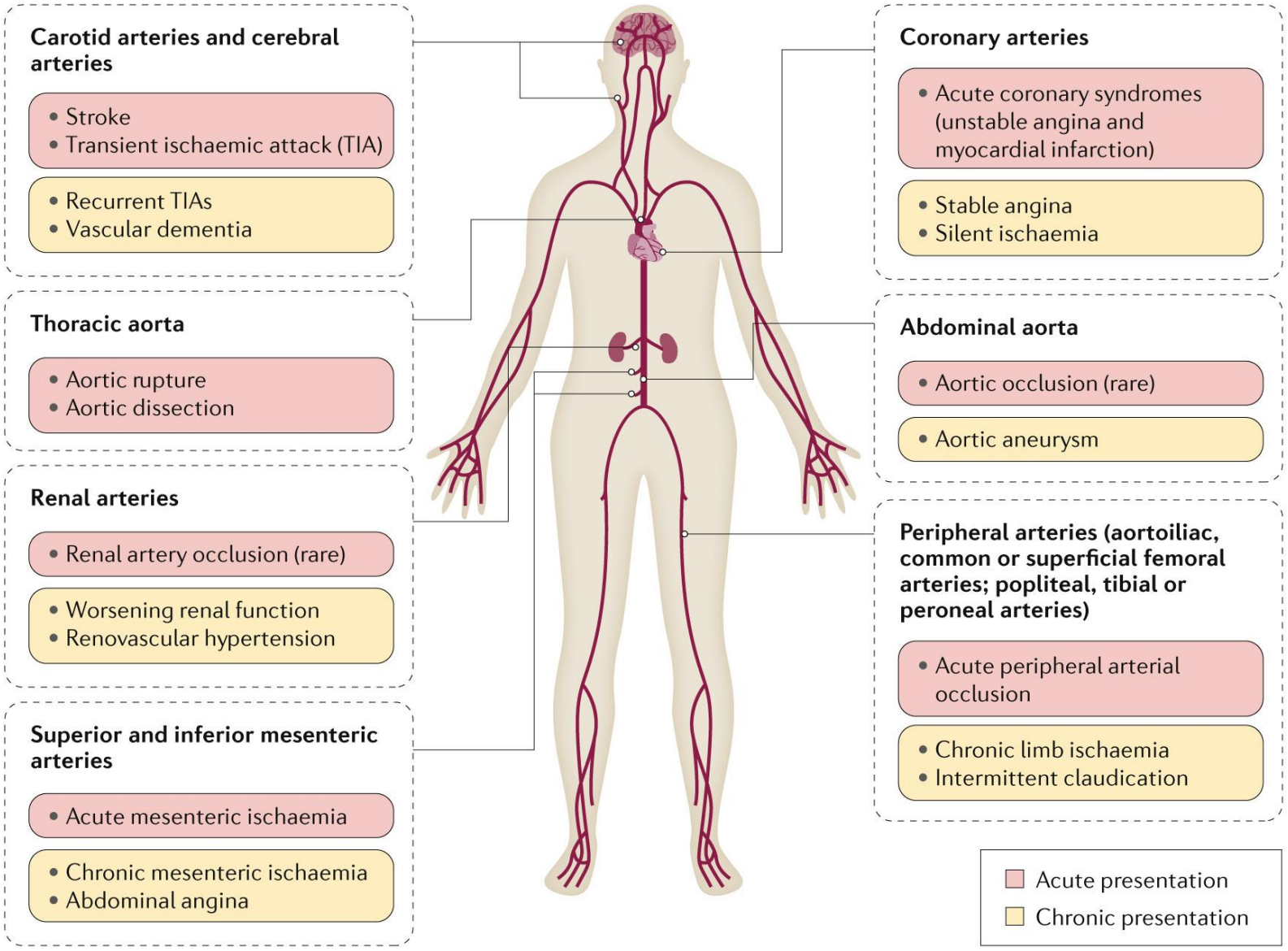
Clinical manifestations of AS in different predilection sites



- AS is a systemic disease that may involve multiple vessels
- Consequently, the clinical manifestations vary widely according to the vascular territory involved
- Despite the systemic nature of many risk factors such as hypercholesterolaemia, hypertension, diabetes mellitus and smoking, AS tends to involve primarily specific regions of the arterial tree
- Arterial areas subjected to either disturbed flow or low shear stress have particular susceptibility to atheroma formation
- These conditions prevail at branch points in the arterial tree.

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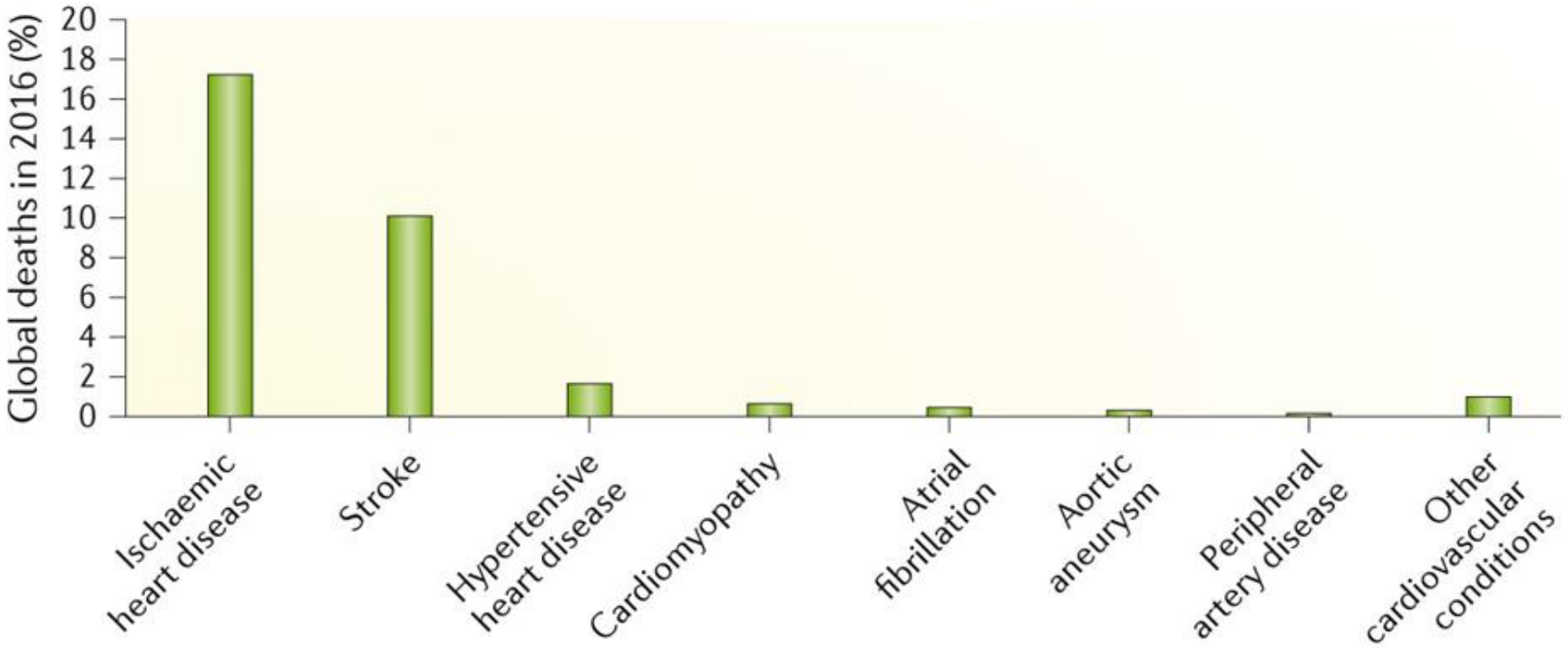
Je AS-based CVD an important epidemiologiclly?



The contribution of cardiovascular diseases to the global burden of death in 2016.These data convey the importance of atherosclerotic cardiovascular disease worldwide. Of note, many stroke deaths may not result directly from atherosclerotic disease but from hypertension, a highly prevalent cardiovascular risk factor. Similarly, not all cases of cardiomyopathy result from ischaemic damage, and some cases of atrial fibrillation may not be associated with atherosclerosis. Data from the Global Burden of Disease.

(cit. Libby, P., Buring, J.E., Badimon, L. et al. Atherosclerosis. Nat Rev Dis Primers 5, 56 (2019). https://doi.org/10.1038/s41572-019-0106-z)

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MYOCARDIAL ISCHEMIA

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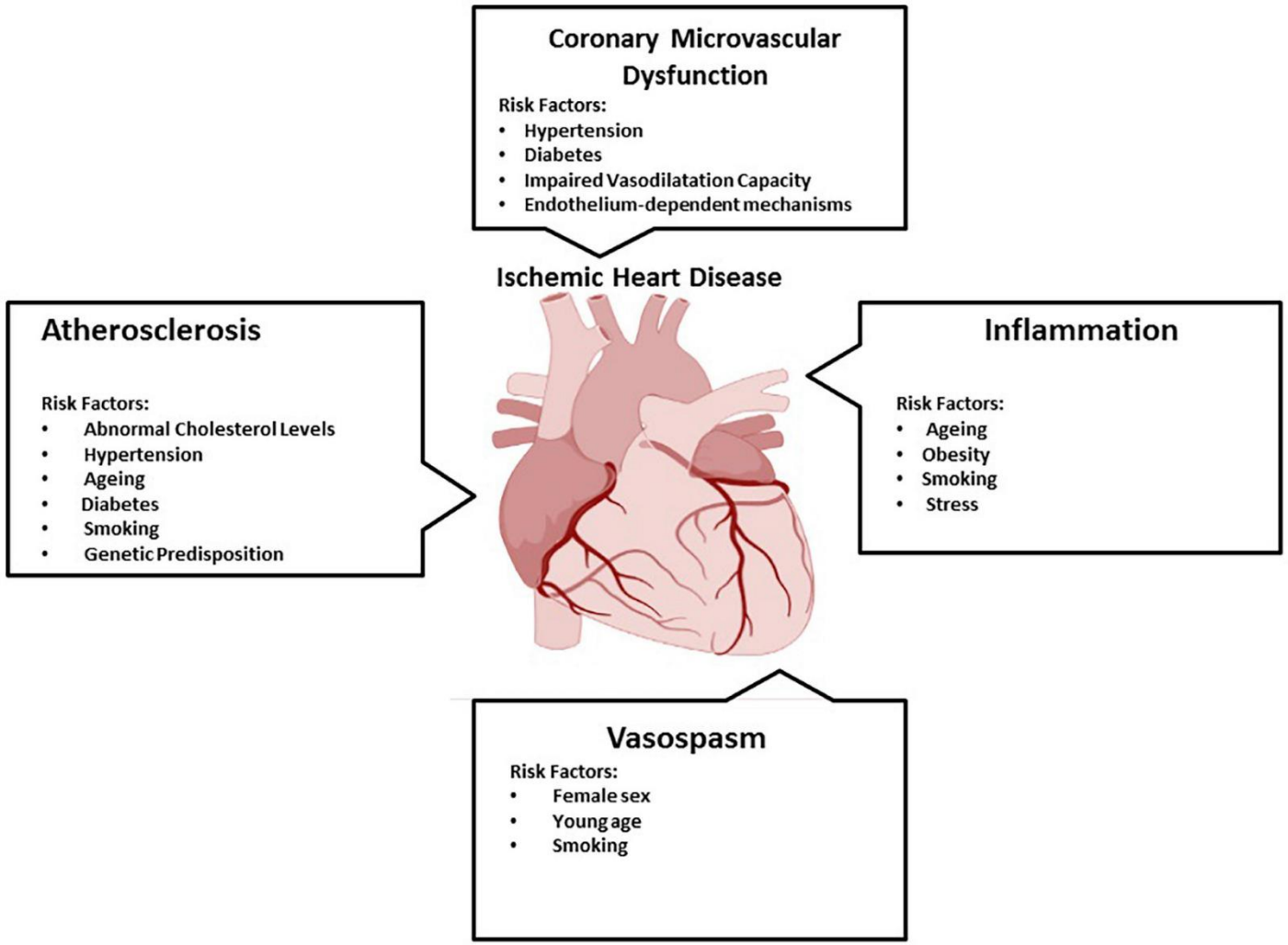
Myocardial ischemia – symptomatic as a IHD



- a consequence of reduced blood flow in coronary arteries, due to a combination of
  - fixed vessel narrowing as a result of **atherosclerosis**
    - length and diameter reduction
  - abnormal vascular tone as a result of **endothelial dysfunction**
    - vasospasm and thrombogenicity
  - condition of **microvasculature**
  - **systemic factors**
    - e.g. anemia, hypoxemia in pulmonary disease, hyperkinetic circulation, blood pressure etc.
  - **local cardiac factors**
    - such as hypertrophy, valvular disease, tachycardia and other heart rhythm abnormalities etc.
- This leads to an imbalance between myocardial oxygen supply and demand

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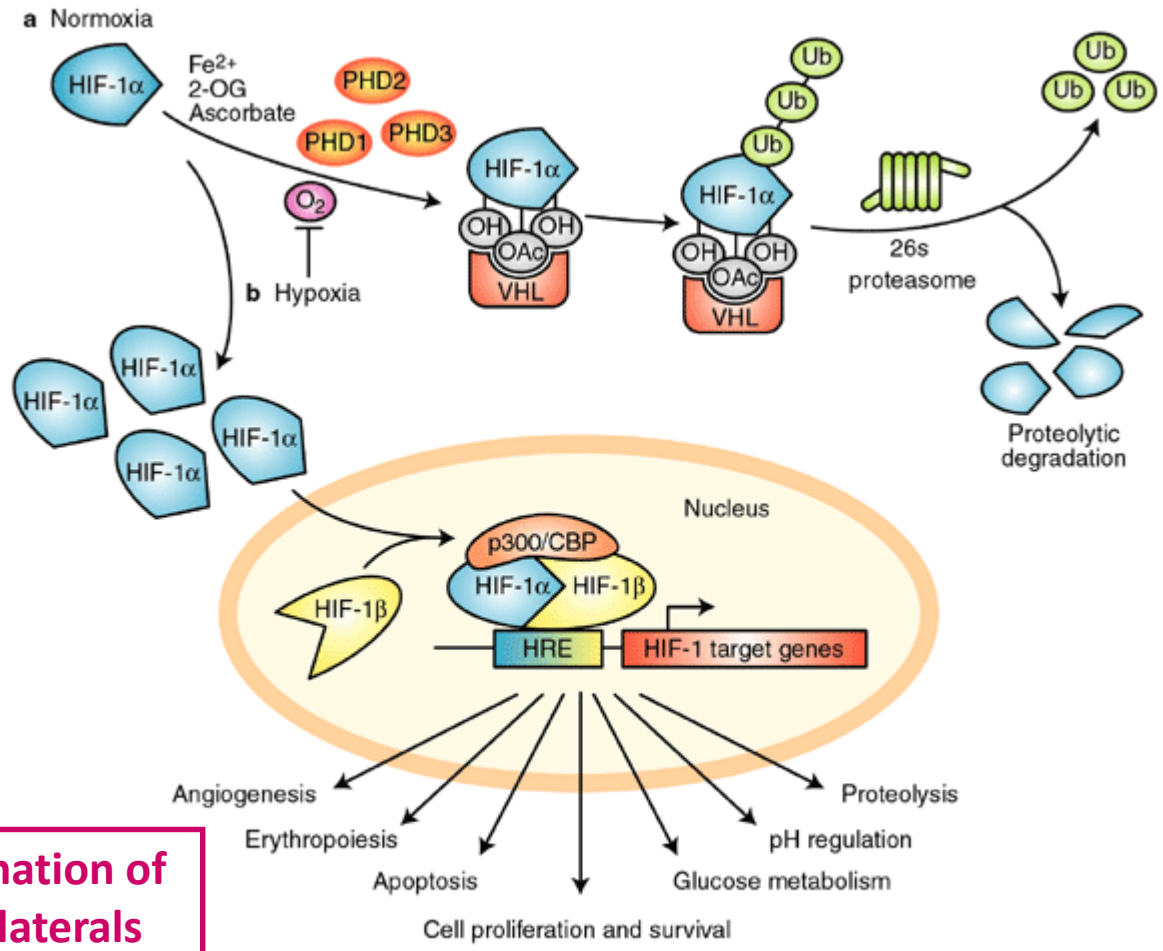
Hypoxia (↓O_2 in tissue) ≠ ischemia (↓tissue perfusion = ↓O_2 + ↓pH + ↑catabolites)



HIF-1α regulation by proline hydroxylation

formation of collaterals

- hypoxia is a common physiological situation both pre- and postnatally driving the tissue homeostasis
  - morphogenesis, wound healing, securing critical organ circulation by collaterals, …
- pathologically involved in many disease processes such as cancer progression, …
- hypoxia stimulates HIF-1 driven transcription program
- pathological hypoxia categories
  - (1) hypoxic hypoxia (due to hypoxemia)
    - lung diseases, blood shunting
  - (2) circulatory/ischemic
    - heart failure, vessel obstruction, embolism, …
  - (3) anemic
    - low Hb or its inability to bind oxygen
  - (4) histotoxic
    - blockade of the mitochondrial respiratory chain by poisons such as cyanide or hydrogen sulphide

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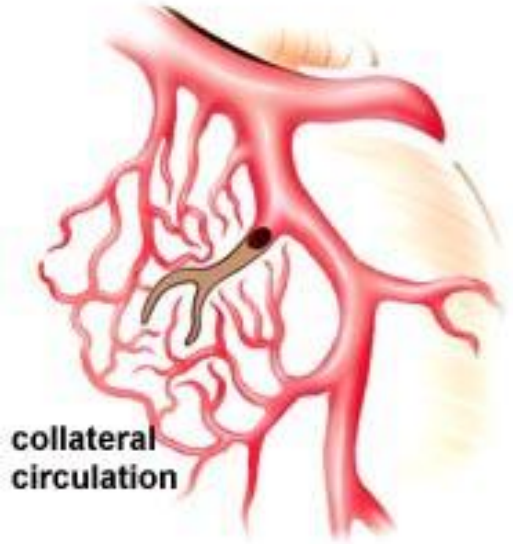
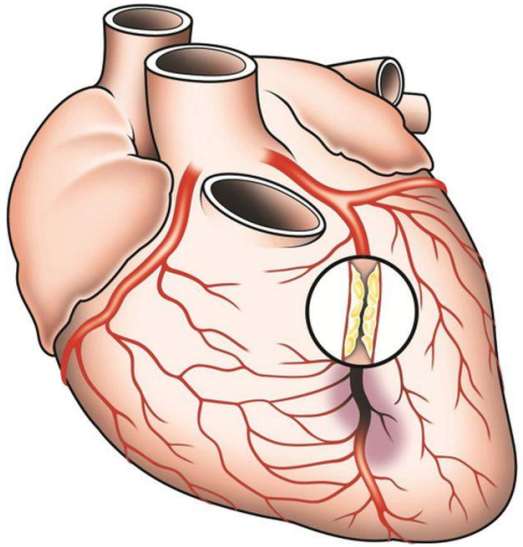
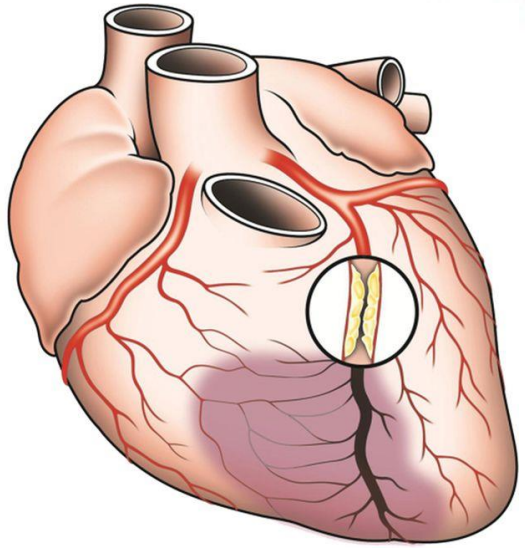
Coronary collaterals & angiogenesis

- enhancement of blood flow to ischaemic myocardium can result from
  - (1) recruitment of pre-existing coronary collaterals (= **arteriogenesis**)
    - variable density among people?
  - (2) de novo **angiogenesis**
    - angiogenesis = budding of capillaries that leads to the formation of new microvessels from pre-existing vascular structures
- orchestrated by hypoxia (HIF-1/VEGF)
- prominent interinidividual variability
- failure of concomitant angiogenesis in hypertrophic myocardium







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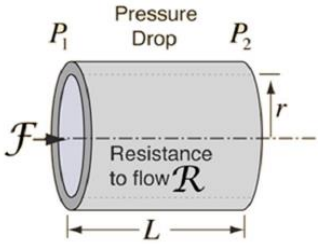
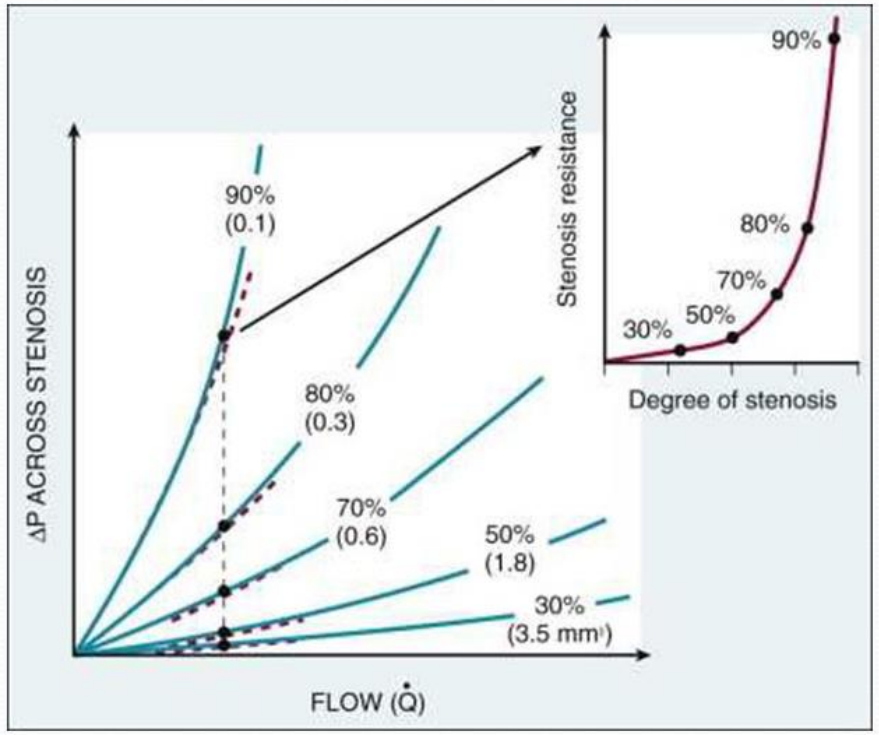
Coronary artery stenosis – haemodynamic consequences

Poiseuille's Law

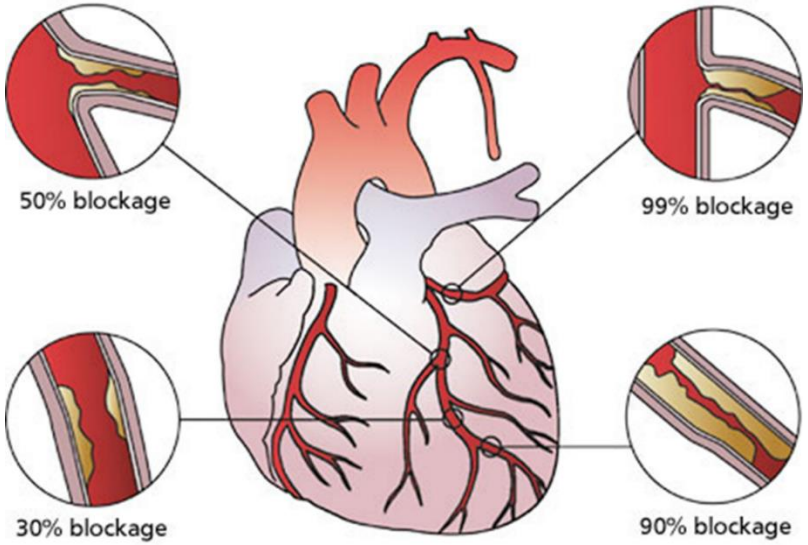
Volume Flowrate $= \mathcal{F} = \frac{P_1 - P_2}{\mathcal{R}}$

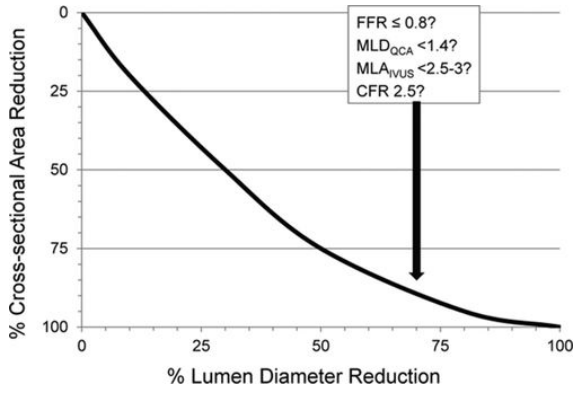
Resistance to Flow $\mathcal{R} = \frac{8\eta L}{\pi r^4}$





- change in vessel **diameter** (i.e. cross-sectional luminal area) produces by far the most significant effect
  - haemodynamically significant stenosis manifests usually after a significant (>50%) reduction in cross-sectional luminal area
  - concomitant factors modify the **severity of myocardial ischemia** significantly
    - condition of microcirculation (endothelial dysfunction)
    - heart rate
    - hypoxia/anemia, hypovolemia
    - aortic stenosis, LV hypertrophy
    - dynamic stenosis (thrombus, eccentric plaque, vasospasm)





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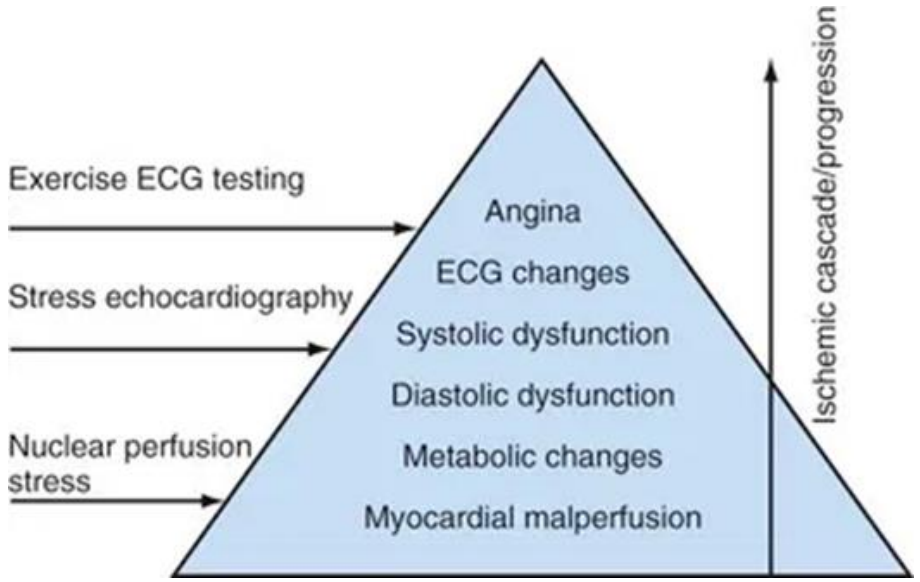
Metabolic and functional consequences of ischemia

- metabolic changes
  - ↓ perfusion → O_2 → ↓ aerobic metabolism → ATP depletion → Na intracellular retention → swelling → impaired Ca handling → accumulation of lactate and other catabolites → metabolic acidosis → efflux of potassium into extracellular space (arrhythmias!) → loss of membrane function and cellular integrity → cardiomyocyte death
  - accumulation of K^+, lactate, serotonin and ADP causes **ischemic pain** (angina)
- functional changes
  - ↓ contractility (= **systolic dysfunction**)
    - ↓ EF (ejection fraction), ↓ SV (stroke volume)
  - ↓ diastolic relaxation (= **diastolic dysfunction**)
    - ↑ EDP (end-diastolic pressure)
- in summary … **↓ CO (cardiac output)**
  - in the most serious form = cardiogenic shock
- (auto)regulatory and systemic regulatory mechanisms cause vasodilation in the intact part of coronary bed - **vascular steal**
  - stenotic arteries do not react to this stimulation and healthy ones further "steal" the blood from already ischemic region
- the extent of perfusion limitation decides whether the above mentioned processes appear only during the exercise, also in the rest or whether myocardial necrosis develops and what is its extent



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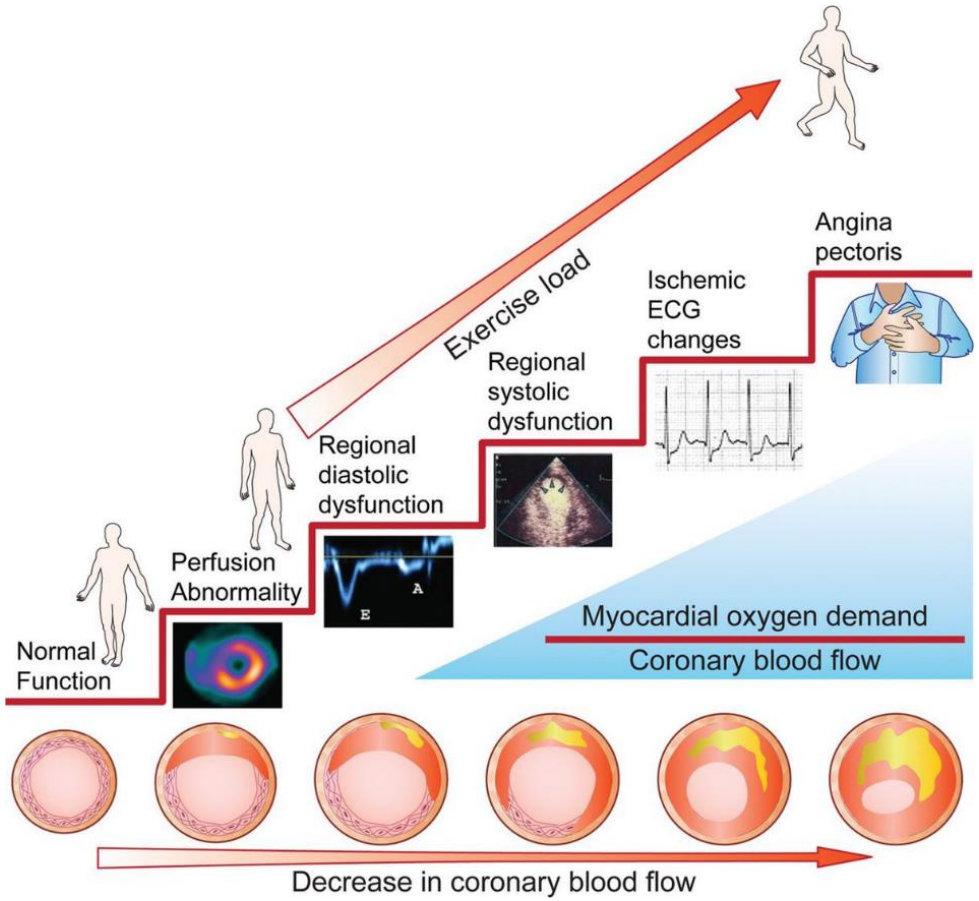
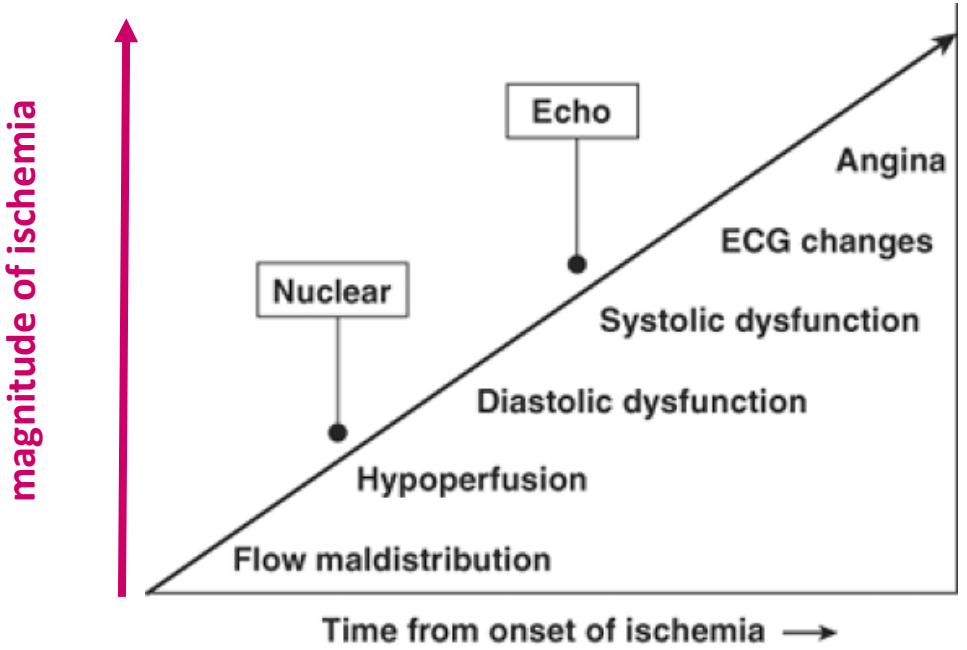
Metabolic and functional consequences of ischaemia

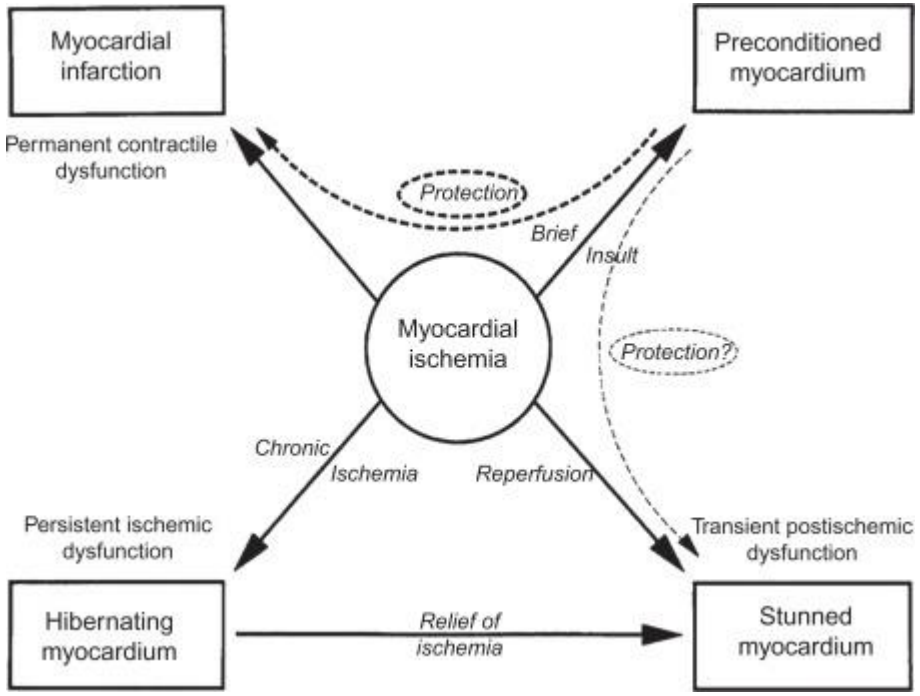
- clinical signs are „tip of the iceberg“
  - earlier changes detectable diagnostically





Consequences of myocardial injury – graded and often co-occurring

- reversible brief / intermittent injury (ischemia) = **preconditioning**
  - due to fixed stenosis and oxygen supply-demand mismatch or pharmacologically
  - molecular mechanisms involve iNOS, COX-2, mitochondrial K-ATP channels
- prolonged ischemia followed by reperfusion = **stunned myocardium**
  - depression of myocardial function despite restored flow
  - function spontaneously normalises in days – weeks
- chronic reduction of flow (at rest) = **hibernating myocardium**
  - myocyte apoptosis, myofilament autophagy, loss of B-adrenergic responsiveness and inhomogeneity in sympathetic activity, fibrosis
  - clinically: arrhythmia (V tachycardia and fibrillation) risk! and LV dysfunction
- irreversible injury and myocyte death = **myocardial infarction**
  - after ~20 min from occlusion coronary artery in then absence of significant collaterals
  - begins in the subendocardium and spreads as a wavefront towards epicardium
  - transmural death completed after 4 - 6 hrs
    - depends on the presence of other factors increasing oxygen consumption, such as tachycardia, anaemia, hypovolemia, and the degree of preconditioning



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Local and systemic parameters modifying severity of myocardial ischemia on top of AS

- many condition leading to oxygen supply/demand mismatch can cause/aggravate myocardial ischemia
- causes:
  - (1) reduction of coronary perfusion due to fixed mechanic obstruction
    - (a) coronary AS (with or without superimposed thrombotisation)
    - (b) thromboembolism (from distant site – e.g. atrial or ventricular thrombus, bacterial endocarditis etc.)

    by far the most important factor (~ 90%)
  - (2) dynamic obstruction due to vascular spasm
  - (3) "small vessel disease"
    - diabetic microangiopathy, polyarteritis nodosa, systemic lupus erythematosus, autoimmune vasculitis
  - (4) hypoxemia, hypoxia, hypotension
    - pulmonary disease, anaemia, abnormal haemoglobin, poisoning, shock, sepsis, …
  - (5) exaggerated oxygen demand
    - ↑↑↑ CO (e.g. thyrotoxicosis, amphetamine or cocaine abuse, …)
    - LV hypertrophy as a consequence of pressure (volume) overload
  - (6) polycythaemia, hyper-coagulation, DIC
- causes (1) and (2) affect larger arteries and branches (ischemia more epicardially)
- causes (3) to (6) smaller terminal branches and often coincide with (1) or (2)
  - note hypoxia ≠ ischemia

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ISCHEMIC HEART (IHD) DISEASE AS A CLINICAL MANIFESTATION OF CAD/CHD

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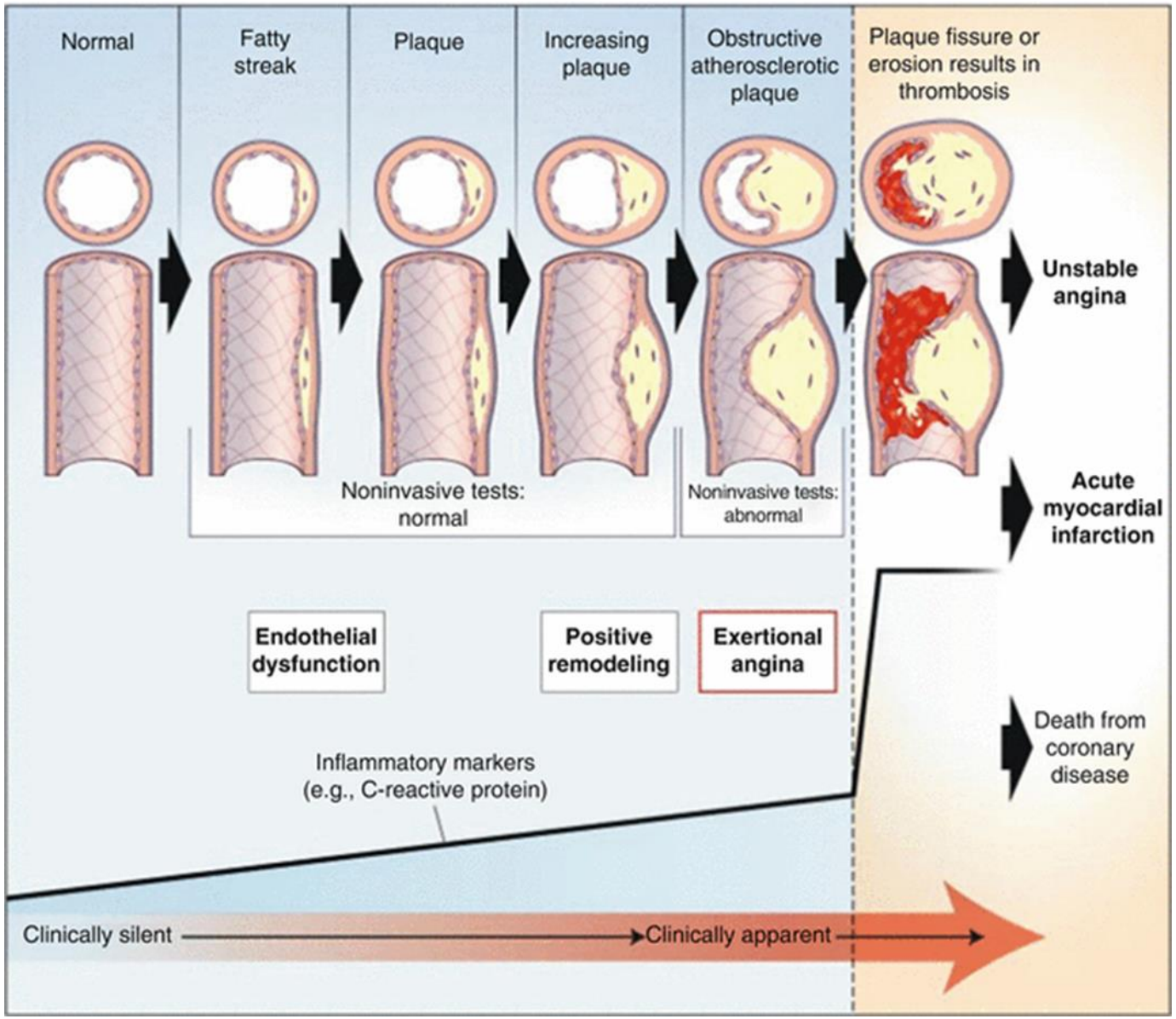
Clinical manifestation is a relatively late event



- AS is slowly progressing and asymptomatic for the most part of its progression
- Initial stages present in the first decade of life
- Subclinical AS present in 63% of the population (71% of men and 48% of women) by 40–54 years of age (Spanish PESA cohort)
- When symptoms do arise, they usually relate to
  - a critical reduction in blood flow caused by the luminal stenosis (narrowing) = **chronic/stable angina pectoris**
    - typically exertional
      - 50% lumen reduction – symptoms during exercise
      - 75% lumen reduction – symptoms at rest
      - but other factors play a role
        - plaque length, eccentricity, outward remodelling, sensitivity to vasodilators etc.
  - or to thrombotic obstruction = **acute coronary syndrome**

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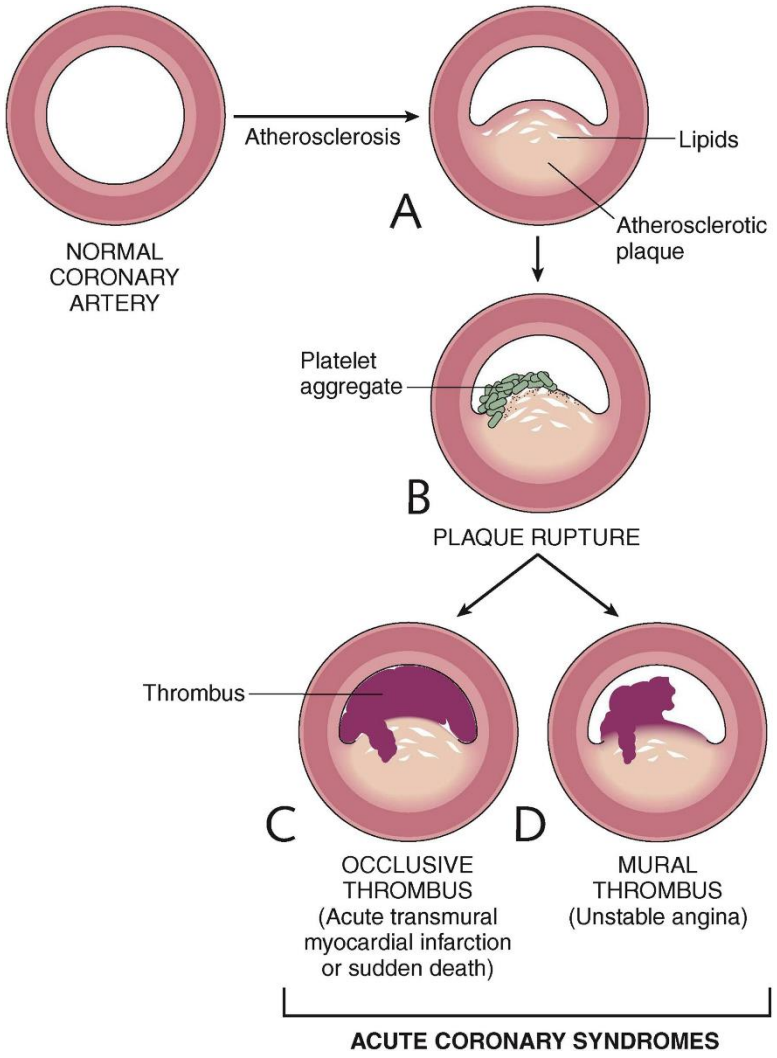
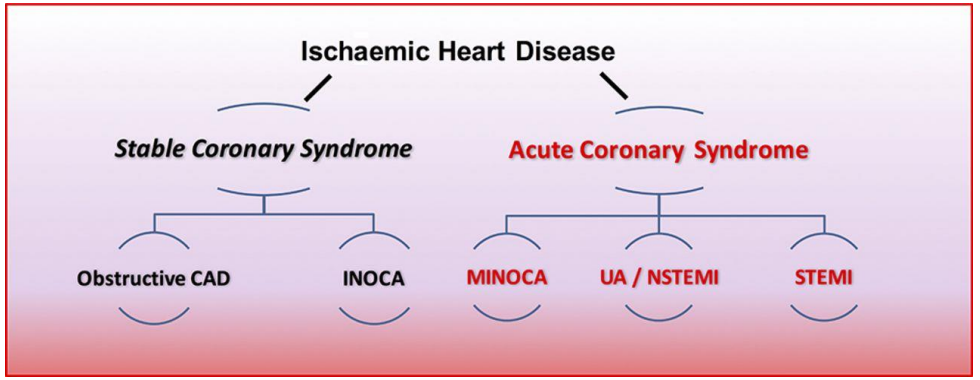
Fate of advanced AS plaque

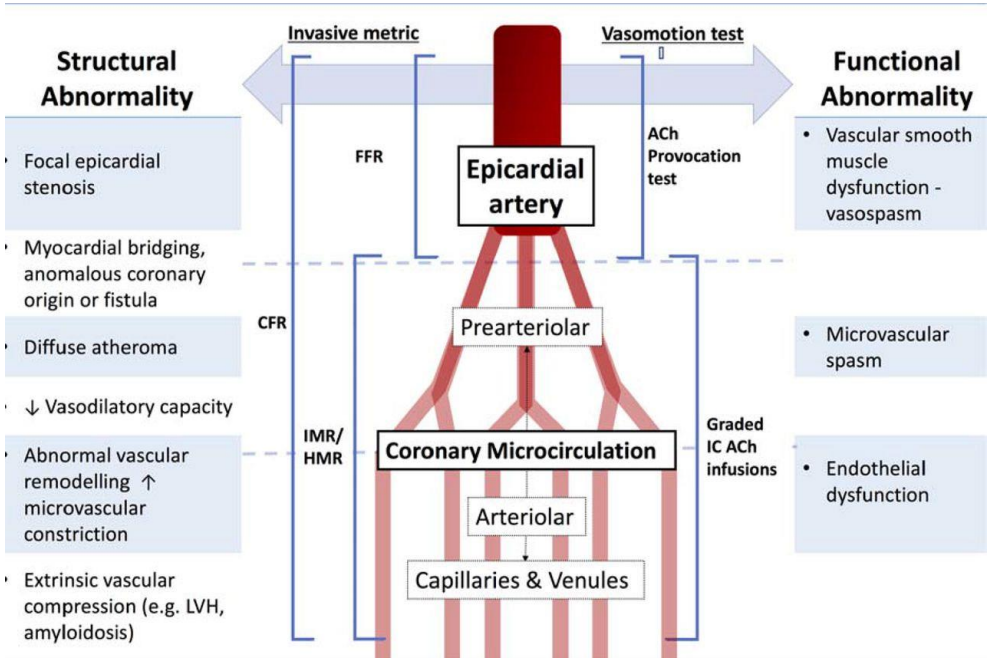
- Pathophysiological scenarios
  - (1) progressive growth of the plaque
    - asymptomatic until >50% of diameter reduction (= >75% cross-sectional area reduction)
    - typical cause of **stable angina**
  - (2) superficial erosion
    - denudation/apoptosis od ECs – mural platelet thrombi – healing – further lumen reduction
  - (3) plaque rupture and thrombosis
    - clinically leads to acute coronary event (**MI or sudden death**) in case of total occlusion of the vessel or **unstable angina** or no symptoms in case of a healing
    - very often happens in haemodynamically insignificant stenosis
    - plaque composition rather than plaques size matters
    - can happen due to the fracture of the fibrous cap or in the „shoulder“
      - imbalance between forces/mechanical strength



Clinical forms of CAD/CHD/IHD

- CAD/CHD/IHD is the leading global cause of death and lost life years in adults
  - despite reductions in morbidity and mortality in general, these are not consistent across subgroups
- classification/clinical forms
  - **stable coronary syndromes** = stable angina pectoris
    - recurrent, transient episodes of chest pain due to demand-supply mismatch
    - causes
      - obstructive CAD (angiographically proven)
      - INOCA (ischaemia and no obstructive coronary artery disease), formerly „coronary syndrome X“ (negative coronary angiography) – **10-20%**
        - due to coronary microvascular dysfunction (i.e. functional and/or structural abnormalities in the coronary microcirculation
        - due to coronary vasospasm (Prinzmetal variant angina)
        - due to other local or systemic causes
        - abnormal pain perception
    - **silent myocardial ischemia** (both obstructive and INOCA)
      - sometimes mixed – some episodes of ischemia with chest pain, others silent
  - **acute coronary syndromes**
    - unstable angina
    - myocardial infarction (heart attack) = frank cardiac necrosis
      - STEMI / transmural / Q-wave MI
        - ECG: ST-segment elevation present
      - non-STEMI / subendocardial / non-Q wave MI
        - ECG: ST-segment elevation absent
    - sudden cardiac death due to MI complications (usually ventricular arrhythmias)
  - **heart failure due to IHD**





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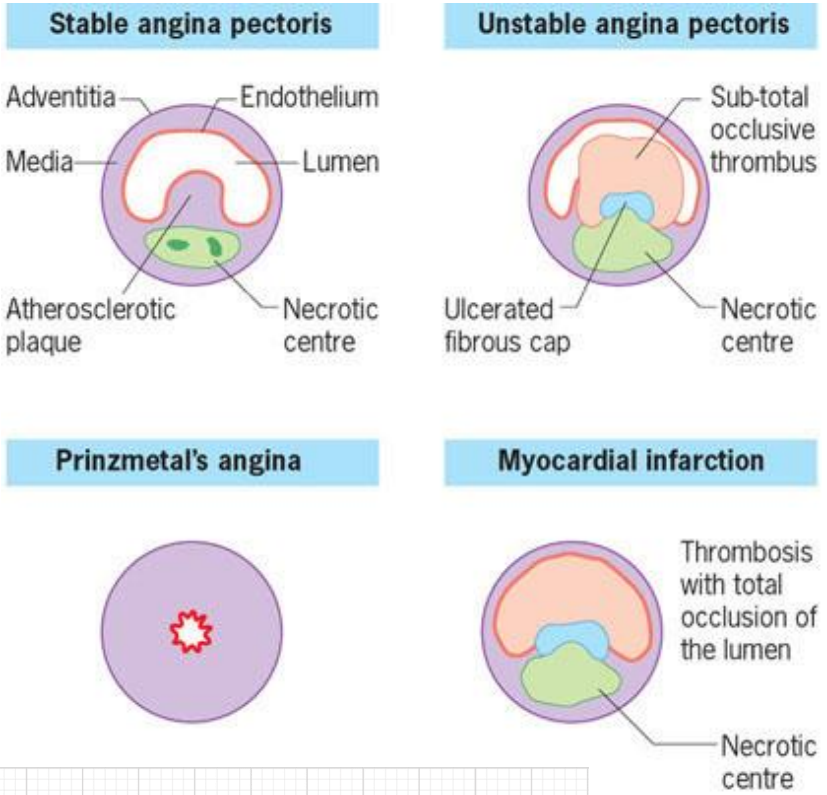
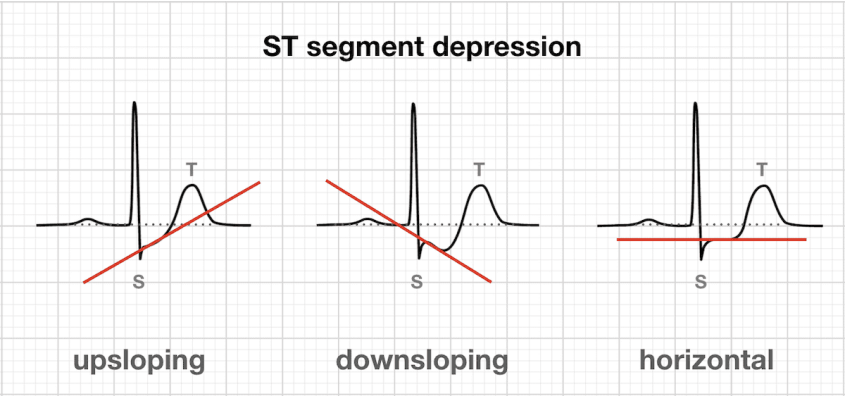
Angina pectoris

- diagnosis of angina is largely based on the clinical history
  - the chest pain/dyscomfort is generally described as 'heavy', 'tight' or 'gripping‘
  - typically, the pain is central/retrosternal and may radiate to the jaw and/or arms
  - it can range from a mild ache to a most severe pain that provokes sweating and fear, there may be associated breathlessness
  - typically exertional
  - dyspnoea can be a consequence of severe LV dysfunction (↑ LV filling pressure)
  - nocturnal angina in combination with sleep apnoea
  - grading systems
  - ECG finding tent to be normal at rest, ST segment abnormalities (typically depression) during angina
    - additional changes such as LBBB and LAFB associated with impaired LV function and indicate poor prognosis
- types – manifestation:
  - stable
    - provoked by physical exertion, especially after meals and in cold
    - aggravated by anger or excitement
    - pain occurs predictably at a certain level of exertion and fades with rest (the threshold for developing pain is variable depending on the extent of the stenosis)
  - unstable
    - angina of recent onset (less than 1 month)
    - worsening angina (previously stable for certain time)
    - angina at rest
- causes
  - obstructive CAD
  - INOCA
    - cardiac syndrome X
      - personal history of angina + positive exercise test + angiographically normal coronary arteries
      - heterogeneous group (more common in women)
      - due to microvascular abnormalities
    - variant (Prinzmetal) angina
      - occurs without provocation, usually at rest or night, as a result of coronary artery spasm
      - more frequently in women





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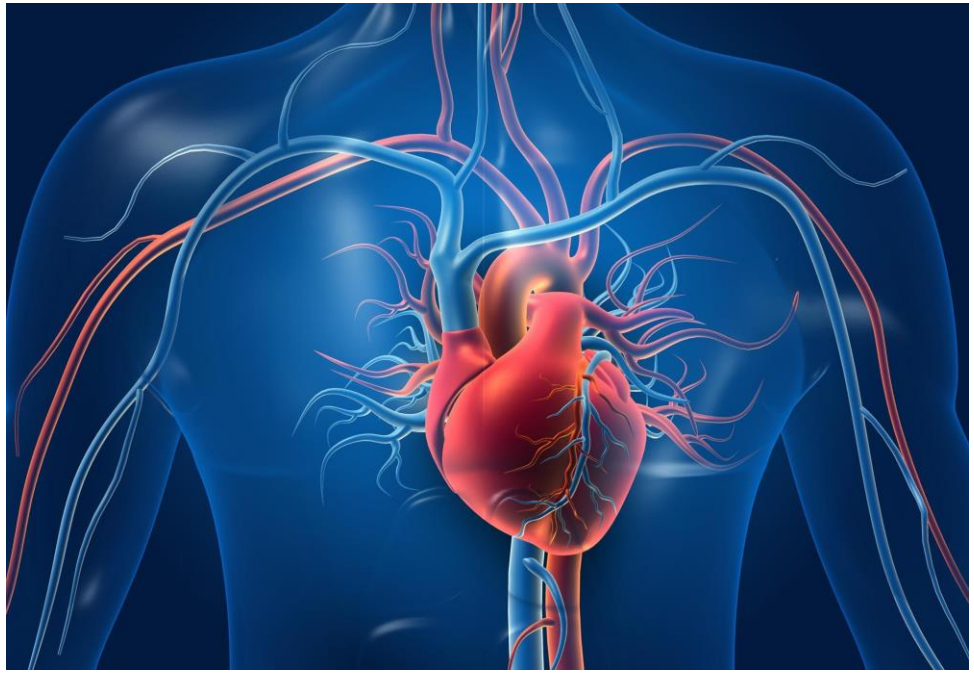

ACUTE CORONARY SYNDROMES

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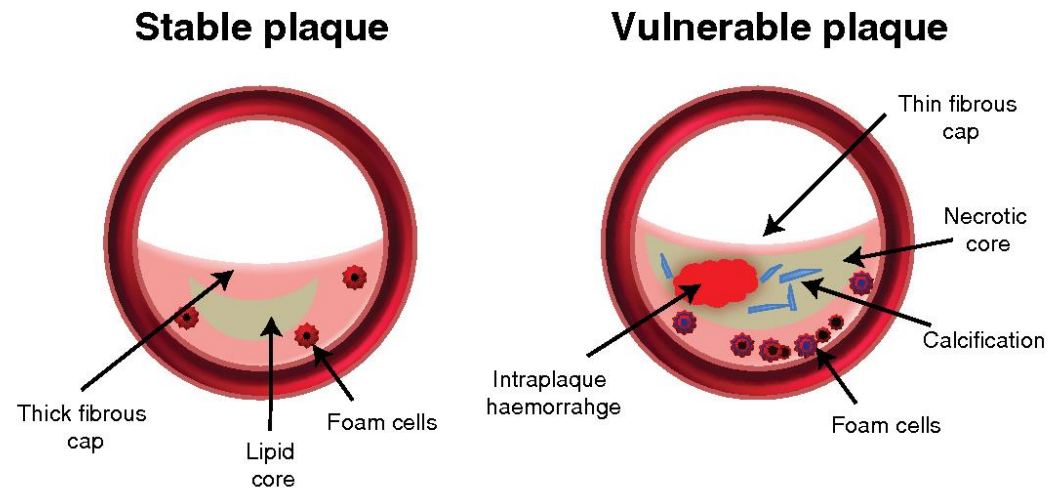
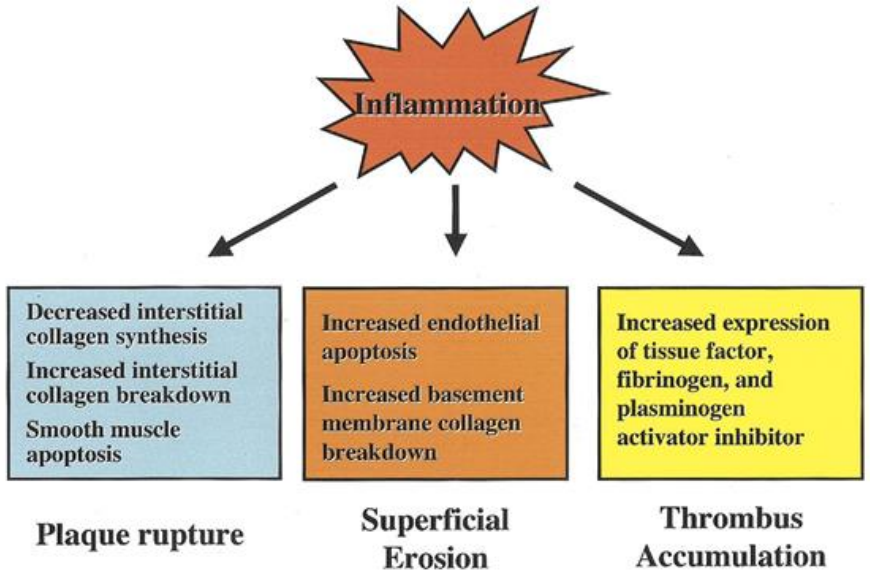
Atherothrombosis due to the rupture of vulnerable plaque

- Typical features of vulnerable plaque
  - a thin fibrous cap (thin cap fibroatheroma)
  - extensive inflammatory infiltration by macrophages and T lymphocytes
  - large lipid core
  - small numbers of SMCs
  - intra-plaque haemorrhage or angiogenesis
    - from vasa vasorum
  - tendency to lower extent of calcification
    - more often spotty calcification
- inflammation is the most important part of progression and destabilization of an atherosclerotic plaque
  - release of pro-inflammatory cytokines and matrix metalloproteinases contributes to the degradation of collagenous components in the fibrous cap of the atheroma
  - apoptosis of collagen synthesizing SMCs
  - tissue factor produced by intra-plaque inflammatory cells
- **identification of vulnerable plaque (= prone to rupture) is clinically extremely important**





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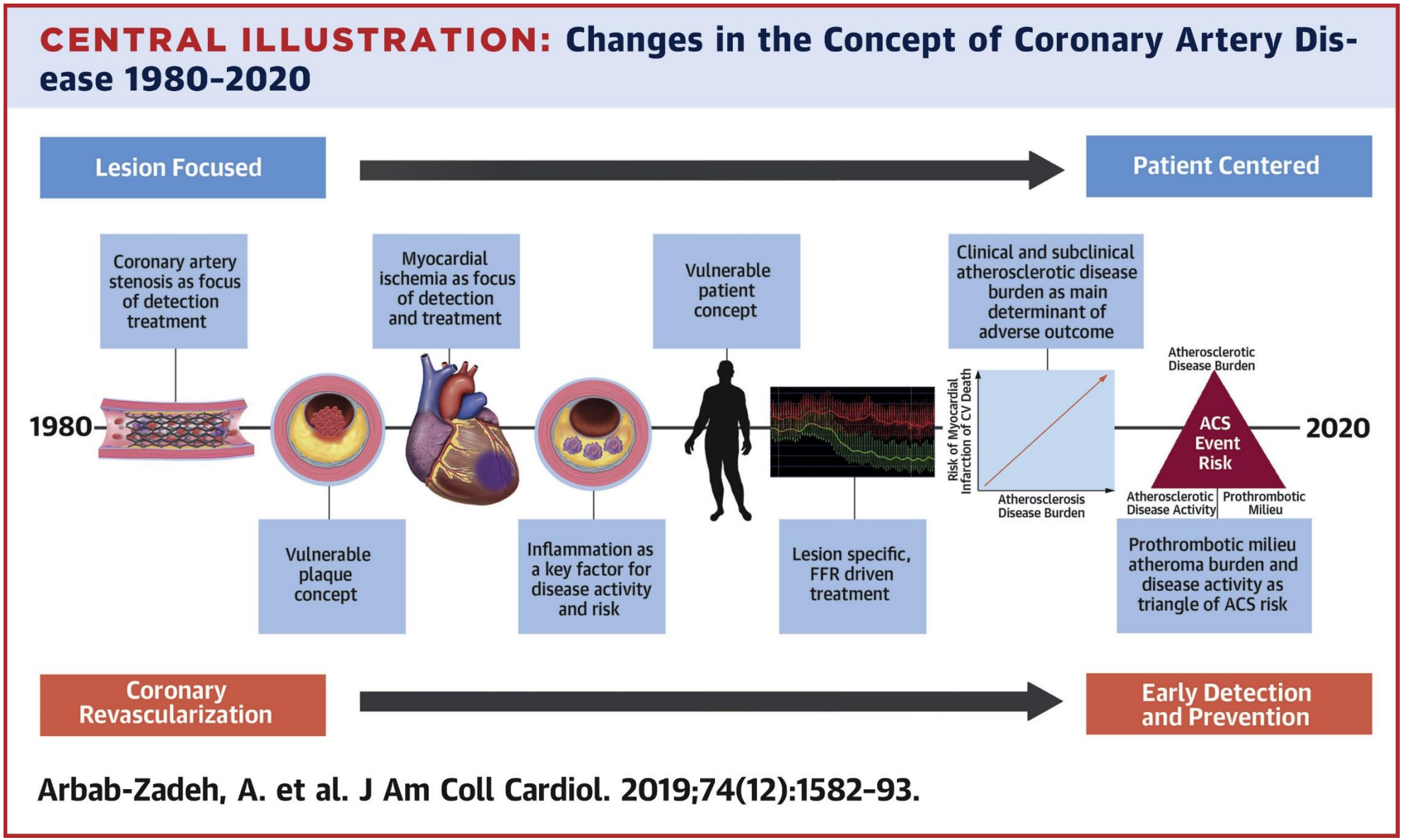
Shift from „vulnerable plaque“ to „vulnerable patient concept“



Arbab-Zadeh, A. et al. J Am Coll Cardiol. 2019;74(12):1582-93.

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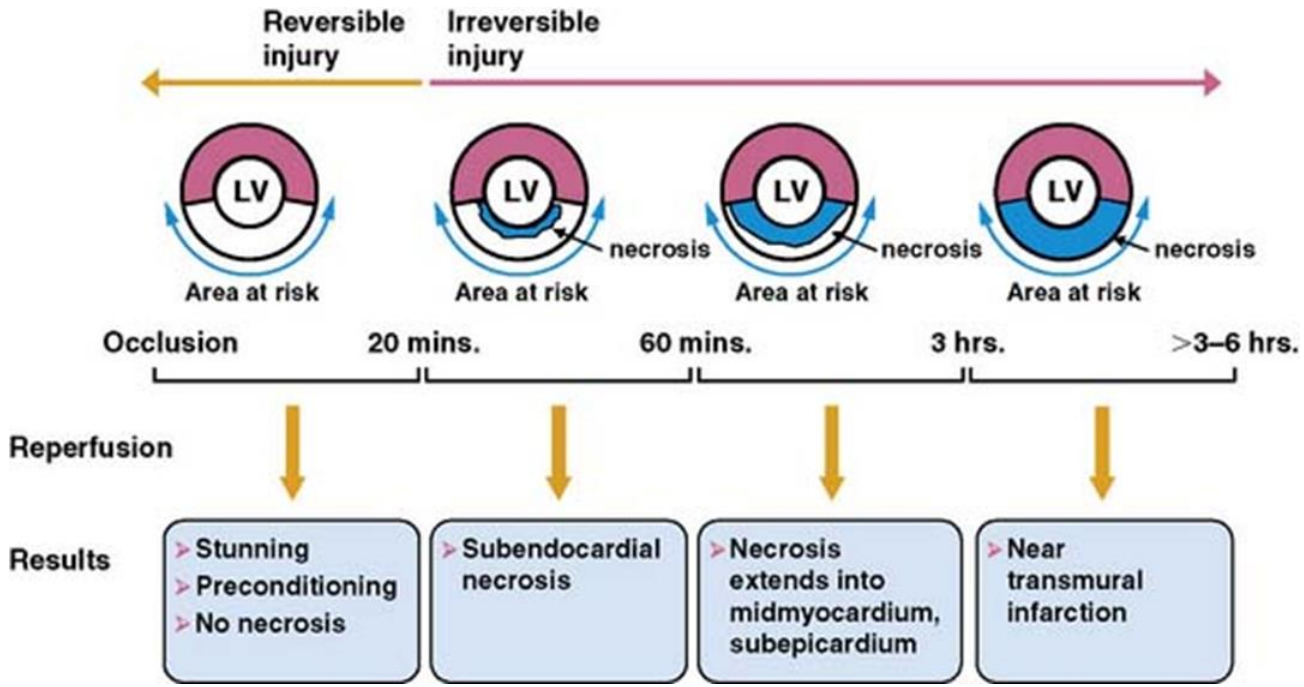
Myocardial infarction (MI) = heart attack

- Occlusive thrombus consists of a platelet-rich core ('white clot') and a surrounding fibrin-rich ('red') clot
- The infarct develops in a typical **wave front manner**, starting in the subendocardial layers in the centre of the area at risk and progressing into subepicardial layers and to the border zones of area at risk with ongoing duration of coronary occlusion
  - **timing defines the extent of necrosis**
    - irreversible changes develop 20-40 min after complete occlusion of the artery
    - initially always subendocardial non-STEMI
    - spreads epicardially
    - eventually, after >3hrs STEMI develops
- Therefore, **the size of the resulting infarction** depends on
  - (i) the size of the ischaemic area at risk
    - where the stenosis/occlusion happens
  - (ii) the duration and intermittency of coronary occlusion
    - time of reperfusion (spontaneous or induced)
  - (iii) the magnitude of residual collateral blood flow
  - (iv) condition of preconditioned x hibernating myocardium
  - (v) the extent of coronary microvascular dysfunction
  - (vi) intensity of the pain
    - event. silent



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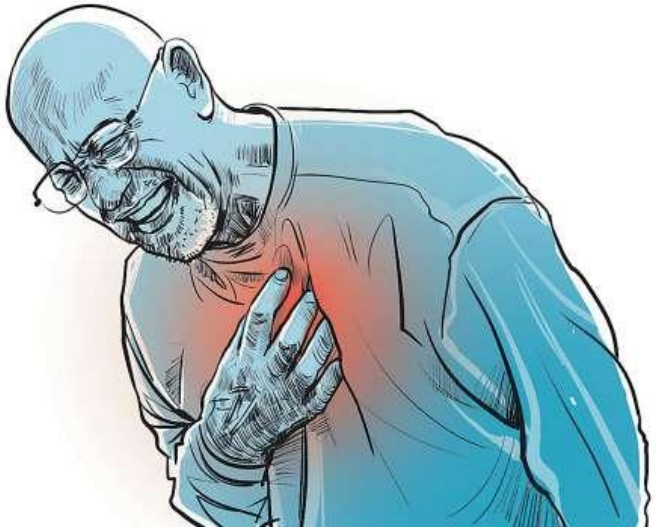
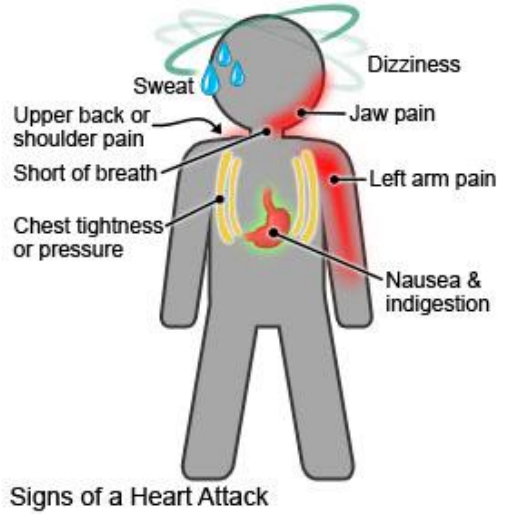
Clinical features of MI

- severe (crushing) chest pain
  - onset is usually sudden, often occurring at rest, and persists fairly constantly for some hours
  - however, as many as 20% of patients with MI have no pain
    - so-called 'silent' myocardial infarctions are more common in diabetics and the elderly
- symptoms are produced directly by MI/ischemia (heart, brain, …)
  - chest pain, dizziness,
- or, indirectly, by autonomous nervous system activation
  - sympathetic
    - sinus tachycardia and the fourth heart sound
    - sweating
    - restlessness
  - parasympathetic
    - nausea, vomiting
- pulmonary congestion due to diastolic dysfunction
  - dyspnoea/breathlessness
- referred pain (back, jaw, shoulder, …) – important for differential diagnosis!
- modest fever (up to 38°C) due to myocardial necrosis often occurs over the course of the first 5 days





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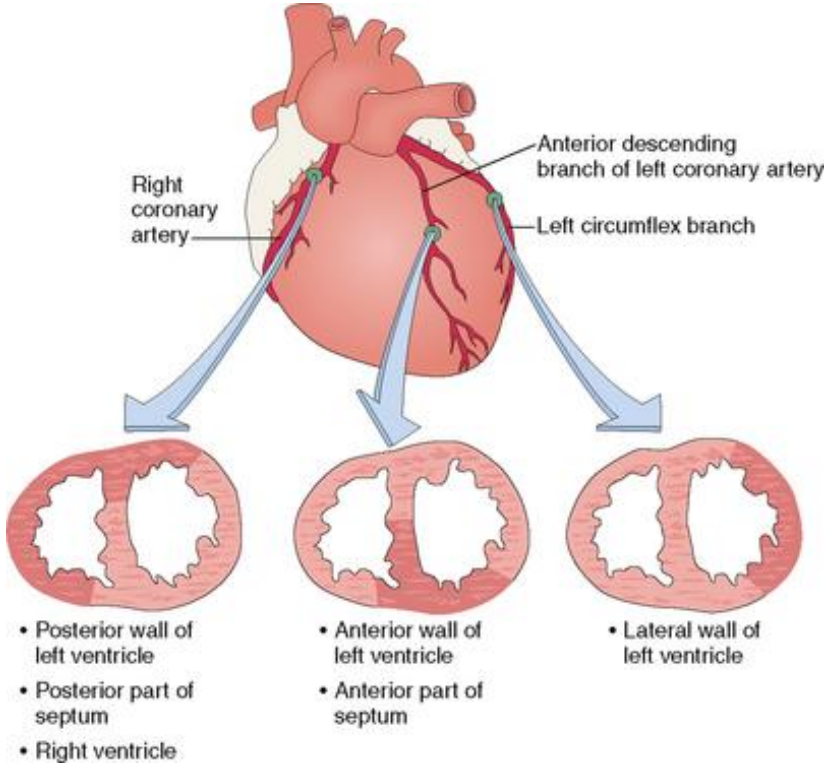
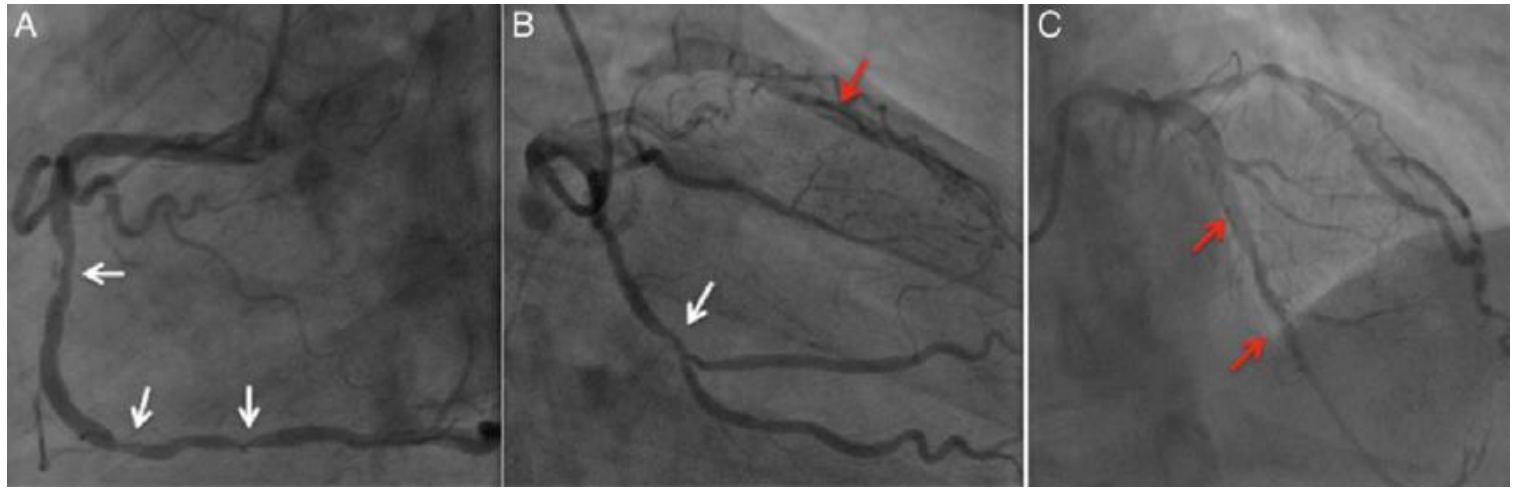
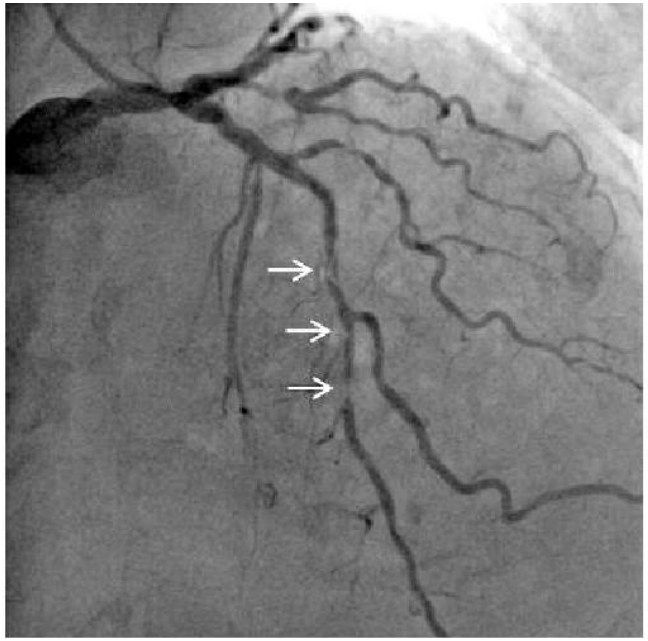
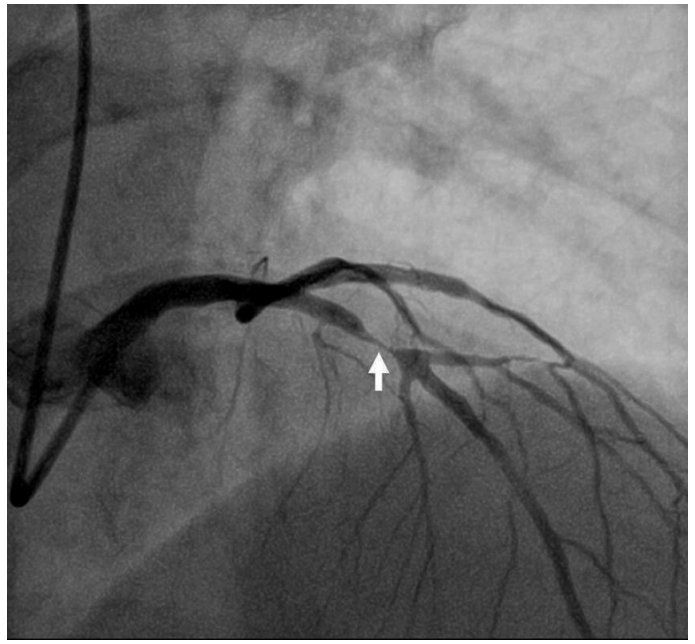
Localisation of MI depends on obstructed artery









- Majority of stenoses and subsequent **ruptures** or **erosions** of an **AS plaque** develop in proximal parts of epicardial arteries (or 1st order branches)
  - thus can be assessed by coronarography
  - stenoses in intramyocardial (penetrating) branches are rare
- LV much more commonly affected
  - 40-50% cases LAD
  - 15-20 % cases LCX
- RV and atria rarely
  - 30-40% cases RCA

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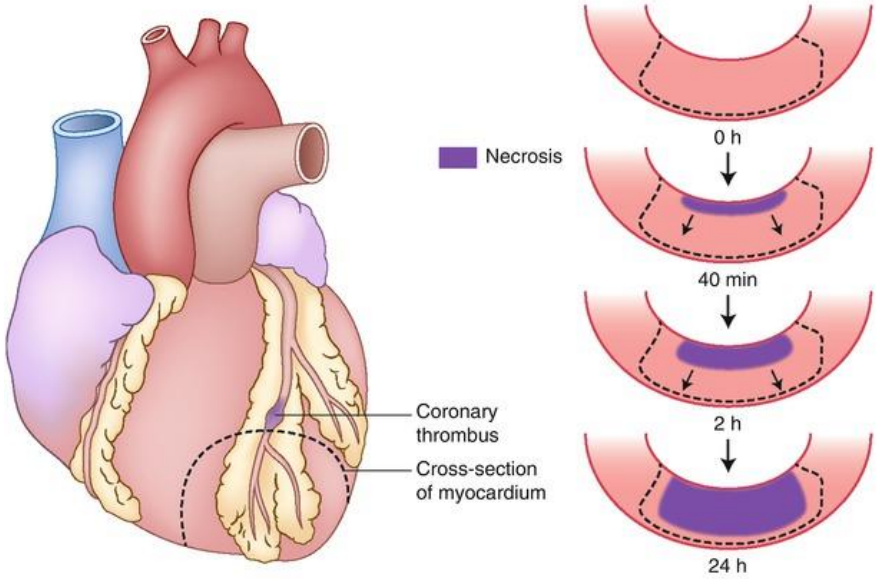
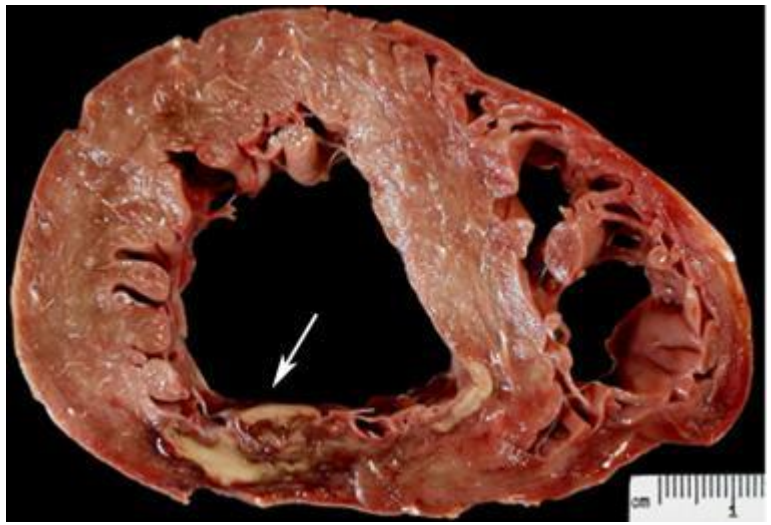
Pathology of MI

- irreversible changes develop 20-40 min after complete occlusion of the artery
  - swelling, electrolyte abnormalities
- 6 hours after the onset of infarction, the myocardium is swollen and pale
  - coagulation necrosis
- in 24 hours the necrotic tissue appears deep red owing to haemorrhage
  - LV wall in infarct zone weakened and dilated
- during the next few weeks, an inflammatory reaction develops and the infarcted tissue turns grey and gradually forms a thin, fibrous scar
- late remodelling
  - alteration in size, shape and thickness of both the infarcted myocardium (which thins and expands) and the compensatory hypertrophy that occurs in other areas of the viable myocardium





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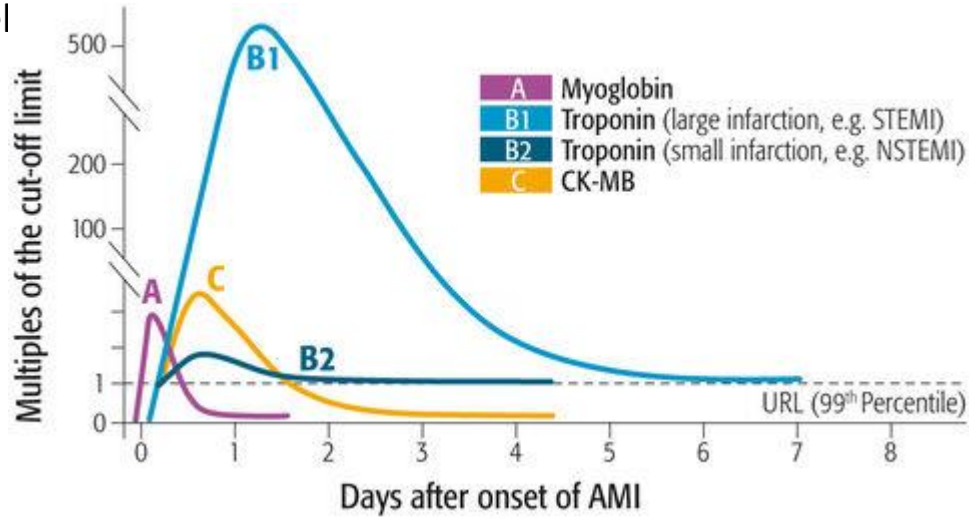
Cardiac markers of myocardial damage / acute MI

- necrotic cardiac tissue releases several enzymes and proteins into the serum:
  - **CK - creatinkinase**
    - peaks within 24hrs and is usually back to normal by 48hrs (also produced by damaged skeletal muscle and brain)
    - **cardiac-specific isoforms (CK-MB)** allows greater diagnostic accuracy
    - the size of the enzyme rise is broadly proportional to the infarction size
    - possibility to detect re-infarcion
  - **Troponins I and T**
    - consists of three subunits, troponin I (TnI), troponin T (TnT) and troponin C (TnC), each subunit is responsible for part of troponin complex function
      - TnI inhibits ATP-ase activity of acto-myosin
      - TnT and TnI are presented in cardiac muscles in different forms than in skeletal muscles
      - only one tissue-specific isoform of TnI is described for cardiac muscle tissue (cTnI)
    - considered to be more sensitive and significantly more specific in diagnosis of MI than the CK-MB and LDH isoenzymes
    - cTnI can be detected in blood 3 – 6 hrs after onset of the chest pain, reaching peak level within 16 – 30hrs
  - **Myoglobin**
  - historically AST - aspartate aminotransferase and LDH - lactate del
    - AST and LDH rarely used now for the diagnosis of MI
    - LDH peaks at 3-4 days and remains elevated for up to 10 days and can be useful for confirming myocardial infarction in patients presenting several days after



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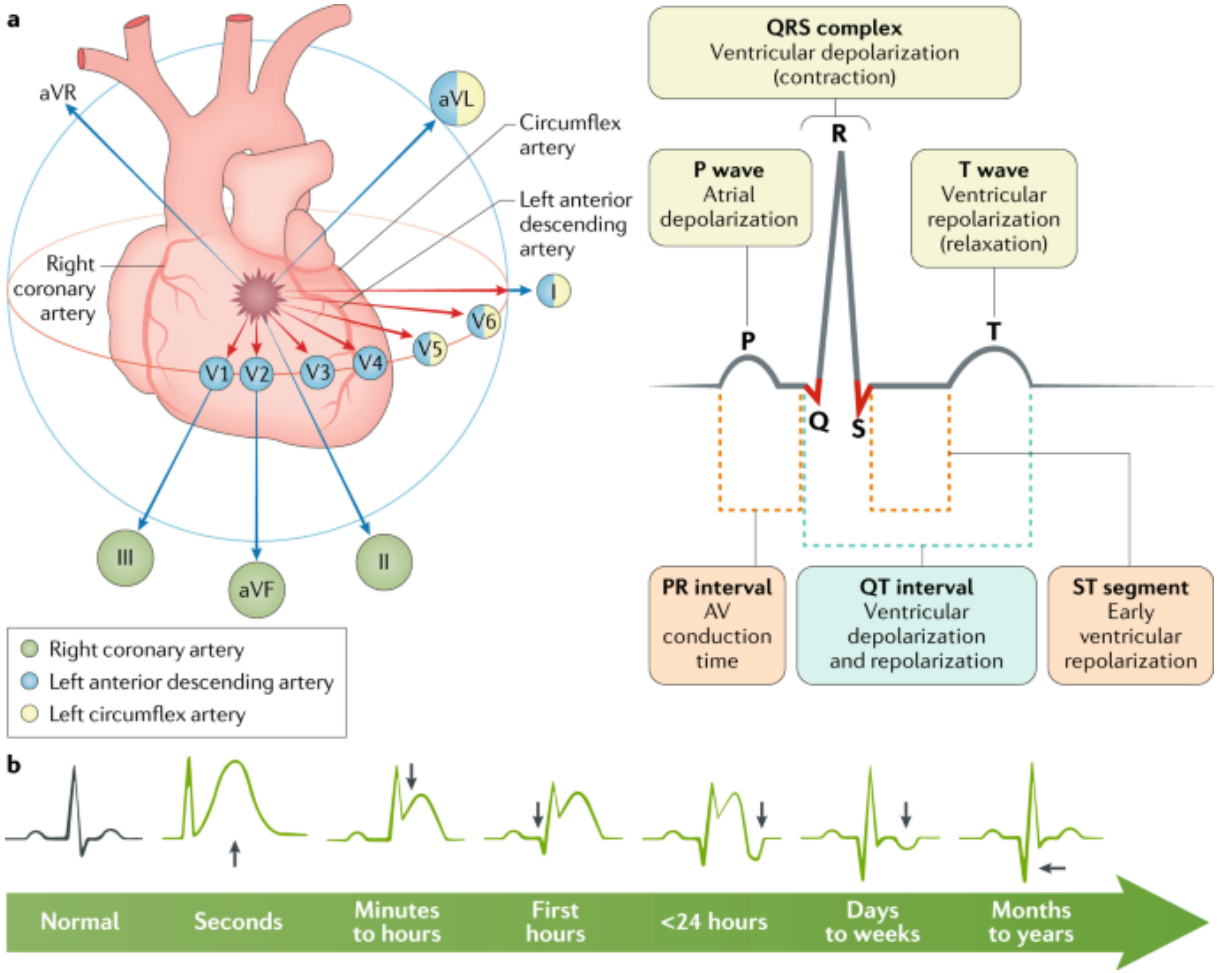
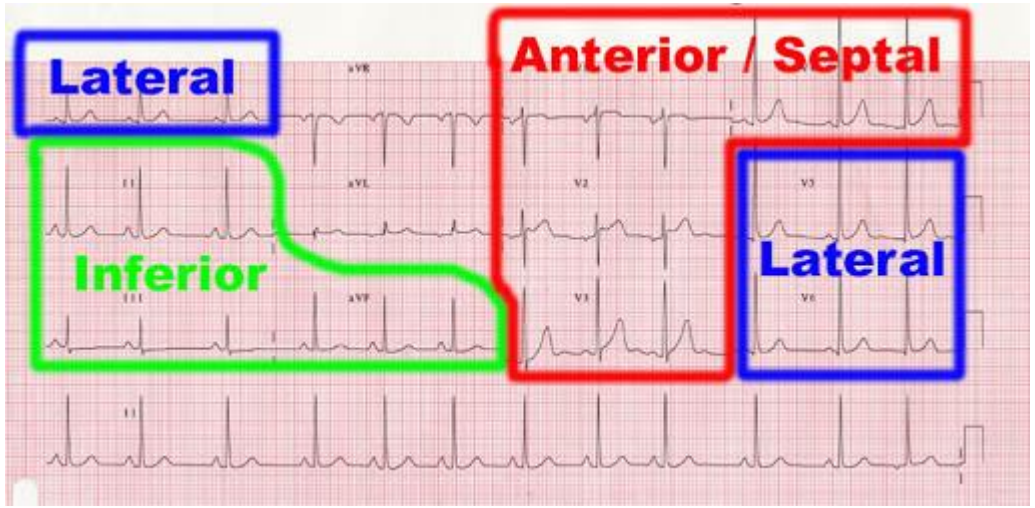
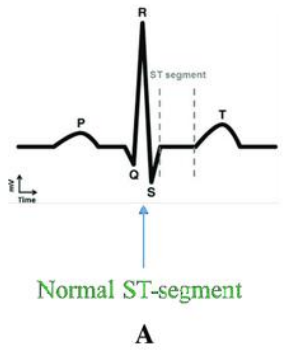
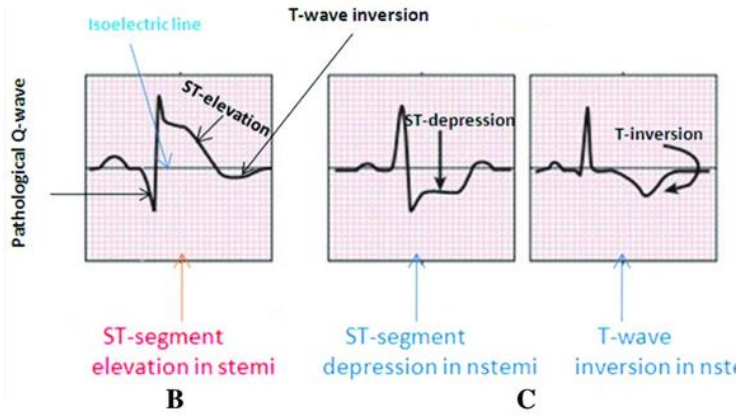
ECG changes evolve in parallel with tissue changes









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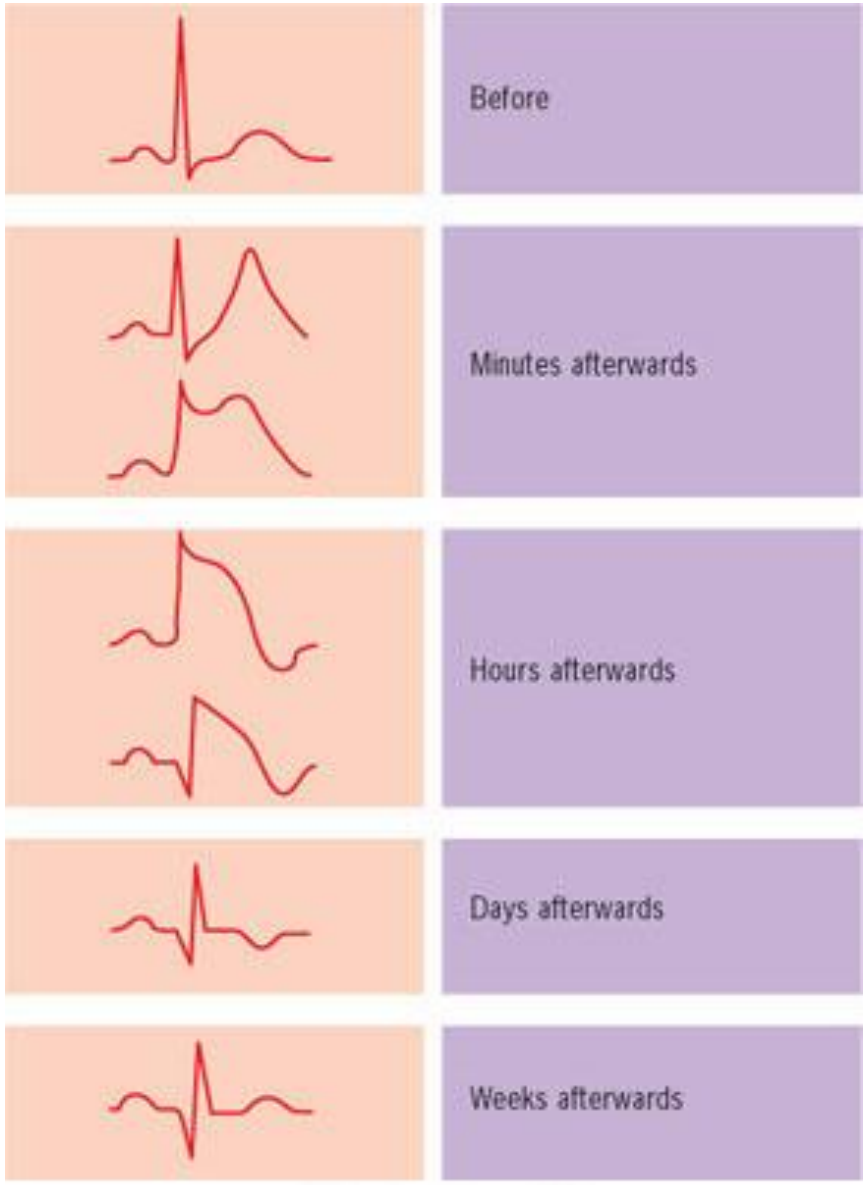
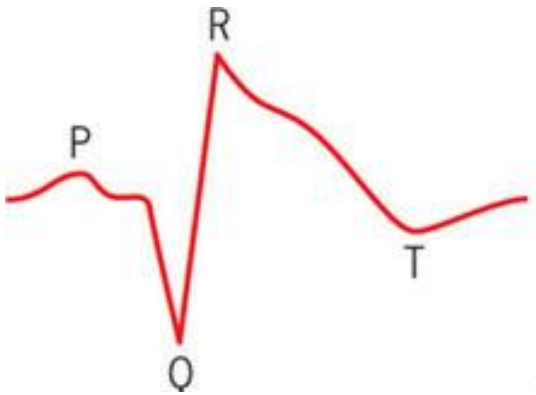
Temporal ECG changes during STEMI



- first few minutes – tall spiked T waves
- during first hours - ST segment elevation develops (Parde waves)
- after the first few hours - the T wave inverts
- during days after onset - the R wave voltage is decreased and Q waves develop
- after a few days - the ST segment returns to normal
- after weeks or months - the T wave may return to normal
- deep Q wave remains forever or may disappear



Q ≥ 1 mm wide (0.04 s)
and/or
Q ≥ 2 mm deep (0.2 mV)

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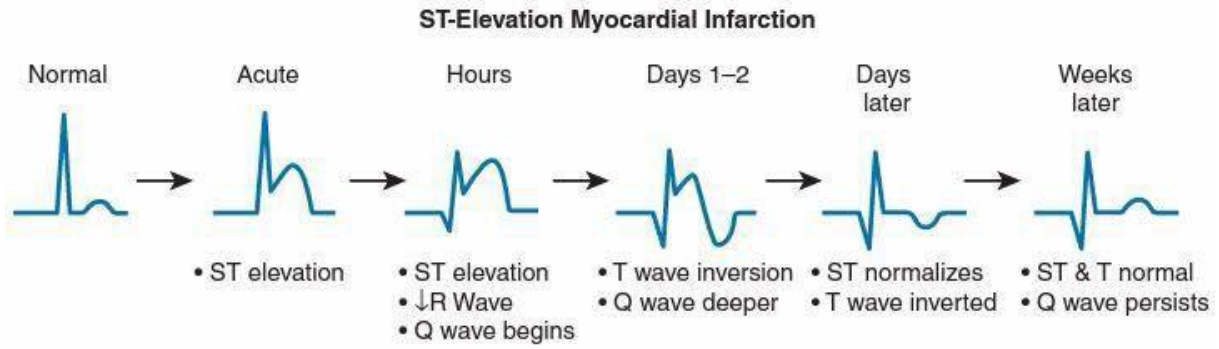
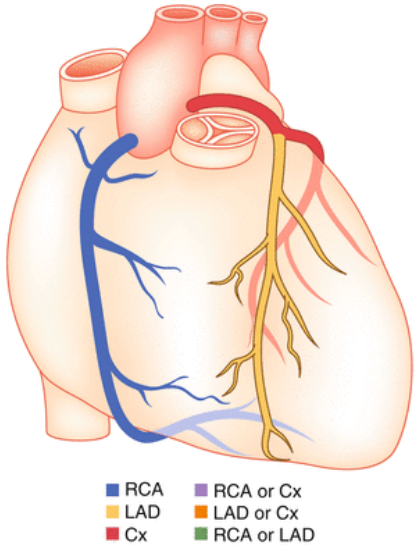
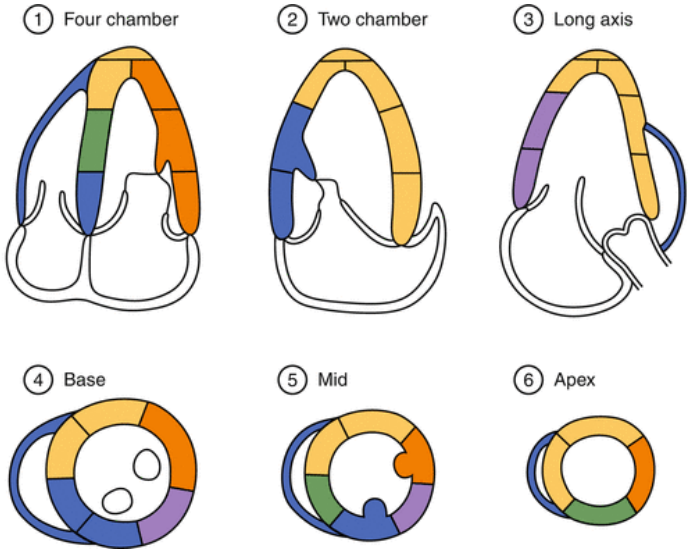
Evolution of STEMI (and to some extent of non-STEMI)

- **STEMI** is a dynamic process that **does not occur in instant**
  - changing ECG and echocardiography pattern parallels the evolution
- substantial **area at risk** (30–50%) is still viable and therefore **salvageable** by reperfusion after some time from the onset of angina symptoms
- early and late complication of MI are function of its size
  - recent meta-analyses emphasized the pivotal importance of infarct size within 1 month after MI as a determinant of all-cause mortality and hospitalization for heart failure at 1 year
- spontaneous reperfusion begins after 12-24 hrs
- to salvage at risk and stunned myocardium **reperfusion therapy** should be initiated as soon as possible
    - first line therapy nowadays together with strategies decreasing myocardial oxygen demands
  - pharmacological = thrombolysis / fibrinolysis
    - time! decreased efficacy as coronary thrombi mature
    - administration of t-PA
  - mechanical = PCI (percutaneous coronary intervention)
    - balloon angioplasty
    - stent deployment







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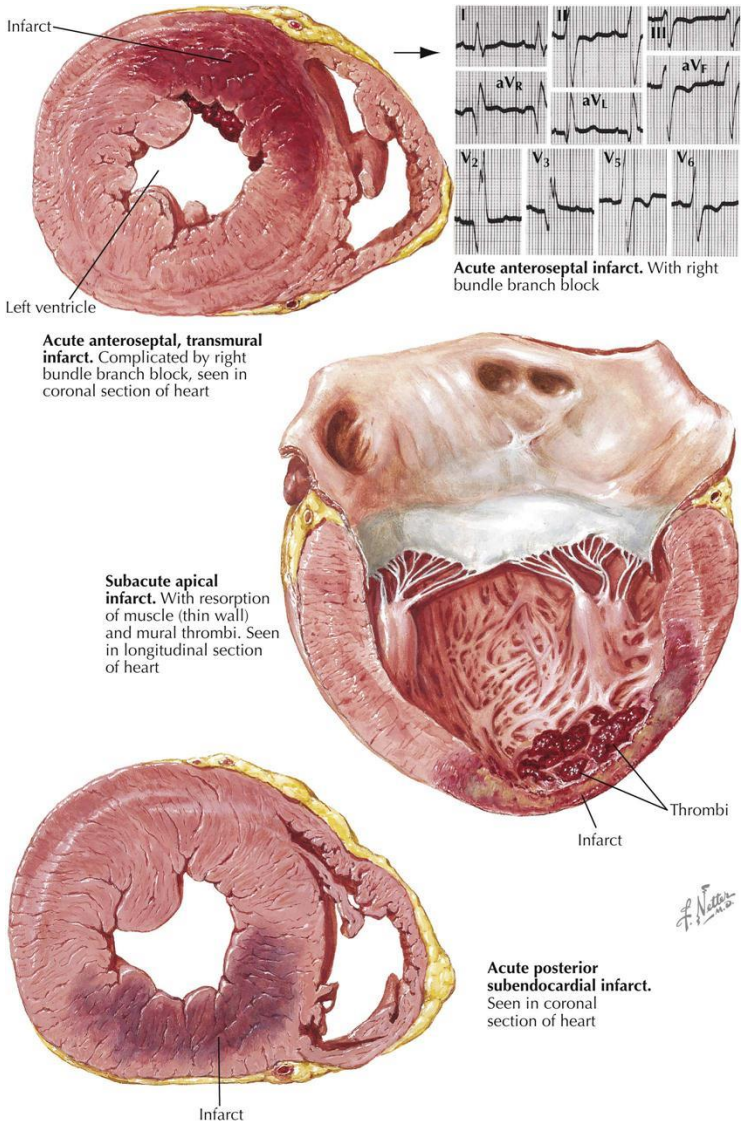
Differential dg. of ACS

	Unstable angina (UA)	Non-ST-elevation myocardial infarction (NSTEMI)	ST-elevation myocardial infarction (STEMI)
Thrombus size	partially occlusive	partially occlusive	completely occlusive
Myocardial necrosis	absent	present in small amount	present in large amount
Serum biomarkers (cTnT, cTnI, CK-MB)	absent	present	present

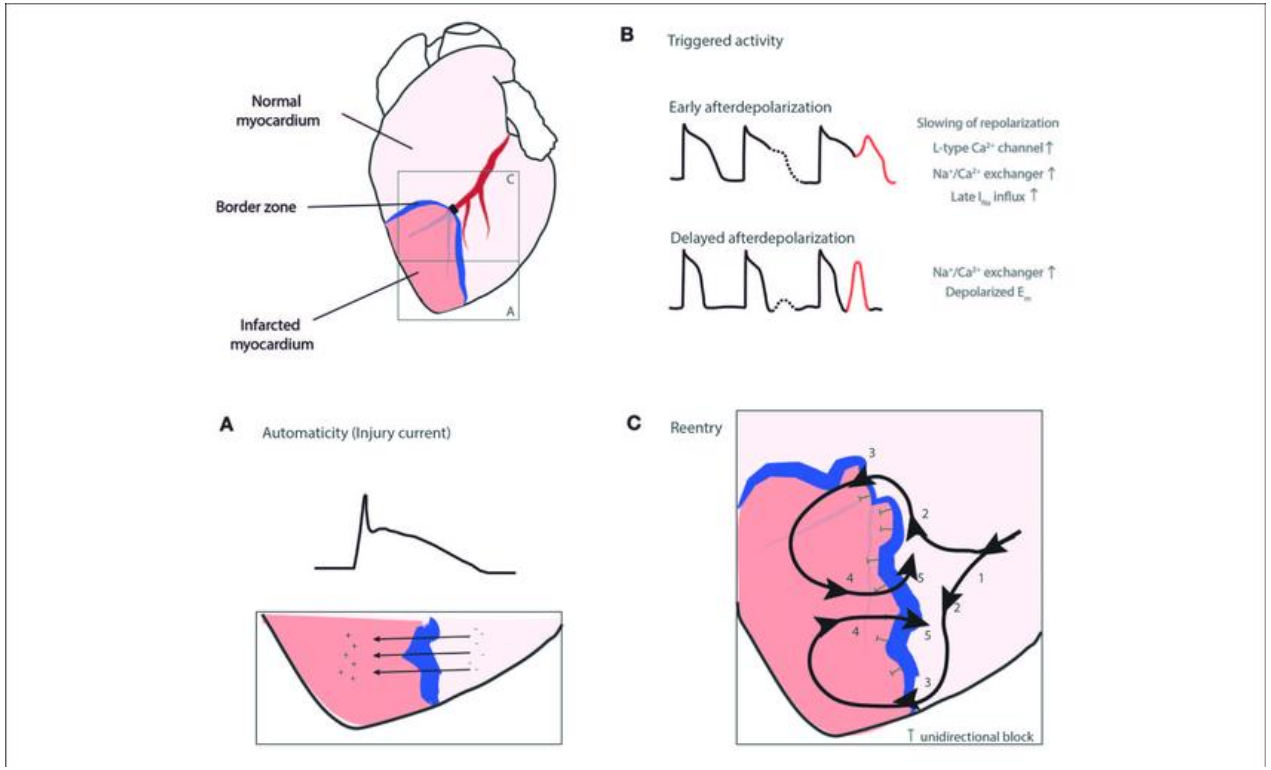
Complications of STEMI (and to some extent of non-STEMI)

- Early changes in infarction (minutes to days)
  - ↓ tissue O2 levels → rapid conversion from aerobic to anaerobic metabolism →
    - impaired ATP production
      - → impaired contractile protein function = **systolic dysfunction**
        - loss of synchronous myocyte contraction → compromised cardiac output
      - → reduced ventricular compliance (i.e. impaired relaxation due to Ca cytoplasmic retention) and elevation of ventricular filling pressures = **diastolic dysfunction**
      - → impairment of transmembrane Na-K-ATPase → increased intracellular Na → intracellular edema and increased extracellular K → alteration in transmembrane potential → **electrical instability** and susceptibility to **arrhythmias**
      - → increased intracellular Ca → activation of degradative lipases and proteases → **tissue necrosis**
- Intermediate changes in infarction (days)
  - resorption of irreversibly injured/dead myocytes by macrophages → structural weakness of ventricular wall and susceptibility to **myocardial wall rupture**



Sudden cardiac death

- **cardiogenic shock**
  - due to single massive MI or MI superimposed on multiple prior MIs
    - area of abnormal contraction > 25% results in HF
    - area of abnormal contraction > 40% results in cardiogenic shock
- **arrhythmias**
  - leading mechanism in acute phase is **re-entry**
    - ventricular extrasystoles
    - ventricular tachycardia (may degenerate into ventricular fibrillation)
    - atrial fibrillation (in about 10% of patients with MI)
    - sinus bradycardia (associated with acute inferior wall MI)
      - escape rhythm such as idioventricular rhythm (wide QRS complexes with a regular rhythm at 50-100 b.p.m.) or idiojunctional rhythm (narrow QRS complexes) may occur
    - sinus tachycardia
    - AV nodal delay (first-degree AV block) or higher degrees of block
      - may occur during acute MI, especially of the inferior wall (the right coronary artery usually supplies the SA and AV nodes)
      - acute anterior wall MI may also produce damage to the distal conduction system (the His bundle or bundle branches)
      - development of complete heart block usually implies a large MI and a poor prognosis
- **LV wall rupture**
  - death from hemopericardium and **cardiac tamponade**
  - occasionally pseudoaneurysm
- **rupture of the papillary muscle**
  - from inferior wall MI
  - massive regurgitation



- The three mechanisms, automaticity (A), triggered activity (B), and reentry (C) can play a role in arrhythmogenesis during ischemia.
  - (A) Injury current across the border zone leading to ST elevation in the electrocardiogram,
  - (B) Triggered activity mainly caused by Ca 2+ overload in cardiomyocytes or Purkinje fibers.
  - (C) Reentry.
- Electrical activation wave front (1) is deflected at the border zone due to unidirectional block (T) into two wave fronts (2), eventually passing the border zone (3) and exciting the infarct zone (4) and finally passing the unidirectional block re-exciting the area in front of the block (5). I to , transient outward potassium current; [K +] o , extracellular potassium concentration; [Na +] i , intracellular sodium concentration.

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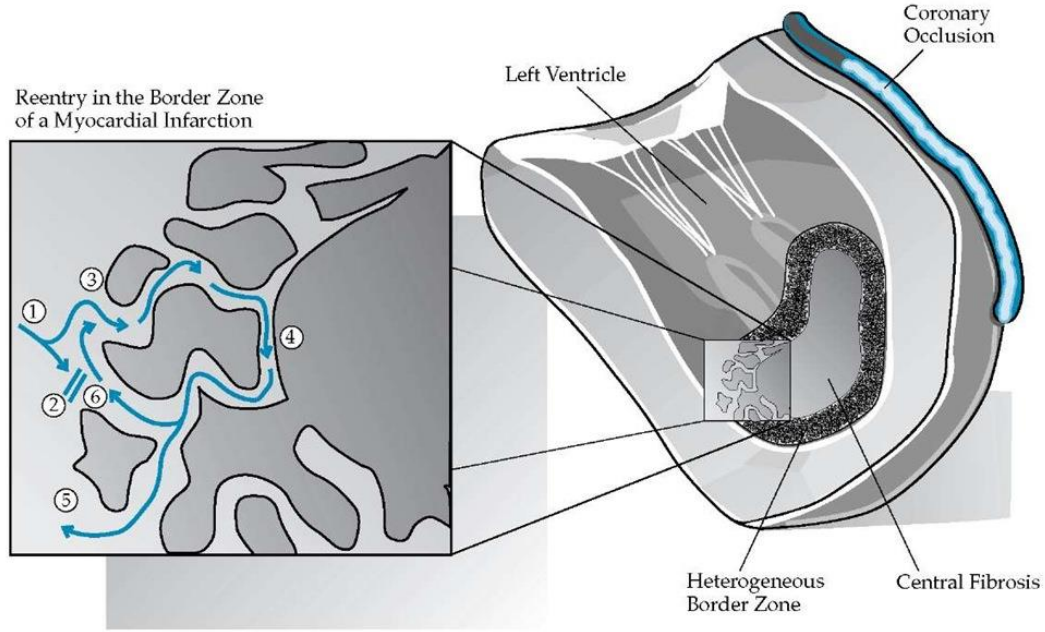
Complications of STEMI (and to some extent of non-STEMI)

- **Late changes in infarction (days to weeks)**
  - fibrous tissue deposition and scarring
  - ventricular remodeling
    - thinning and dilatation of necrotic tissue without additional necrosis
    - increased ventricular wall stress
    - further impairment in systolic contractile function
    - increased likelihood of ventricular aneurysm formation
  - remodeling of non-infarcted ventricle
    - dilatation of overworked non-infarcted segments subjected to increased wall stress
    - enlargement initially compensatory to increase cardiac output via Frank-Starling mechanism, but can eventually predispose to ventricular arrhythmias and lead to heart failure
  - pericarditis
  - thromboembolism
    - intra-ventricular thrombus formation can arise from stasis of blood flow in regions of impaired LV contraction, especially when the infarction involves the apex or when an aneurysm has formed
  - mitral valve regurgitation
  - post-MI syndrome (Dressler's syndrome)
    - chronic v.s. autoimmune pericarditis
  - recurrent cardiac arrhythmias
  - recurrent infarction



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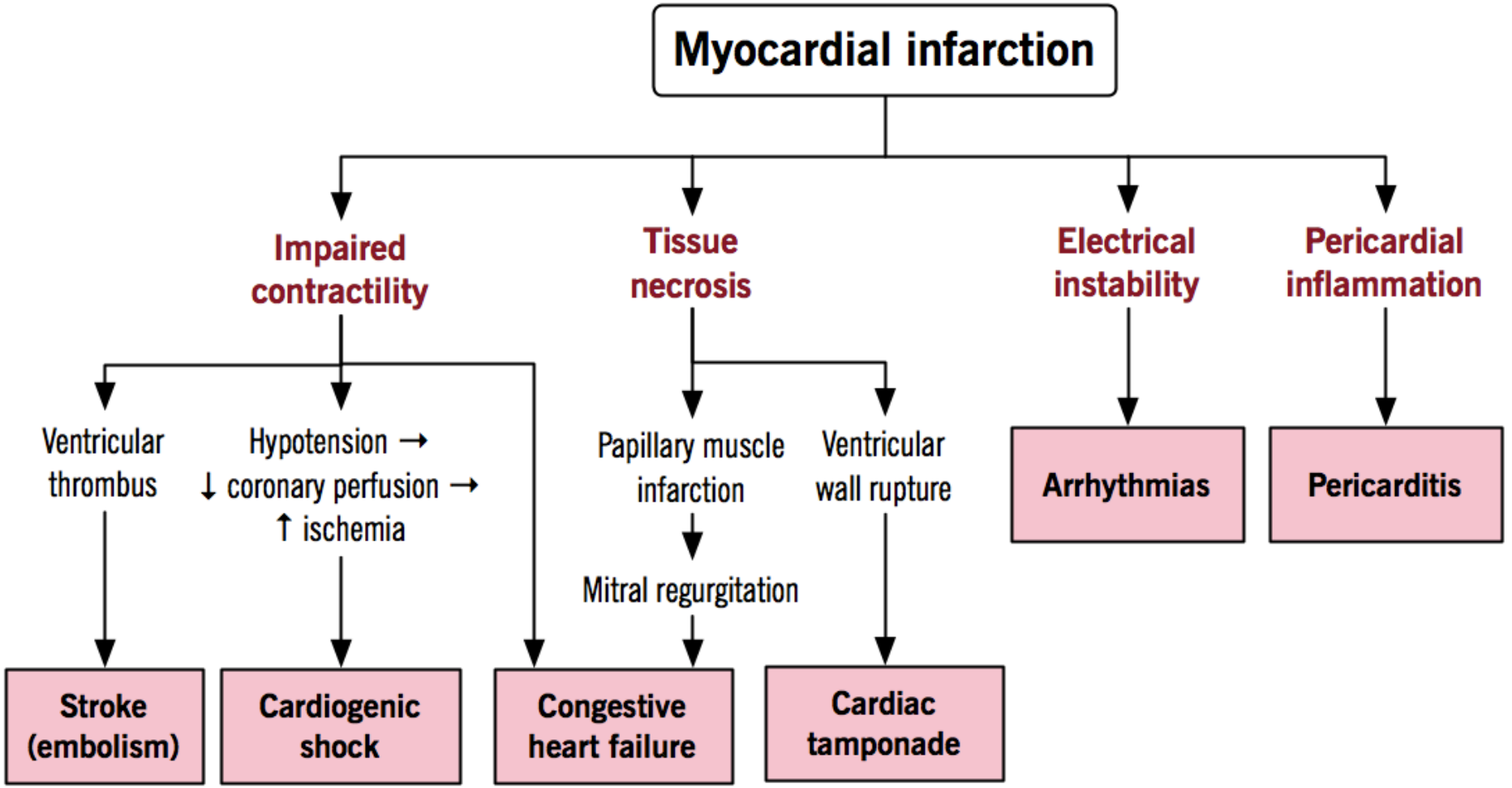
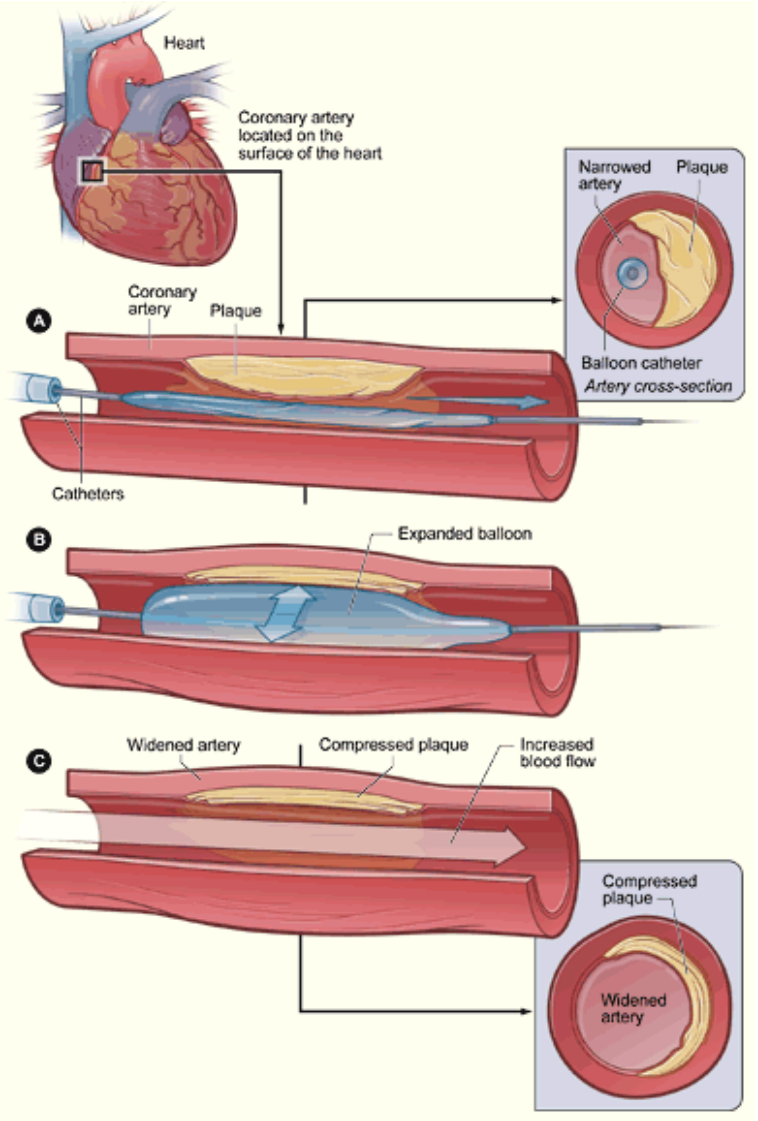
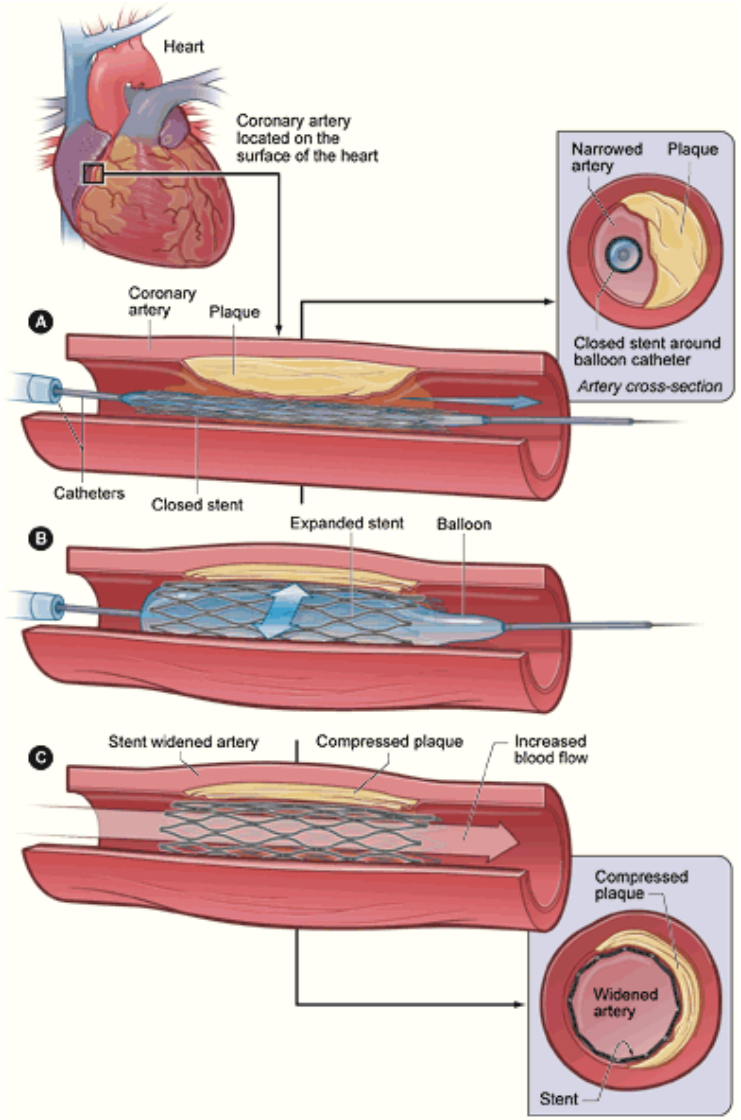
Complications of myocardial infarction

Dominique Yelle



Percutaneous coronary interventions (PCI) –





- balloon catheters only
  - rarely used – risk of re-stenosis
- bare metal stents
  - plus anti-platelet therapy
    - ASA + P2Y-receptor antagonists (i.e. ticlopidine, clopidogrel)
- drug-eluting stents
  - sirolimus-eluting stents
  - paclitaxel-eluting stents

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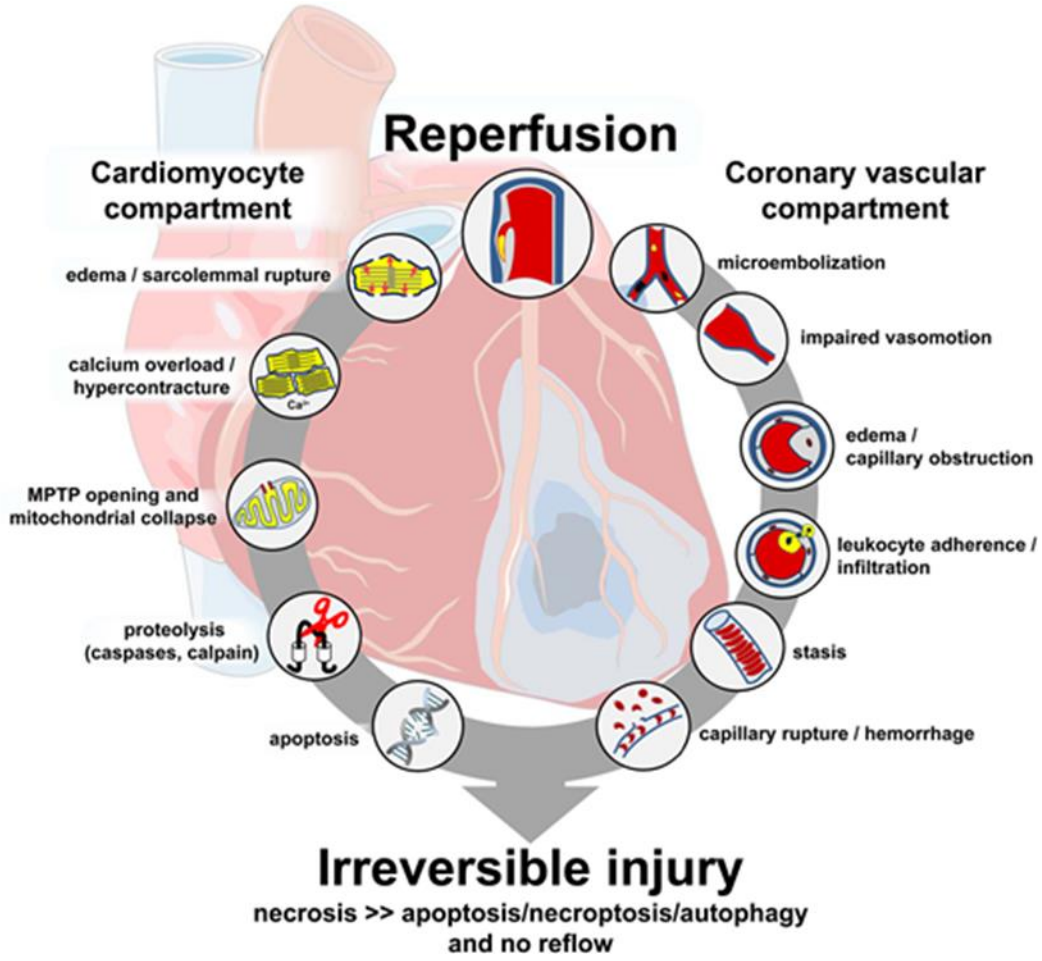
Limitation of infarct size - reperfusion

- BUT reperfusion also inflicts additional damage!
- **reperfusion injury** – damage due to restoration of blood flow
- mechanisms
  - reversible
    - stunned myocardium
      - prolonged period of contractile dysfunction in salvaged myocytes
    - reperfusion arrhythmias
    - microvascular damage
  - irreversible = increase of infarction size
    - no-reflow phenomenon as an extreme reperfusion injury
- ongoing modification of reperfusion techniques in order to perform ‘safe’ gentle reperfusion
  - ischemic post-conditioning
    - alternating cycles of reperfusion and coronary re-occlusion
  - pharmacological



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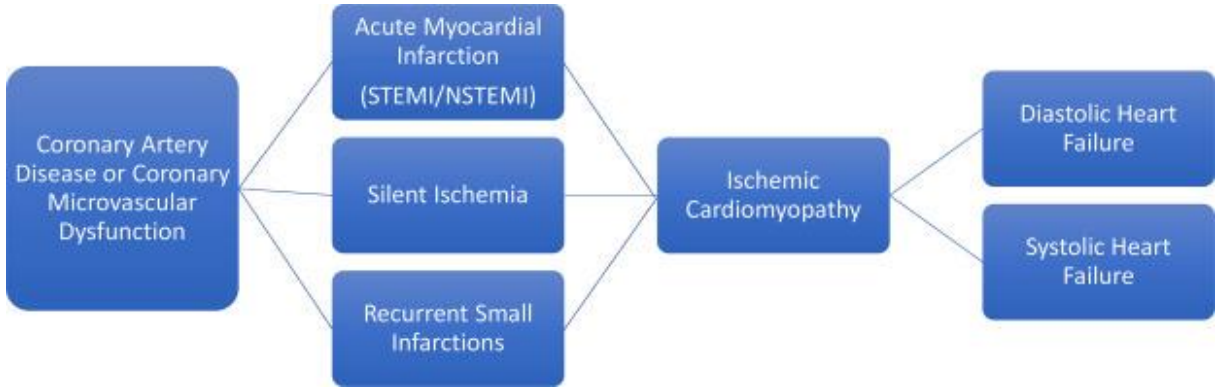
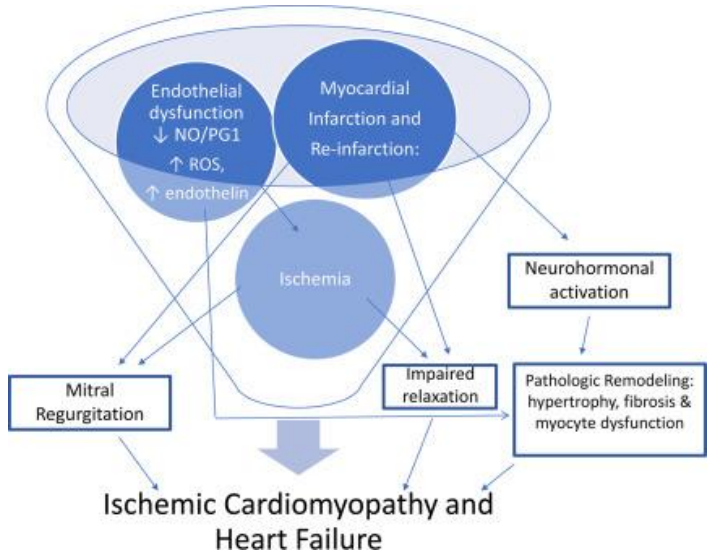
Ischemic cardiomyopathy / heart failure

- the most common aetiology of HF
  - accounts for more than 60% of cases of congestive heart failure
- results from
  - myocardial ischemia – hibernating myocardium
    - the larger the contribution the better the effect od revascularisation
  - diffuse fibrosis and LV remodelling
  - event. plus multiple scaring due to MI
  - event. mitral regurgitation due to papillary muscle dysfunction
  - event. LV aneurysm
- angina might or may not be present
  - silent ischemia and confusion with dilated cardiomyopathy





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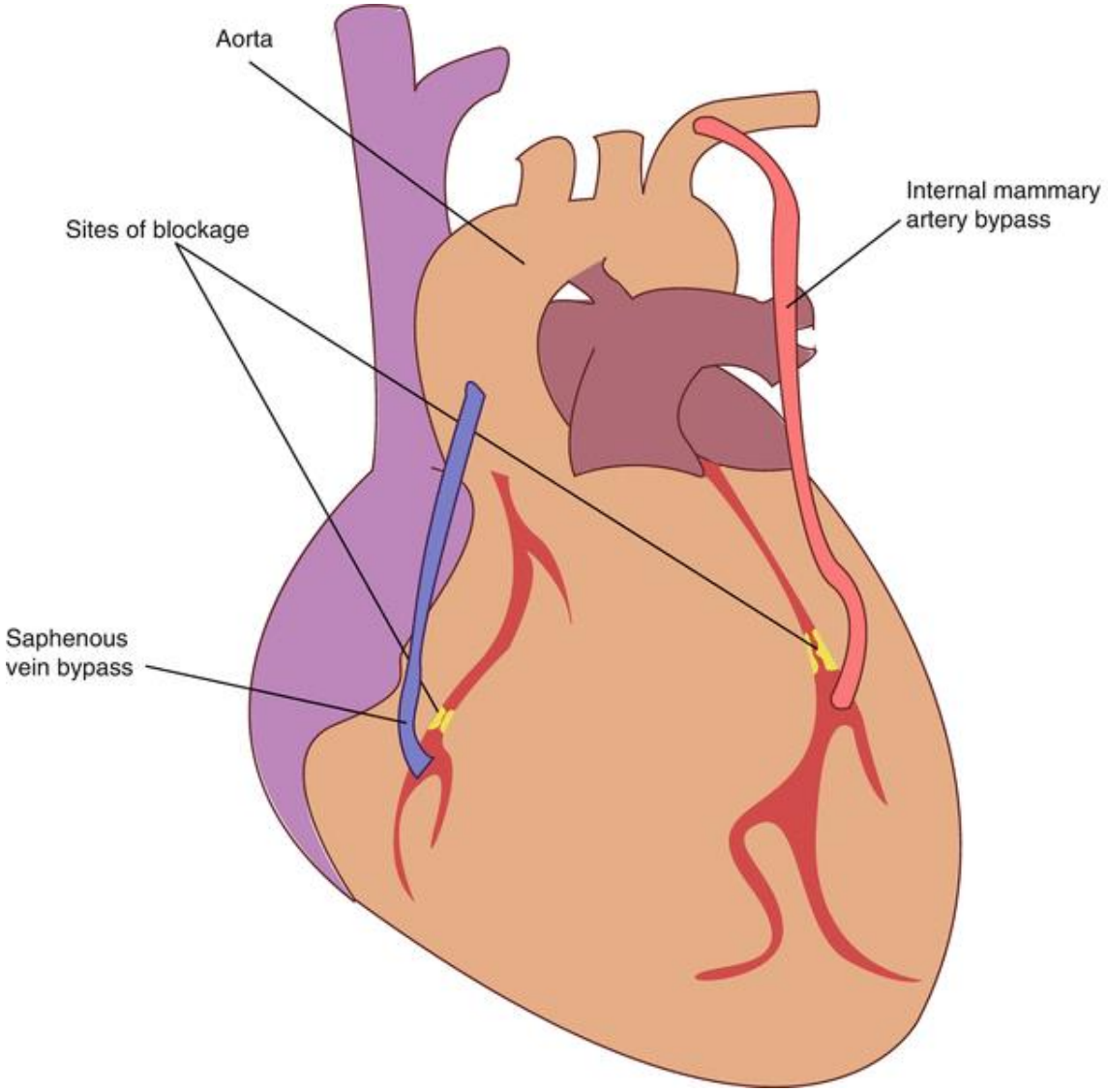
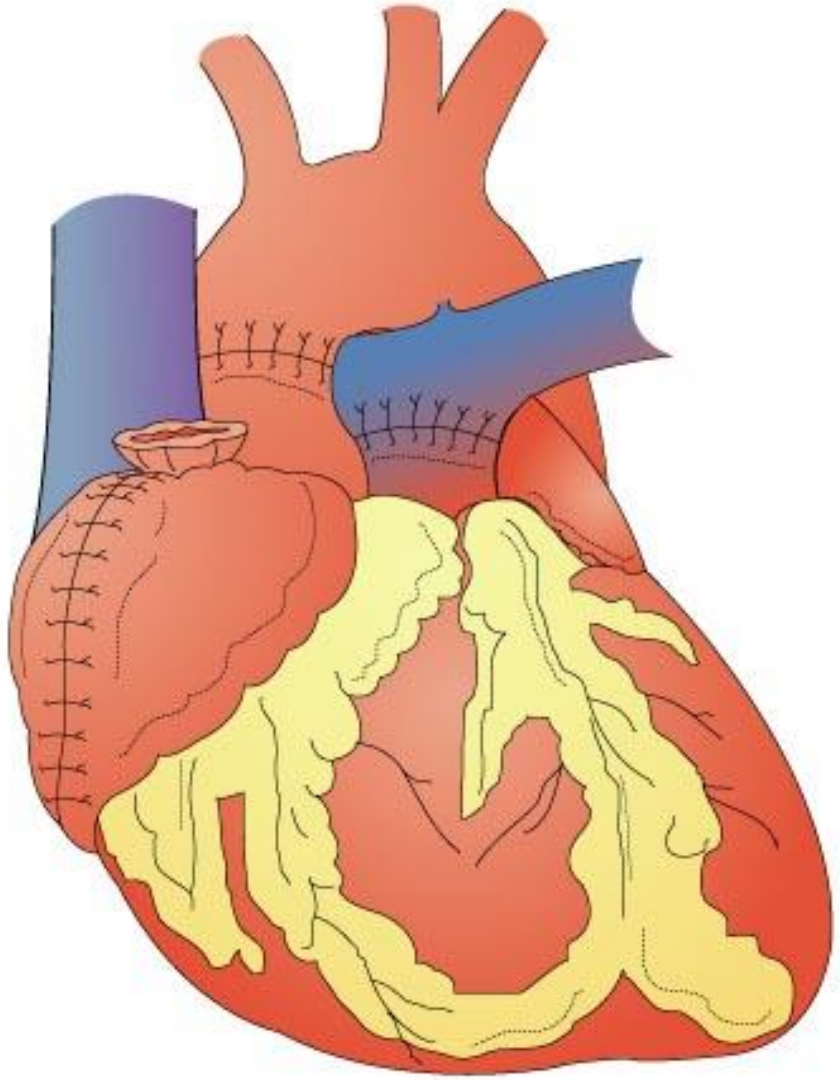
Follow-up interventions – by-pass surgery &





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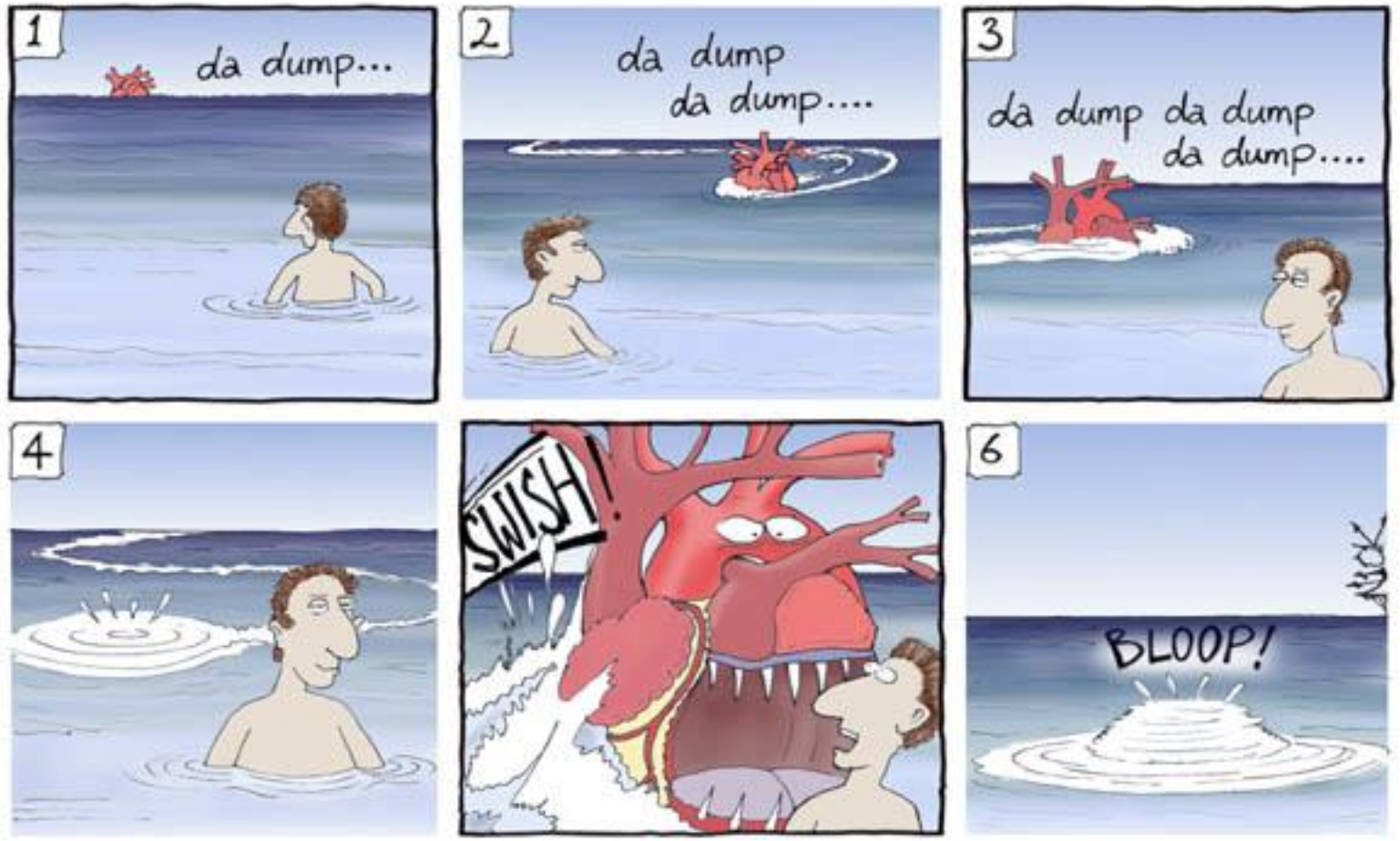

TOO BAD DESMOND HAD NEVER LEARNED TO RECOGNIZE
THE EARLY WARNING SIGNS OF A HEART ATTACK.

- ‘wellness maintenance’ and not just ‘disease treatment’.

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