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PHARMACOLOGY OF CARDIOVASCULAR SYSTEM

Part I

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Risk Factors of Cardiovascular Diseases

- Non-modifiable:
- sex (males)
- age
- genetic predisposition

- Modifiable:
- atherosclerosis
- hypertension
- nutrition (obesity)
- high plasm. conc. of total and/or LDL CHOL, increased TAG
- low conc. of HDL CHOL
- diabetes mellitus
- smoking
- lack of exercise (sedentary lifestyle)
- long term stress; and other factors

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Cardiovascular Disorders

- ARRHYTHMIAS
- IHD (Ischemic Heart Disease)
  - Acute forms: unstable angina pectoris (AP); myocardial infarction (MI)
  - Chronic forms: asymptom. IHD; exertional AP, mixed, variant; after MI; dysrrhytmic form of IHD
- HYPERTENSION

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Disturbances of cardiac rhythm

– Origin

- based on disturbances of speed, regularity, formation and conduction

– Cause

- damage to the heart muscle, caused by hypoxemia, ischemia, hypokalemia or effect of drugs

– Goal of Therapy

- restore normal rhythm, prevent arrhythmia return, reduce risk of the most serious arrhythmias (ventricular fibrillation)

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Antiarrhythmics

- Inhibit membrane ion channels, receptors and autonomic functions
- Classification by Vaughan–Williams
- Arrhythmia treatment
  - depends on the type and the length of its duration, severity and presence of organic heart disease

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Treatment of arrhythmia

– Pharmacotherapy

AA + antithrombotics, I-ACE, and hypolipidemics

– Non-pharmacological approaches

- cardioversion, cardioverters → defibrillators, pacemakers, radiofrequency ablation
- surgical treatment

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Classification of Antiarrhythmics

Ia) blockade of Na^+ channels
– *quinidine* – cardioversion of atrial fibrillation

Ib) blockade of Na^+ channels
– *lidocaine*, *mexiletine* – ventricular tachycardia

Ic) blockade of Na^+ channels
– *propafenone* – cardioversion of atrial fibrillation, paroxysmal supraventricular (SV) tachycardia

II) adrenergic beta-blockade
– *β-blockers* – control of ventricular response in supraventricular tachycardia

III) blockade of K^+ channels
– *amiodarone*, *sotalol* – supraventricular and ventricular tachycardia

IV) blockade of Ca^{2+} channels
– *verapamil*, *diltiazem* – control of ventricular response in SV tachycardia

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Class Ia) Antiarrhythmics

- Reduce the rate of rise of cardiac action potential (AP),

  extend the duration of AP and slow repolarization

- Extend conduction in atria, in Purkinje fibers and ventricles

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Quinidine

- Clinical use in pharmacological cardioversion of atrial fibrilation and flutter

- **SE:** GIT, allergic symptoms, conduction abnormalities, the risk of ventricular fibrillation

- Numerous drug interactions

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Class Ib) Antiarrhythmics

- Block of Na^+ channel, do not affect the speed of AP increase

- **Shorten the AP** duration and refractory period

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Lidocaine, trimecaine

- Do not affect sinus node automatism, but suppress automatism of ventricular centers

- Administered (i.v.) in the acute stages of ventricular arrhythmias, MI, and in unstable AP

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Mexiletine

- High efficiency even after p.o. administration
- Dose: 3x day
- Inhibits the transport of Na^+ and slow speed and maximum duration of AP depolarization
- **I:** restricted to use in life-threatening conditions only

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Class Ic) Antiarrhythmics

- Blockade of Na^+ channel, **reduces the steepness of the onset of AP**

- Slow conduction, only a small effect on the repolarization

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Propafenone

- Reduction of heart rate and BP
- **I:** Paroxysmal SV arrhythmias, life-threatening ventricular arrhythmias; after MI
- Regular ECG monitoring is needed, the risk of arrhythmias
- After i.v. application: effect immediately, lasts for 4 h
- Registered on market: Rytmonorm, Propanorm, Prolekofen, Propafenon

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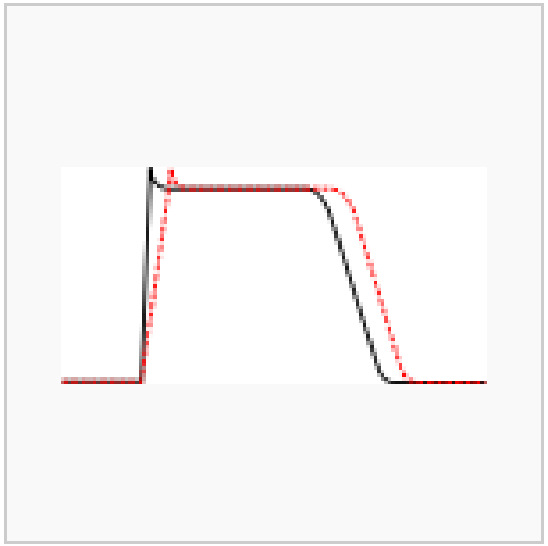
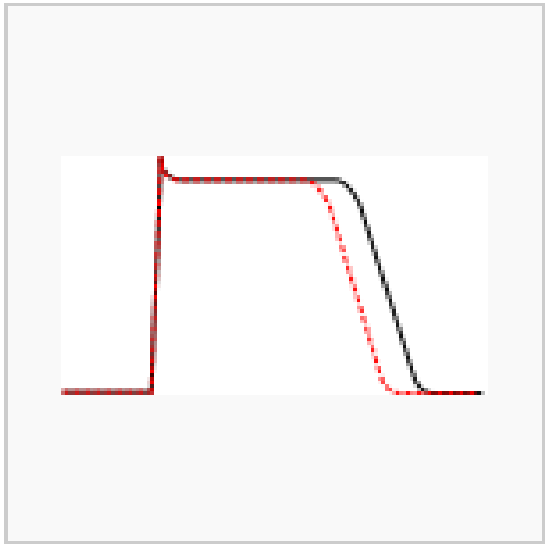
Class I agents are divided into three groups (Ia, Ib and Ic) based upon their effect on the length of the action potential.[3][4]

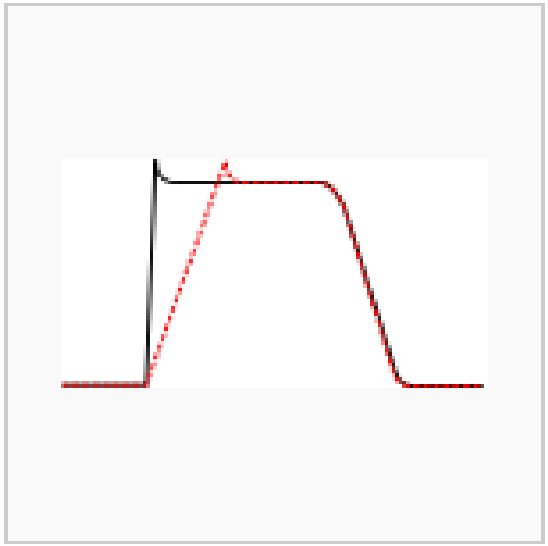
- Ia lengthens the action potential (right shift)
- Ib shortens the action potential (left shift)
- Ic does not significantly affect the action potential (no shift)



Class Ia



Class Ib



Class Ic

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Class II Antiarrhythmics

- β-blockers
- Prevents the action of catecholamines on the myocardium
- They reduce sympathetic stimulation, increased vagal tone and increase the fibrillation threshold
- Antiischemic effects (Reduce consumption of O_2)
- Antiatherosclerotic and antithrombotic effects
- Secondary prevention of MI and sudden death

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Sotalol

- **Extends the duration of AP**, and slows repolarization
- Reduces myocardial O_2 consumption and leads to a decline in cardiac work
- **I:** sinus and SV arrhythmia, atrial and extraventricular extrasystoles

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Class III) Antiarrhythmics

- **Amiodarone**, bretylium
- Block K^+ channels **extend AP** and reduces sympathetic activity
- **I:** SV and ventricular tachycardia

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Amiodarone

- Extremely long half-life
- TDM needed
- Most effective AA in suppressing ventricular and SV tachycardia
- Reduces arrhythmic mortality and morbidity
- **I:** after acute MI, at high risk of arrhythmic death
- **SE:** thyroid disorders, hepatotoxicity, arrhythmic activity
- Registered on market: Cordarone, Amiohexal, Rivodaron, Amiokordin

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Class IV) Antiarrhythmics

- Ca^{2+} channel blockers
- Verapamil, diltiazem
- Prolong the refractory phase
- Reduce the frequency of impulses in the SA node

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Adenosine

- i.v. application
- Decreases automaticity of sinus node and slows conduction in the SA node, slow response of ventricular arrhythmia during SV arrhythmia
- Drug of choice

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ANGINA PECTORIS

- Algic form of IHD (chest pain)
- Imbalance between myocardial MTB demands and supply by O_2
- Reduction in coronary perfusion, arterial stenosis, coronary artery spasm
- Goals of pharmacotherapy: adjustment of imbalances, improve blood flow, influence of atherogenesis, inhibition of vascular thrombus occlusion

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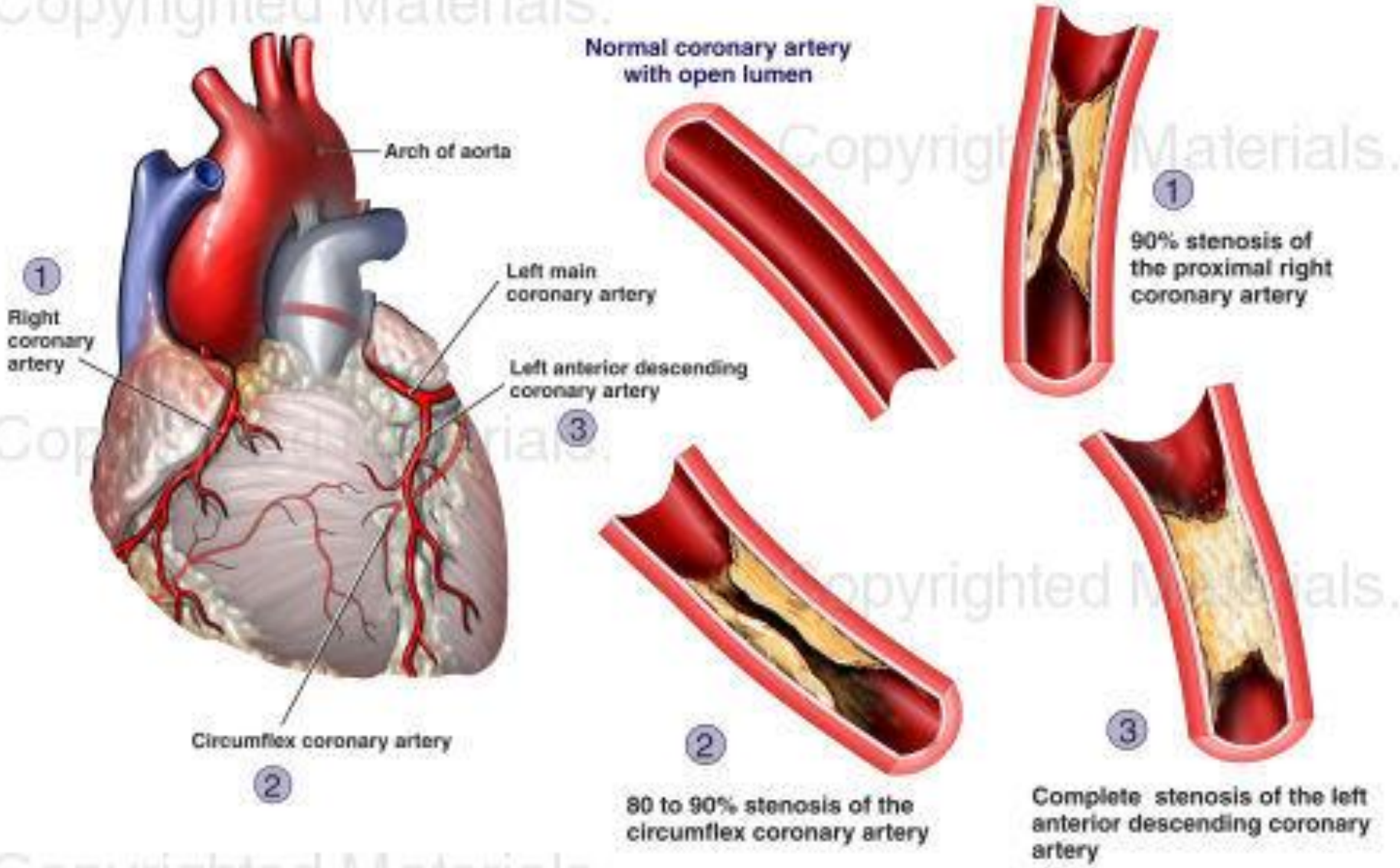
Advanced Coronary Artery Disease



Pharmacotherapy of Angina Pectoris

- Nitrates
- β-blockers
- Blockers of Ca^{2+} channels
- ASA

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Nitrates (Nitrodilators)

- Vasodilator effect is caused by the release of *NO*
- Arterial dilation, decreased venous return
- Reduces left ventricular filling and myocardial O_2 consumption decreases
- Essential **symptomatic** drug for AP; removes acute pain
- In prophylactic administration they reduce the frequency of attacks
- Subling. nitroglycerine: a rapid onset of action, drug of choice for acute attacks of AP

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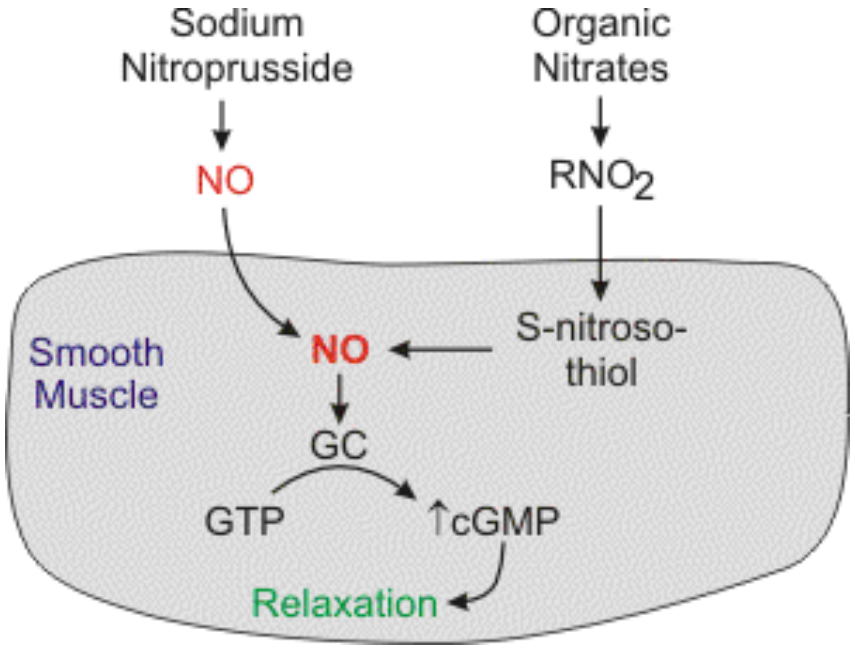
Nitrodilators

- nitroglycerin
- sodium nitroprusside



- isosorbide dinitrate
- isosorbide mononitrate
  - longer onset of action and duration of action than nitroglycerin
  - long-term prophylaxis and management of coronary artery disease

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Cardiovascular actions of nitrodilators

– **Systemic vasculature**

- vasodilation (venous dilation > arterial dilation)
- decreased venous pressure, and arterial pressure (small effect)

– **Cardiac**

- reduced preload and afterload
  (decreased wall stress)
- decreased oxygen demand

– **Coronary**

- prevents/reverses vasospasm
- vasodilation (primarily epicardial vessels)
- improves subendocardial perfusion
- increased oxygen delivery

Beta-blockers

- Slow heart rate
- Reduce peripheral vascular resistance and myocardial contractility
- Improve coronary flow and reduce myocardial O_2 demands
- Reduce the incidence of anginal attacks and CV complications

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Calcium channel blockers

- Reduce Ca^{2+} in the cytoplasm of smooth muscle cells
- Diltiazem (Diacordin®), verapamil (Isoptin®, Lekoptin®), nifedipine (Cordipin ret®), dihydropyridins of II. generation
- Effects:
  - Vasodilation, decreased blood pressure, decreased heart rate
  - Slowing of conduction in the myocardium
- Administration only in slow-releasing dosage form

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MYOCARDIAL INFARCTION

1. Before hospitalization: mesocain, β-blockers (metipranolol)
2. During the transport: diazepam, morphine, pethidine, O_2
3. Fibrinolytic therapy: tPA – tissue plasminogen activator
4. Anticoagulant therapy: heparin, NOAC
5. Antiplatelet therapy: ASA, dipyridamole, ticlopidine
6. Nitrates
7. β-blockers

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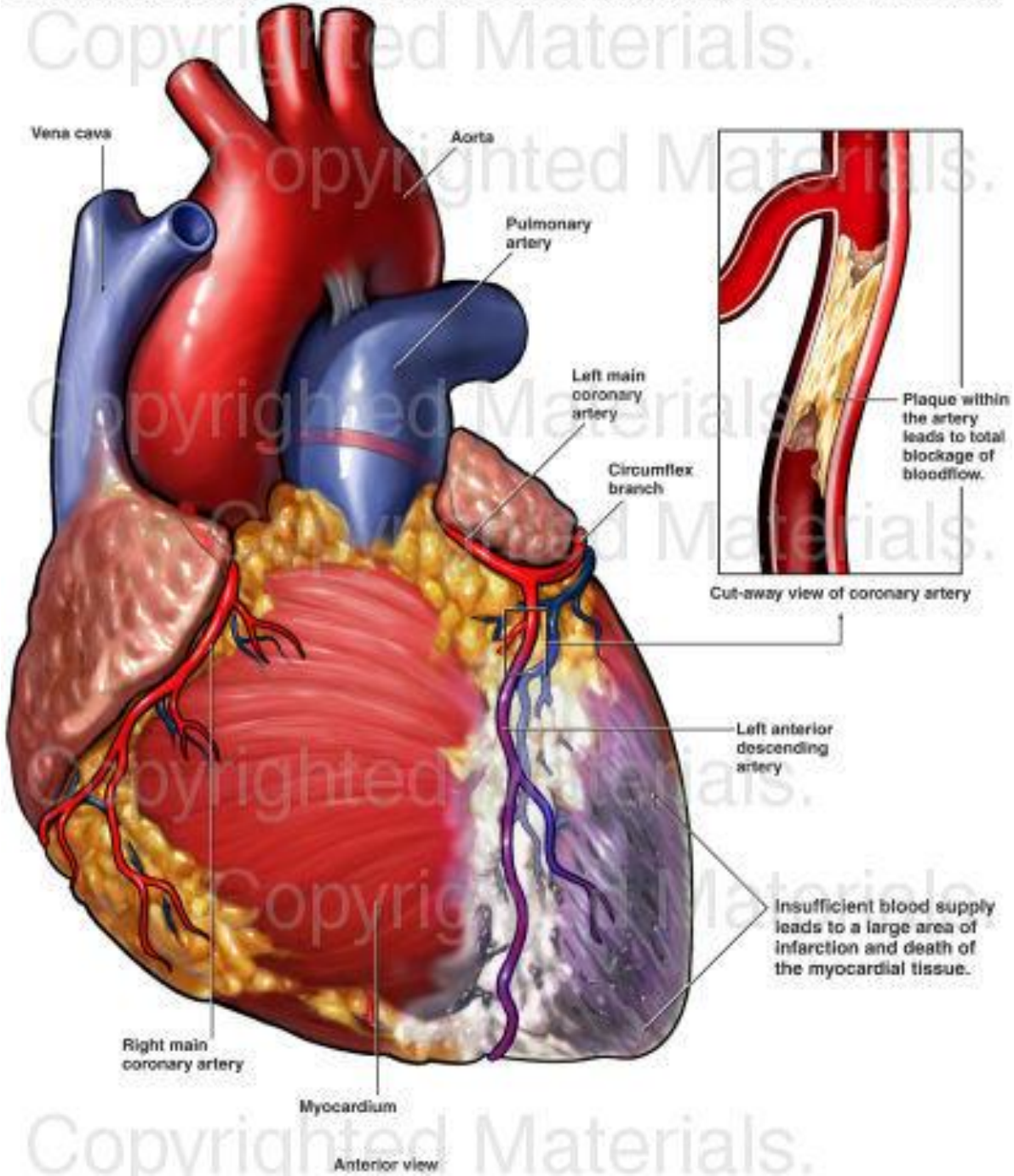
Coronary Artery Stenosis with Subsequent Myocardial Infarction



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Heart Failure

- Drugs with a positive inotropic effect:
  - Digitalis (cardiac) glycosides
- Diuretics
- Vasodilatators:
  - I-ACE, Inhibitors of AT II

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Cardiac Glycosides

Digoxin

- inhibition of the Na^+/K^+ ATPase, the rise of IC Ca^{2+}, increases myocardial contractility, impulse formation slows
- Chronic heart failure, impaired left ventricle, atrial fibrillation
- Reduce morbidity, **do not** reduce mortality
- Small therapeutic width
- High risk of intoxication

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Thank you
for your attention

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