Antianginal drugs
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Angina pectoris - consequence of myocardial oxygen demand exceeding myocardial oxygen supplay. It can be manifested clinically in many ways besides angina, from no symptoms (e.g., silent myocardial ischemia) to unstable angina, MI, or sudden cardiac death.
Coronary heart disease:

- Stable angina
- Unstable angina
- Myocardial infarction
- Vasospastic angina (Prinzmetal angina)
- Silent ischemia

The goal of antianginal therapy is:

- reduction of mortality
- primary/secondary prevention of myocardial infarction
- improving excercise tolerance
- prevention/relieving angina symptoms

Classical antianginals (first choice drugs)

- nitrates
- beta-blockers
- Ca-channel antagonists
- ACE inhibitors

Newer antianginals (second choice drugs)

- Ivabradine
- Trimetazidine
- Ranolzanine

and

- antiplatelet agents
- anticoagulants
- antithrombotic agents
- lipid-lowering agents

1. Nitrates: widely prescribed for antianginal treatment and are effective when they are administered sublingually, orally, or topically **-** nitroglycerin, isosorbide dinitrate, isosorbide mononitrate.

- are sources of NO (↑cGMP, ↑ Ca^{2+}, ↑ relaxation of vascular smooth muscle, dilation of veins at standard dose, which predominates dilation of arteries, dilation of arteries occurs at high dose)
- decrease O_2 demand (↓ afterload, ↓preload, ↓blood pressure)
- decreased end-diastolic pressure, cardiac output
- redistribution of blood flow in the heart
- dilation of epicardial coronary arteries
- nitroglycerine inhibits platelet aggregation

- **Short-acting nitrates:** sublingual nitroglycerin or oral spray can terminate an angina attack and can be used as prophylaxis to prevent exertional angina. At the onset of angina symptoms, the patient should rest in a sitting position taking sublingually nitroglycerin (standing promotes syncope, and lying down enhances venous return and preload)

- tablets 0.3-0.6 mg (sublingually and not swallowed)

or

- spray 0.4 mg to the tongue and not swallowed or inhaled every 5 min until the pain disappears
- maximum of 1.2 mg can be taken within 15 min (one dose every 5 min.).
- BP and heart rate control
- NTG should not be administered if SBP is below 90 mmHg

- **Long-acting nitrates** (isosorbide mononitarte, isosorbide dinitarte, nitroglycerin) administered orally or transdermally are used to prevent angina and to improve exercise tolerance as second choice drugs in chronic therapy.

Pharmacokinetics:

- hepatic first-pass metabolism is high and oral bioavailability is low for nitroglycerin (GTN) and isosorbide dinitrate (ISDN). Sublingual or transdermal administration of these agents avoids the first-pass effect
- Isosorbide mononitrate (5-ISMN) is not subject to first-pass metabolism and is 100% available after oral administration
- Hepatic blood flow and disease can affect the pharmacokinetics of GTN and ISDN

Indications:

- Unstable angina
- Prinzmetal's angina

Used in every type of angina

- Treatment and prophylaxis of acute angina episodes (short-acting nitrates) and prophylaxis of chronic angina (long-lasting nitrates)

and

- treatment of moderate to severe congestive heart failure and myocardial infarction

Immediate treatment of angina (s.l.); severe, recurrent rest angina (i.v.); maintenance therapy of angina (slow-release forms)

Adverse effect: headache, hypotension and reflex tachycardia, long-acting nitrates – tolarence, methemoglobinemia, ↑ intraocular pressure

Contraindications:

- severe hypotension and hypovolemia
- hypersensitivity
- head trauma
- cerebral hemorrhage
- severe anemia
- glaucoma?
- hypertrophic obstructive cardiomyopathy
- severe aortic stenosis

2. Beta-blockers – prevent the binding of catecholamines to the β-adrenergic receptor, lower heart rate and myocardial contractility, thereby reducing myocardial workload, myocardial oxygen demand, and ischemia and anginal symptoms. β-blockers raise the

ischemic threshold and delay or prevent the onset of angina with exercise. β-blockers also reduce the rate of secondary cardiac events and sudden cardiac death in post-MI patients. All β-blockers (**carvedilol, nebivolol, bisoprolol, metoprolol**) appear to be equally effective in patients with chronic stable angina.

Pharmacological effects:

- chronotropic negative
- inotropic negative
- batmotropic negative

- protect against remodeling
- positive changes in metabolism of heart muscle (beta-oxidation of FFA – anaerobic glucose metabolism)
- antiarrhythmic effects: decrease in adrenergic stimulation, decrease in ischemia and loss of potassium ions from the cells
- attention: variant angina (contraindicated)

After MI – key role in reducing morbidity and mortality due to cardiovascular diseases and heart attack by 30%

Adverse effect: hypotension, bradycardia, A-V block, fatigue and weakness, mask signs of hypoglycemia, hallucinations, depression, ↑ TG, ↓ HDL cholesterol, discontinuation after long-acting therapy exacerbates angina

Contraindications: severe bronchial asthma, severe COPD, A-V block, peripheral vascular disease, hypotension, vasospastic angina

3. **Ca-channel blockers** protect tissue by inhibiting the entrance of Ca into cardiac and smooth muscle cells of the coronary and systemic arterial beds, improve oxygen delivery to ischemic myocardium.

Non-dihydropyridines – verapamil, diltiazem (used in angina, first line agent in chronic therapy only)

By blocking Ca channels cause myocardial depression (negative chronotropic , inotropic , and dromotropic effects on the myocardium). By slowing the heart rate, calcium blockers reduce the oxygen demand of the heart and reduce the frequency of angina attacks but this group is recommended for patients with contraindications for beta blockers or who are not responsive to beta blockers.

Dihydropyridines (are considered the agents of choice in patients with vasospastic angina or in patients with angina when hypertension coexists):

- Nicardipine
- Amlodipine
- Nitrendipine
- Lercanidipine

Non-dihydropyridines (have greater effect on vascular smooth muscle, are better peripheral vasodilators, and hence may have advantages for use in the hypertensive patient with angina)

Dihydropyridines act mainly on vascular smooth muscle (only in arteries), nondihydropyridines act mainly on the heart muscle.

Pharmacological effects:

- decrease contractility and heart rate (verapamil, diltiazem),
- decrease arteriolar resistance

- decrease myocardial O_2 demand due to: arteriolal dilation, ↓ vascular resistance, ↓ afterload
- adverse effects (non-dihydropiridines): bradycardia, heart blocks, cardiac insufficiency, hypotonia

Other indications:
supraventricular tachycardia – non-dihydropyridines
hypertension – dihydropyridines
Raynaud phenomenon – dihydropyridines
Side effects:
Verapamil/diltiazem

- **Bradycardia, AV-block**
- Heart conduction defect
- Decreased inotropism
- Constipation
- Gingival hyperplasia

Dihydropyridines

- Hadache
- Ankle swelling
- Fatigue
- Flushing
- Reflex **tachycardia**
- Gingival hyperplasia

4. ACE-inhibitors (ramipril, lisinopril, perindopril, enalapril)
Angiotensin converting enzyme (ACE)-inhibitors are established in the treatment of arterial hypertension and heart failure. In recent years ACE-inhibitors have also been used in the treatment of patients with coronary artery disease. Inhibiting converting enzyme they inhibit agiotensin II synthesis thus preventing angiotensyn II mediated effects.

- decrease peripheral vascular resistance and blood pressure
- decrease preload and afterload
- antiarrhythmic effect (potassium sparing effect)
- inhibit sympathetic nervous system
- captopril decreases the nitrates tolerance

Advantages of ACE-I:

- **inhibition of remodeling**
- **nephroprotective effect in diabetes mellitus** (blocade of Ang II dilation of efferent arteriole, ↓ glomerular pressure, ↓ GFR, anti-proteinuric effect, preservation of kidney)
- improved endothelial function
- lack metabolic side effects and do not alter serum lipids

Use:

- **coronary heart disease** : in acute myocardial infarction (prevention of heart failure, decreased late mortality), past myocardial infarction in patients with impaired left ventricle hemodynamic, every type of angina without past infarction **when hypertension or heart failure coexists.**

- **other** : hypertension (first-choice therapy), congestive heart failure, diabetic nephropathy

Adverse effect: hypotonia, dry cough, hyperkalemia, teratogenity, loss of taste
Contraindications: pregnancy, hyperkalemia (potassium>5,5mmol/L), bilateral renal artery stenosis, previous angioneurotic oedema

Newer antianginals

1. Ivabradine – direct bradycardiac agent

- for the symptomatic management of stable angina pectoris
- acts by reducing the heart rate
- classified as a *cardiotonic agent*
- indicated for the symptomatic treatment of stable angina in patients with normal sinus rhythm, who have a contraindication to or intolerance to beta blockers

2. Trimetazidine - Inhibits β-oxidation pathway of fatty acid metabolism, (block ketoacyl coenzyme-A thiolase),
↓FFA oxidation = ↑ compensatory glucose metabolism
= ↓ oxygen consumption

3. Ranolazine - acts by reducing intracellular calcium overload in ischemic myocytes by inhibiting late inward sodium current entry. The net effect of reduced late inward sodium current is a reduction in LV wall tension and myocardial oxygen demand, thereby reducing angina and ischemia. Ranolazine increases exercise tolerance in patients with stable angina, reduces episodes of recurrent ischemia, and provides additional antianginal benefit in patients who are already receiving intensive antianginal therapy with β-blockers and calcium-channel blockers

Additional agents:

Antiplatelet drugs – block platelet aggregation

- clopidogrel,
- aspirin,
- glucoprotein IIb/IIIa inhibitors (administered intravenously) – abciximab, tirofiban

Anticoagulants –

- enoxaparin,
- unfractionated heparin,

Antithrombotic agents - bivalirudin (directly inhibit even clot-bound thrombin, are not affected by circulating inhibitors, and function independently of antithrombin III)

Lipid-lowering agents - statins