Ischemic heart disease drugs

Organic nitrates

- They are effective in the three types of angina pectoris.

Adverse effects:
- Headache
- High doses can cause postural hypotension syncope & tachycardia
- Sildinafil (Viagra) potentiates the action of nitrates → dangerous hypotension
- Tolerance to the action of nitrates can be overcame by providing a daily "nitrate free intervals: 10-12 h at night"

*Nitroglycerine (GTN)
- Action not antagonized by any known antagonist
- Significant first pass metabolism → So it administrated sublingually or transdermally (patch)
- Fast onset of action: 1-3 minutes, Peaks at 10 minutes.
- Short duration: 15-30 minutes
- Causes: 1) Arteriolar dilation: short lived (5-10 min), ↓ systemic blood pressure (afterload), causes reflex tachycardia, ↑ contractility, ↑ MVO_2

2) Venous dilation: more intense, lasts for 30 minutes, ↓ venous return (preload), ↓ MVO_2

Uses: for rapid relief of an ongoing attack that precipitate by exercise & emotional stress (used sublingual) (or spray form).

Side effects:
- Headache, hypotension, tachycardia, methemoglobinemia, ↑ intraocular & intracranial pressures

Tolerance: only for the arteriolar effects

*Isosorbide mononitrate: fast onset of action (1 h) [hepatic breakdown]
- Better bioavailability & long duration "Not subjected to
- *Isosorbide dinonitrate:
- oral // // undergoes denitration to two mononitrates → antianginal activity

	Drug	Duration of action
Short acting	Nitroglycerin, sublingual	10-30 m
	Isosorbide dinitrate, sublingual	10-60 m
	Amyl nitrate, inhalant	3-5 m
Long acting	Nitroglycerin, oral	6-8 h
	// , 2% ointment, transdermal	3-6 h
	// , slow release, buccal	3-6 h
	// , // // patch, transdermal	8-10 h
	Isosorbide dinitrate, sublingual	1.5-2 h
	// // , oral	4-6 h
	// //, chewable oral	2-3 h
	// mononitrate, oral	6-10 h

β blockers
- Prevent actions of catecholamines, so more effective during exertion
- Don't dilate coronary arteries
- Don't increase collateral blood flow
- ↓ anginal episodes, nitroglycerine consumption, enhanced exercise tolerance & improved ECG
- Block β 1 receptors: ↓ cardiac output & BP

Uses: Stable & unstable angina / MI / reduce the risk of death & MI in patients who have had a prior MI / improve morbidity in patient with HTN & HF with ↓ ejection fraction

Contraindication: Varient angina / bronchial asthma / bradycardia (Pindolol is contraindicated in these cases).

*Acebutol, atenolol, metoprolol: β 1 blockers.

Newer antianginal drugs

*Fasudil: inhibits Rho kinase (this enzyme inhibits vascular relaxation, excessive activity of this enzyme has been implicated in coronary spasm, pulmonary hypertension & apoptosis) & ↓ coronary vasospasm in animals.

*Ivabravineit: has improved performance in stress tests in patients with CAD.

*Allopurinol: inhibits xanthine oxidase → ↓ oxidative stress & endothelial dysfunction.
- High dose of it prolongs exercise time in patients with atherosclerotic angina.

*Dipyridamole: inhibits the uptake of adenosine & PDE3 inhibitor
- Good coronary dilator
- Antiplatelet drug
- ↑ blood flow to the normal area "coronary steal Phenomenon"
- Enhances exercise induced myocardial ischemia → it's not used as an antiplatelet agent in patient with stable angina.

*Others:-
- ACEI
- Anticoagulants / Thrombolytic therapy.
- Cholesterol lowering agents
- Angioplasty
- Surgery

Ischemic heart disease drugs

Ca^{++} channel blockers

Are arteriolar vasodilators:
↓smooth muscle tone & vascular resistance
→treat vasospastic angina

↓myocardial oxygen consumption →
treat effort induced angina

Phenilalkylamines

Verapamil

-Slow cardiac conduction directly ↓oxygen demand, has -ve inotropic effect → so it's contraindicated in patient with congestive HF

Benzothiazepines

Diltiazem

Uses:

-Produce less hypotension and may be better tolerated in patients with relatively low BP.
-Provide a distinct advantage (antiarrhythmic effects) in patients with a history of atrial tachycardia, flutter & fibrillation.

Side effects
Hypotension/flushing/peripheral edema/headache & dizziness

Dihydropyridines

1st generation

Nifedipine

- Arterioles vasodilation effect with minimal effect on heart.
- Is useful in the treatments of variant angina.

2nd generation

- Isradipine
- Nicadipine
- Felodipine

3rd generation

Amlodipine

Can cause further deleterious lowering of pressure in patients with relatively low BP.

Ivabradine

-Bradycardic drug, relatively selective if Na^+ channel: reduce cardiac rate by inhibiting the Na^+ channel in SA node (inhibition of pacemaker current)
-Advantage: no effect on GI & bronchial smooth muscle.
-↓anginal attacks with similar efficacy to that of Ca^{++} channel blockers & β blockers.
-Effective as β blocker atenolol & comparable with amlodipine in the managment of chronic stable angina.
Uses: heart related chest pain & heart failure / is used in combination with β blockers in people with HF with LVEF < 35%
Side effects: luminous phenomena / bradycardia / 1st degree AV block / ventricular extrasystoles / blured vision.

Trimetazidine

1st cytoprotective anti-ischemic agent.
-pFOX inhibitor: inhibits FA BO
-Preserves energy metabolism in cells exposed to hypoxia → prevent ↓ in intracellular ATP levels.

Ranolazine

Newer antianginal drugs

↓late Na^+ current (I Na) that facilitates Ca^{++} entry via Na^+-Ca^{++} exchanger → ↓Ca^{++} → ↓cardiac contraction ↑diastolic function
-Has antianginal & antiarrhythmic properties.
Uses: patients who have failed other antianginal therapies.
-Metabolized in liver by CYP3A & CYPD6
-A substrate of P-glycoprotein
Adverse effects: ↑QT → it's contraindicated with other drugs that ↑QT.

	Nitrate alone	β blockers or Ca^{++} channel blockers	Combined nitrates with β blockers or Ca^{++} channel blockers
Heart rate	reflex ↑	↓	↓
Arterial pressure	↓	↓	↓
EDV	↓	↑	non or ↓
Contractility	reflex ↑	↓	non
Ejection time	↓	↑	non

Revise slide 37 & 38