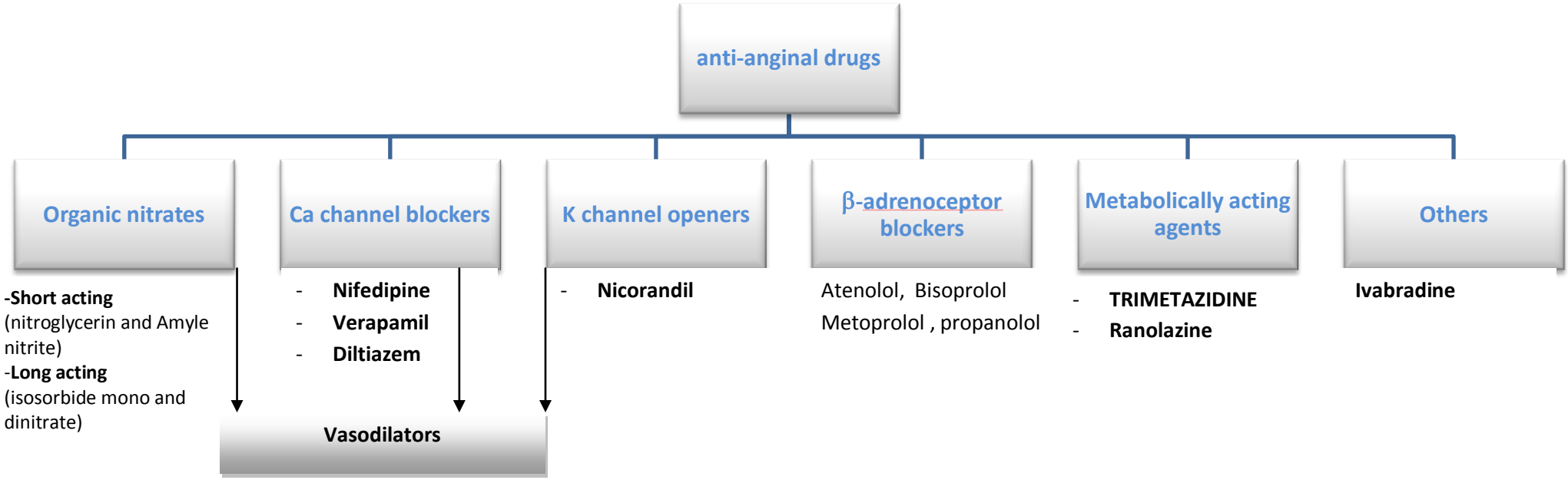
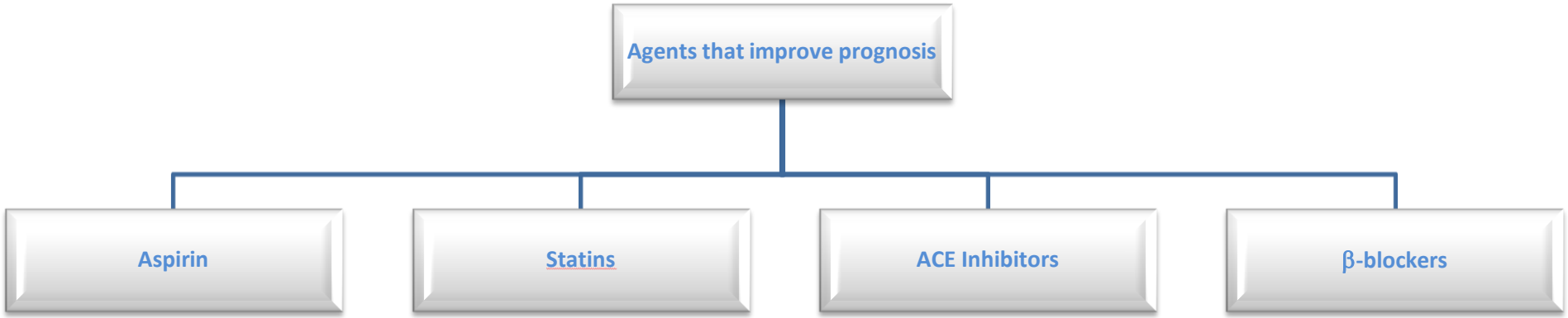
Treatment of angina





Organic Nitrate	**Nitroglycerine "GTN"** in acute cases	**Isosorbide mono & dinitrate** as prophylaxis
M.O.A	- they release NO→ NO binds to Guanylyl Cyclase "GC"→ this will↑ cGMP→ this will make PKG inhibit MLCK→ no contraction in muscle (**relaxation**) "MLCK is an enzyme needed for phosphorylation of Myosin Light Chain (MLC) so the process of contraction in muscles begin" The improving of angina is done by these actions: -↑ **myocardial O_2 supply** (by vasodilatation of coronary vessels which lead to increase of blood flow) -↓ **O_2 demand in heart** (by decreasing the cardiac work, so heart doesn't need more O_2) -↓ **platelet aggregation** (by the increase of cGMP)	
Pharmacokinetics	If given orally first pass metabolism occurs in the liver (10-20%BV) So it's given sublingual or via transdermal patches or IV	Orally is Very well absorbed & 100% BV The dinitrate undergoes denitration to two mononitrates, both are anti-anginal
Uses "indications"	-Acute symptom relief and variant angina (sublingual) -Unstable angina and Refractory AHF "acute heart failure" and Acute MI (IV) -Severe bronchial asthma (inhaled or sublingual) -Amyle nitrite is used in cyanide poisoning *mechanism in the other file*	-Regular prophylaxis -CHF "chronic heart failure" (given with hydralazine) "just when treatment is contraindicated with ACE inhibitors"
Adverse Effects	- **Postural hypotension** with **reflex tachycardia**. - **Nitrite syncope** with fainting & collapse due to ↑ dilatation of venous capacitance vessels + severe ↓ of venous return leading to ↓CO & BP. - **Flushing** of blush area (face, neck and upper trunk) and **drug rash** - Throbbing **headache** (>common) & tendency to ↑ intra-cranial pressure → used cautiously in cerebral bleeding & head trauma.- - **Visual disturbance** - **Carcinogenesis** - **Met-hemoglobinemia** (in overdose & accidental poisoning) - **Nitrate tolerance** (loss of VD response after continuous use) can be overcome by smaller doses at increasing intervals or use it with other drugs "captopril"	
Precautions during use	-10 hours nitrate free period. -Do not take double dose.	-Never stop nitrate therapy suddenly -Do not use after expiry date; GTN is volatile; shelf-life ~6w after opening.
Contraindications	-Organic nitrates sensitivity - Head trauma or cerebral hemorrhage - Glaucoma - Uncorrected hypovolemia -Concomitant administration of PDE_5 Inhibitors for the treatment of erectile dysfunction →↓BP →↑Myocardial Ischemia	

Ca channel blockers	Dihydropyridine group (Nifedipine, Nicardipine)	Verapamil	Diltiazem
Main effects	act mainly on vascular smooth muscles "VSMC" and used as vasodilators	act more on the Cardiomyocytes and used as anti-arrhythmic drug	intermediate effect
M.O.A	Anti anginal action: - Decrease VSMC contraction - Decrease cardiomyocytes contraction (Decrease O_2 demand by decreasing afterload and cardiac work. Increase O_2 supply by vasodilatation of coronary vessels)		
Uses "indications"	- stable angina - antianginal with CHF (no ↓ contractility) - Cerebral dilators	- stable angina - anti-anginal with hypotension (less vasoactivity) - Migraine - Arrhythmias	- stable angina - anti-anginal with hypotension (less vasoactivity)

K channel openers	Nicorandil
M.O.A	1. Opens K_{ATP} channels (> arteriolar dilator) 2. NO donner as it has a nitrate moiety (> venular dilator)
Pharmacokinetics	Given orally, 80% BV Protein bound 25%, $t_{1/2}$ =1 hr Hepatiac metabolism, renal excretion
Uses	Prophylactic 2nd line therapy for stable angina & refractory variant angina
Adverse Effects	Flushing, headache, Hypotension, palpitation, weakness, Mouth & peri-anal ulcers, nausea and vomiting

β- blockers	**Atenolol Bisoprolol Metoprolol** (selective), **propanolol** (non selective)
M.O.A	- **decrease O_2 demand** (by decreasing the cardiac work through their –ve inotropic and chronotropic effect and decrease rennin angiotensin release) - **increase O_2 supply** (increasing diastole, which give more time for perfusion and lead to increased coronary blood flow)
Uses	- **stable angina** (used as prophylaxis, β-selective blockers are 1st choice on prolonged use, they prevent ventricular arrhythmias) - **unstable angina** (stop its progression to Acute MI or reduce infarct size "CARDIOPROTECTIVE") contraindicated in variant angina because it doesn't have vasodilatation action
Precautions	- should be withdrawn gradually (if not β-receptors are up-regulated, and it gives rise to Rebound angina, arrhythmia, MI & hypertension) - Non-selective are better avoided (they blocks vasodilator effects of sympathetic stim.) - Given to diabetics with ischemic heart disease ➔ [Benefits > hazards) & ACE inhibitor must too be added specially in ACSs

Metabolically acting agents	TRIMETAZIDINE
M.O.A	↓OXYGEN DEMAND WITHOUT ALTERING HEMODYNAMICS by: - -O_2 requirement for glucose utilization is less than that required for FFA "free fatty acids" utilization - During ischemia, metabolism shifts to oxidation of FFA. However still, the ↑FFA→blunts glucose utilization. - Partial FFA oxidation inhibitors - Restores energy balance in the cell (↓ fatty acid metabolism, inhibiting anaerobic glycolysis, Allowing only aerobic glycolysis)
Pharmacokinetics	- Rapidly absorbed, Peak concentration= 2 hrs - $t_{1/2}$ = 6hrs - Excretion, mainly unchanged in urine
Uses	Used when ever needed as add on therapy to nitrates, Ca Channel Blockers or β-blockers
Adverse Effects	GIT disturbances
Contraindications	Hypersensitivity reaction and In pregnancy & lactation

Ranolazine newly introduced considered one of the metabolically acting agents like trimetazedine

+ Affects Na dependent-Ca Channels → prevents Ca load → ↓ apoptosis → cardioprotective.

It prolongs the QT interval so not given with; Class Ia & III antiarrhthmics Toxicity develops due to interaction with CYT 450 inhibitors as; *diltiazem, verapamil, ketoconazole, macrolide antibiotics, grapefruit juice*

Ivabradine not classified drug

Acts on the "Funny Channel" a special Na channel in SAN →↓HR→↓myocardial work →↓Myocardial O_2 demand