All drugs in Pharma (mid)

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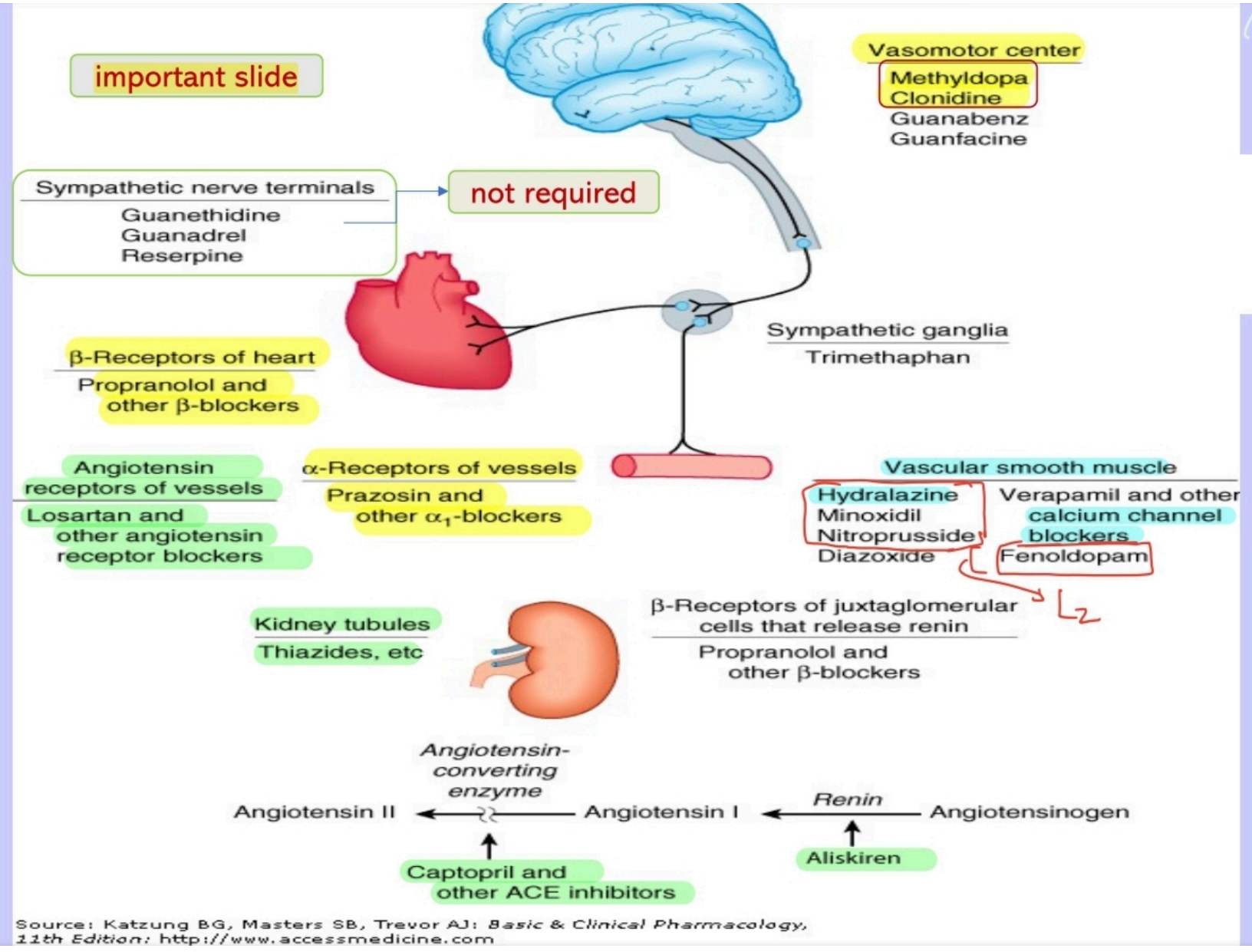
Anti-hypertensive drugs

👉 We divide antihypertensive drugs into three main categories:
1. Centrally acting drugs that target the sympathetic nervous system or the nervous system in general.
2. Renal-active drugs that affect kidney function.
3. local agents.



❗ First line therapy of hypertension in Jordanian --> diuretics, ACE inhibitors, or ARBs.
❗ First line therapy of hypertension in African Americans --> Calcium Channels Blockers “verapamil”.

Drug name	MOA	Indecations	Side effects
1. Methyldopa and Clonidine The definition of an alpha-2 agonist applies to Clonidine, not Methyldopa	Vasomotor center: Alpha-2 agonists - By reducing the release of norepinephrine, beta-1 receptors are less stimulated, and alpha-1 receptors are not activated, leading to vasodilation, a reduction in cardiac output, and decreased contractility of the heart. - Methyldopa actually inhibits the production of dopamine and catecholamines, which leads to a decrease in the amount of norepinephrine in neuron.	Clonidine is used for patients with resistant hypertension. **Methyldopa is the drug of choice for managing gestational hypertension during pregnancy**.	The only side effect of Clonidine is sedation. Sudden stop of Clonidine can lead to rebound hypertension. The Most common side effect of methyldopa are sedation and drowsiness.
2. Alfuzosin, doxazosin, prazosin, terazosin. **Silodosin is** selective to alpha 1 in prostate it has no relation with hypertension.	Alpha-1 receptors antagonist >> blood vessels dilate (widen), which leads to lower blood pressure.	They bind with Alpha-1 receptors on vessels and prostate so, we treat the hypertension and the prostate	1. Orthostatic hypotension (A sudden drop in BP when standing up) >> that happen in the arteries mainly. 2. First-dose syncope (or first-dose hypotension) is a significant drop in blood pressure that can occur after the initial dose of alpha blockers. This effect can lead to dizziness, lightheadedness, or fainting (syncope) due to the sudden decrease in blood pressure. 3.Reflex tachycardia. 4.Retention of water and sodium. 5. Headache
3. Thiazides diuretics (not dose dependent drug)	Giving diuretic --> secreting water --> lowering blood pressure. ☺ Thiazide diuretics work by inhibiting sodium reabsorption in the distal tubules of the kidneys, leading to increased sodium and water excretion, which lowers blood volume and blood pressure. Over time (6-8 weeks), the body adapts by activating the sodium-calcium exchanger, retaining some sodium to prevent excessive loss, but this adaptation does not fully reverse the blood pressure-lowering effect, as thiazides also induce vasodilation, relaxing blood vessels.	Without side effects (such as orthostatic hypotension, reflex tachycardia, angioedema, or headache). **Therefore, this drug remains the First-line therapy of hypertension to this day.** Giving the drug with salt --> useless effect of the drug.	1. Hypokalemia (the effect is minimal) but it may be hazardous in persons taking digitalis, those who have chronic arrhythmias. 2. Hyperuricemia because of drug interaction on the excretion site. Uric acid and thiazides compete for the same excretion site, which can lead to the reabsorption of uric acid, resulting in hyperuricemia. **If the patient already has gout, thiazides are not prescribed.** 3.Hyperglycemia 4. Hypercalcemia

- Analogs of thiazides diuretics:
- Chlorothiazide, given orally, 1-2 times a day.
- Hydrochlorothiazide, 1-2 times a day.

4. Loop diuretics Furosemide (Lasix) [Furosemide has sulfur], Ethacrynic acid, and bumetanide	- Same idea of diuretics but they work on loop of Henle. (Loop of Henle has pumps that are responsible for reabsorption of sodium (25%), so this is a substantial effect). - They inhibit reabsorption of water, sodium, magnesium, calcium, and potassium.	Loop diuretics drugs are not good drugs for hypertension unless in 2 situations: 1- Too much fluid in their bodies. 2- A Glomerular Filtration Rate (GFR) under 30 is problematic because, for Thiazides to work, they must first be secreted and then bind to their receptors from that side. If the GFR is under 30, thiazide is not even secreted, so it can't bind to the pump inhibiting it.	Hyponatremia, Hypomagnesemia, Hypocalcemia, Hypokalemia, and hypovolemia. Because loop diuretics are not usually followed by compensatory actions (unlike thiazide which causes hypercalcemia as a late compensatory mechanism from the body to try to correct the initial Na+ loss—> drawing Ca2+ back to the body along with Na+ reabsorption) loop diuretics are not preferred to be administered at night, due to their relatively high diuretic effects.
5. Aliskiren	Act on renin enzyme	(it is not effective so forget about it).	
6. ACE inhibitors (ACEI): any drug ending in "pril" like: captopril Contraindicated in: 1. pregnancy 2. with spironolactone or ARBs. (these combinations can lead to excessive hyperkalemia).	1. Inhibit the transformation of Angiotensin I into Angiotensin II [the strongest vasoconstrictor in the body] by inhibition of Angiotensin converting enzyme (ACE). (cause a decrease in aldosterone-mediated sodium and water retention) 2. ACE is responsible for the metabolism of bradykinin [an inflammatory mediator] therefore, inhibiting ACE will prevent the breakdown of bradykinin. In terms of hypertension, it is good because bradykinin will cause inflammation --> vasodilation --> good effect.	1. First line therapy of hypertension in Jordanian --> Diuretics (firstly) then if not effective we use ACE inhibitors, or ARBs. 2. The most common combination for treating hypertension is an ACEI or ARB with thiazides, a combination marketed as Co-Diovan. 3. ACEIs and ARBs are beneficial in cases of kidney failure [When angiotensin II levels increase, it causes constriction of the efferent arterioles, which raises pressure in the glomerulus and increases glomerular filtration pressure. Prolonged high pressure can damage the glomerulus, leading to proteinuria (protein leakage into the urine). ACEIs and ARBs help lower glomerular pressure, which protects the kidneys and reduces the risk of proteinuria. 4. Black Americans are recommended to start treatment with calcium channel blockers for hypertension. However, if they have hypertension with kidney	1. Dry cough with irritation (due to accumulation of bradykinin in the upper and lower respiratory regions). 2. Angioedema (If the patient very sensitive (especially naive patients) they might have high inflammation --> leakage of fluid --> causing Angioedema). 3. First-dose syncope (due to inhibition of Angiotensin II which is a potent vasoconstrictor). 4.Hyperkalemia (aldosterone secretion is inhibited >> Na^+ is excreted, and K^+ is reabsorbed)

		impairment, the treatment should start with ACE inhibitors. 5. ACEIs are recommended for diabetic patients, even in the absence of hypertension.	
7. ARBs: drugs end with the suffix "sartan." Like: losartan Contraindicated in: 1. pregnancy 2. with spironolactone or ACEIs (these combinations can lead to excessive hyperkalemia).	1. Angiotensin II receptor blockers (ARBs), which act directly on the receptor itself. 2. Similar to ACE Inhibitors (vasodilation, block aldesterone secretion), however they do not increase the bardykinin levels	**Mentioned with ACEIs**	Their adverse effects are similar to ACEIs although the risks of cough and angioedema are significantly decreased. Hyperkalemia (aldosterone secretion is inhibited >> Na^+ is excreted, and K^+ is reabsorbed)

2) β-adrenergic blocking agents:

1.Nonselective: Propranolol, Timolol, Nadolol, Pindolol, Penbutolol, carvedilol.
they don't discriminate between β1 and β2 receptors, so that they are contraindicated in patients with: **Asthma, COPD**.
2.Cardio-selective: Metoprolol, Acebutolol, and Atenolol, Esmolol and sotalol.

😊 Uses:
1. Metoprolol and atenolol, which are cardio-selective, are the most widely used blockers in the treatment of hypertension.
2. Pindolol, acebutolol (important), and penbutolol are partial agonists (intrinsic sympathomimetic activity).
- MOA of partial agonists >> They are agonists that bind to β receptors and compete with endogenous sympathetic signals like (epinephrin and norepinephrine) but they have a much weaker effect, so instead of giving the full effect from endogenous signals they imply a weaker signal, so the overall effect is antagonism.

3. Labetalol, Carvedilol: totally non-selective blockers where they block both α and β receptors, so they have a very strong effect on hypertension, used only in emergencies. For hypertension we mainly use labetalol and avoid carvedilol, though carvedilol is used more for heart failure.

4. Esmolol: The drug of choice for management of intraoperative and postoperative hypertension and sometimes for hypertensive emergencies associated with tachycardia.Esmolol is a special β blocker because of its very short half-life (9–10 minutes), it is used in titration (usually in operations) because it is fast acting and has fast resolution.

😊 Indications for beta blockers: Angina pectoris, Atrial fibrillation, Cardiac arrhythmia, Congestive heart failure, Essential tremor, Glaucoma, Hypertension, Migraine prophylaxis, Mitral valve prolapse, Phaeochromocytoma, in conjunction with α-blocker and Symptomatic control (tachycardia, tremor) in anxiety and hyperthyroidism.

😊Note: Even though we said that β blockers are generally contraindicated in heart failure we found out that low doses (¼ of the hypertension dose) of certain β blockers could help in heart failure, and carvedilol is one of them.

NOTE: Sudden withdrawal of Beta blockers may cause rebound hypertension.

😊 Adverse effects: Dizziness, sudden weight gain, irregular heartbeat, congestive heart failure, asthma (non-selective), hypoglycemia (non-selective) in patient with diabetes mellitus, fatigue and masking of hypoglycemia symptoms [If a patient develops hypoglycemia, normally they would experience tachycardia as a compensatory response. But since beta-blockers are blocking the beta receptors, tachycardia may not occur, and the patient may not feel the symptoms of hypoglycemia as they would without the medication].

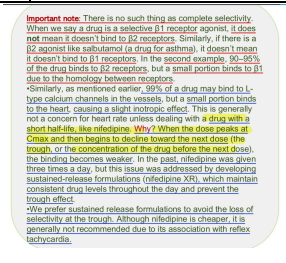
3) Calcium Channels Blockers

- Calcium channel blockers act on L-type Ca+2 channels and block them, leading to the absence of Ca+2, which results in the inability of muscles to contract and causes vasodilation. This effect is more pronounced in arteries than in veins.

- When vasodilation occurs in the arteries, baroreceptors are stimulated, causing reflex tachycardia because arteries are more sensitive to baroreceptors than veins. And if vasodilation occurs in veins, it may lead to orthostatic hypotension.

Drug name	MOA	Indications	SE
1. Ending with the suffix "DIPINE" (Nifedipine, Amlodipine and Nimodipine)	Non-cardio-selective (Vessel selective/Dihydropyridines): 1. They mainly target peripheral arteries, causing strong vasodilation (4 pluses) which significantly lowers blood pressure (4 pluses). 2. They can bind to cardiac cells, resulting in negative inotropic effects (reduced heart contractility).	"Dipine" drugs are generally the best option for Black Americans, except for those with renal impairment, where ACEI are preferred.	1. Reflex tachycardia (due to this strong vasodilation). 2. Headache, flushing, ankle swelling. 3. Nifedipine can cause orthostatic hypotension, though this is not its primary side effect, as it mainly comes from venous dilation.
2. such as: Diltiazem, Verapamil Verapamil is contraindicated 100% in patients with congestive heart failure and never combine it with beta blockers and diltiazem is contraindicated in 90%.	Cardio-selective (Non-Dihydropyridines): They primarily bind toward the channels of the heart producing positive effect toward the SA node (2pluses) and Av node (3,4 pluses respectively) this help in holding the heart back (preventing the arrhythmia).	They are suitable for patients with **arrhythmia and hypertension but without heart failure.**	Diltiazem -> Generally mild Verapamil -> Constipation and Gingival hyperplasia (also a drug called phynytoin causes it).

	NIFEDIPINE*	DILTIAZEM	VERAPAMIL
coronary arteries dill	+ +	+ +	+ +
peripheral arteries dill	+ + + +	+ +	+ + +
negative inotropic	+	+ +	+ + +
slowing AV cond	↔	+ + +	+ + + +
heart rate	↑ ↔	↓ ↔	↓ ↔
↓ blood presure	+ + + +	+ +	+ + +
depression of SA	↔	+ +	+ +
increase in cardiac output	+ +	↔	↔



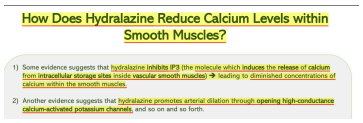
4) Vasodilators

- Keep in mind that all vasodilators are associated with 2 well-known side effects:

1) They produce reflex tachycardia 2) They increase plasma renin concentration which results in sodium & water retention. 3) Headaches

- We control these side effects by combining the vasodilators (ex. Hydralazine) with other drugs, such as diuretics & beta-blockers.
- Hydralazine is combined with a thiazide diuretic & a beta-blocker.
- Minoxidil is combined with a loop of diuretic & a beta-blocker. WHY? Because the water & sodium retention induced by minoxidil is quite profound (as it could lead to edema formation) & could not be controlled by a thiazide diuretic as it is not sufficiently efficacious.

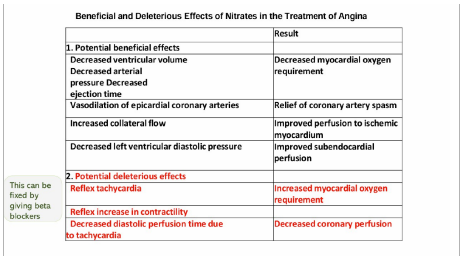
😊 **Note: ALL Vasodilators that we will take about, mainly have the previous 3 side effects in addition to the side effects mentioned in the tables**

Drug name	MOA	Indecations	Side effects
1.Hydralazine (ORALLY) Keep in mind that the MOA of hydralazine is more towards the reduction of calcium levels inside vascular smooth muscles	1. Produce NO (nitrous oxide) which increases intracellular cGMP which will result in the dephosphorylation of the myosin ultimately leading to vascular smooth muscle relaxation. 2. Reduce the level of calcium within the smooth muscles (the most important effect of hydralazine). (It reduces the concentration of calcium intracellularly leading to a nice **arterial dilation rather than venous dilation).**  How Does Hydralazine Reduce Calcium Levels within Smooth Muscles? 1) Some evidence suggests that hydralazine inhibits IP3 (the molecule which induces the release of calcium from intracellular storage sites inside vascular smooth muscles) → leading to diminished concentrations of calcium within the smooth muscles. 2) Another evidence suggests that hydralazine promotes arterial dilation through opening high-conductance calcium-activated potassium channels, and so on and so forth.	**1. African Americans** starts with Hydralazine because it is vasodilator. **2. The drug of choice for congestive heart failure in black people is a combination in of hydralazine and one of the nitrates (isosorbide mononitrate).** 3.Hydralazine is better to be used with **males AND black people.**	lupus-like syndrome (autoimmune disease): 1. This side effect is related to the length of the period of time in which the patient continues administering hydralazine (if a patient keeps taking hydralazine for more than 6 months; then they may develop lupus-like syndrome). 2. It is dose dependent. 3. It is more probable in females than in males and more in caucasians than in black people.

2. Minoxidil (ORALLY)	Minoxidil opens potassium Channels >>causing more efflux of potassium >> leading to increased hyperpolarization >> ultimately Leading to the relaxation of the Smooth muscles (relaxation **occurs more at the level of arteries** (vascular relaxation rather than venous relaxation).	1. Minoxidil can be given topically in order to treat loss of hair; an example of topical minoxidil: **Rogaine** (to treat male pattern baldness and hair thinning & loss in women). 2. Minoxidil is best reserved for the treatment of severe hypertension & if the patient was unresponsive to other therapies. 3. Minoxidil generally is considered a good drug especially in male patients with renal insufficiency.	Hypertrichosis (excessive hair growth on any part of the body: face, back, arms & legs)
3. Nitroprusside (infusion)	Produce NO (nitrous oxide) which increases intracellular cGMP which will result in the dephosphorylation of the myosin ultimately leading to vascular smooth muscle relaxation. (The smooth muscle relaxation effect of nitroprusside affects both arteries & veins which reduces the preload & the afterload).	Nitroprusside is the drug of choice for all patients with hypertension emergency, despite the cause as it works fast with very profound effect, and it finishes fast and it can be easily titrated (our best drug).	Thiocyanosis: (occurrence is more probable to occur when nitroprusside is being administered to the patient for more than 24-48 hours). Thiocyanate toxicity leads to lactic acidosis; which in turn can lead to undesirable effects & problems.
4. Fenoldopam (infusion)	1. An agonist for dopamine-1 receptors, which are present on the blood vessels, (especially the arteries leading to arterial dilation). 2. Fenoldopam can activate these receptors at the level of the kidneys leading to increased renal perfusion.	**1. It is used in hypertension emergency** (but it is not as great as nitroprusside). 2. Very good & nice to patients with **compromised kidney function as it increases the renal perfusion** and it is considered renoprotective	
Labetalol	An alpha & beta-blocker	**The third choice for the treatment of hypertension emergency** is labetalol (or calridol, but labetalol is better, because when it is given by infusion, its effects occur with 5-10 minutes). However, the main issue with labetalol is that it has a long half-life (around 3-4 hours) so, it is quite hard to administer this drug through titration.	

👌 Nitroprusside is considered a special drug; as it is administered through titration.(Nitroprusside works within 30 seconds after administration, and it reaches its peak hypotensive effect within 2 minutes. Also, its hypotensive effect typically stops within 3 minutes after the discontinuation of the infusion.

5) Antianginal drugs:

Drug name	MOA	Indications	SE
1.Beta blockers	They suppress the heart by blocking beta1 receptor, and so reduce the work of the heart by decreasing the cardiac output and blood pressure. They reduce the frequency and the severity of angina attack.	They are the first line treatment of angina. Beta-blockers are used as a prophylactic, not as a treatment for acute attacks, in both stable and unstable angina.	An increase in end-diastolic volume and an increase in ejection time, therefore, the filling of the heart increases so, the stroke volume also increases both of which tend to increase myocardial oxygen requirement. The deleterious effects of beta blockers are counteracted by nitrates.
2.Organic nitrates: isosorbide dinitrate or mononitrate, and Nitroglycerine. Organic nitrates are contraindicated with Sildenafil (Viagra)	1. Organic nitrates are converted into NO (nitric oxide). 2. NO will go to guanylyl cyclase activating the transformation of GTP into cGMP. 3. cGMP will convert phosphorylated myosin into unphosphorylated myosin causing relaxation. - They are more selective toward veins rather than arteries. And they can affect preload and afterload (primarily decreasing preload). By doing this, it reduces the oxygen demand and increases the oxygen supply, helping to relieve an angina pectoris attack.	- Nitroglycerine: (Rescue Agent (emergency drug)) - It is given sublingual or as patches because: 1. Its first pass metabolism is 90%. 2. Enables rapid absorption, delivering the drug directly to the heart to alleviate the attack. - Isosorbide dinitrate and isosorbide mononitrate can be taken orally, with longer half-life and greater bioavailability (take in consideration that isosorbide mononitrate has longer half-life than isosorbide dinitrate).	
3. Calcium channel Blockers: Nifidipine Verapamil and diltiazem. Never ever give those patients short acting Nifedipine, even if you are using beta blockers). Beta blockers are contraindicated with Verapamil	1. Arterial dilation/Coronary after-load reduction. 2. Arterial vasodilation 3. Prevention of coronary vasoconstriction. 4. Enhancement of coronary collateral flow. 5. Improved subendocardial perfusion. 6. Slowing of heart rate with diltiazem,verapamil.	Drugs of choice in treating of Prinzmetal angina are verapamil(the best) and diltiazem. If I have to give Nifedipine, I must combine it with Beta blocker. Long-acting CCB's (e.g. amlodipine) or sustained release formulations of short-acting CCB's (e.g. nifedipine, felodipine, verapamil and diltiazem) are preferred, to minimize fluctuations of plasma concentrations and cardiovascular effect.	Headache, flushing and ankle oedema.

6) Newer Antianginal Drugs

Drug name	MOA	Indications	SE	Containdecations
1. Ivabradine It is metabolized by CYP3A4, there is drug interaction with CYP3A4 inhibitors (like ketoconazole) and inducers (like rifampicin)	Inhibits If current >> reduces SA node firing, leading to a decreased oxygen demand on the heart and reducing the heart rate (-ve chronotropic) results in a reduction in angina symptoms.	1. In angina. 2.In combination with beta blockers in people with heart failure with LVEF lower than 35 and whose heart rate exceeds 70 beats per minute.	1. Luminous phenomena: effect is related to the Ih ion transporters in the retina, which have a structure similar to the If channel. 2. Blurred vision. 3. Headaches. 4. Bradycardia (at doses (high doses)).	contraindicated to be used with verapamil and diltiazem (calcium channel inhibitors)
2. Ranolazine	Inhibits the late sodium influx, reducing calcium overload, lowering myocardial contractility and wall tension, and decreasing oxygen demand, helping to relieve angina symptoms. It doesn't affect heart rate and blood pressure.		Increased level of ranolazine ---> QT prolongation. The drug's effect on the QT interval is increased in the setting of liver dysfunction	In patients with mild to severe liver disease.
3. Trimetazidine	- It has an inhibitory effect on: 1) CPT-1(part of fatty acid utilization toward oxidation) 2) Beta oxidation - A switcher (stimulate glucose consumption by myocardium with no haemodynamic activity (nothing to do with chronotropic and intropic blood pressure).		1. Can cause symptoms of Parkinsons. 2. Extrapyramidal: tremor, rigidity, akinesia, hypertonia and restless leg syndrome.	In patients with Parkinson's disease.
4. Nicorandil	Increases cyclic guanosine monophosphate and facilitates the opening of mitochondrial potassium adenosine triphosphate channels. It opens the K+ channel	Nicorandil is considered as a second-line option to treat patients with stable angina when they do not tolerate or cannot use beta-blockers (or calciumchannel antagonists	Gastrointestinal, skin and mucosal ulcerations (especially if there is concomitant use of acetylsalicylic acid or non-steroidal anti-inflammatory drugs)	