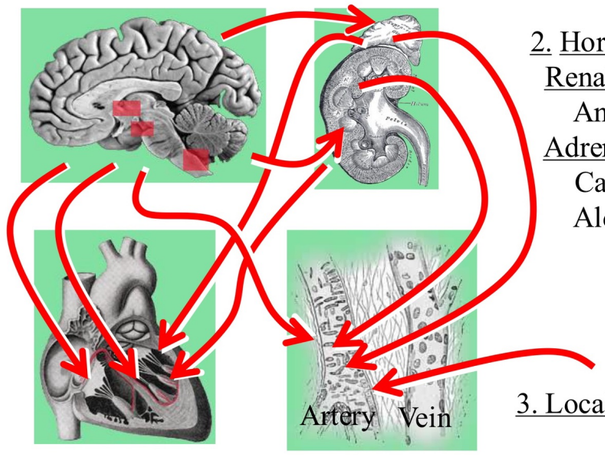
Blood pressure in the body is controlled by → Neuronal [Autonomic] ⇒ fast effect & short
→ Renal [control volume] ⇒ long term effect
→ local [TPR - peripheral resistance]

⇒ Drugs affecting Vasomotor center α/β blockers/agonists
⇒ Diuretics / ACE / ARB
⇒ Vasodilators

Treatment of hypertension depends on ⇒ Drug Combinations ... Why ? → Cmax [their efficacy is low وهيك بدنا]
↳ Addition → Reduce SE
No Synergism

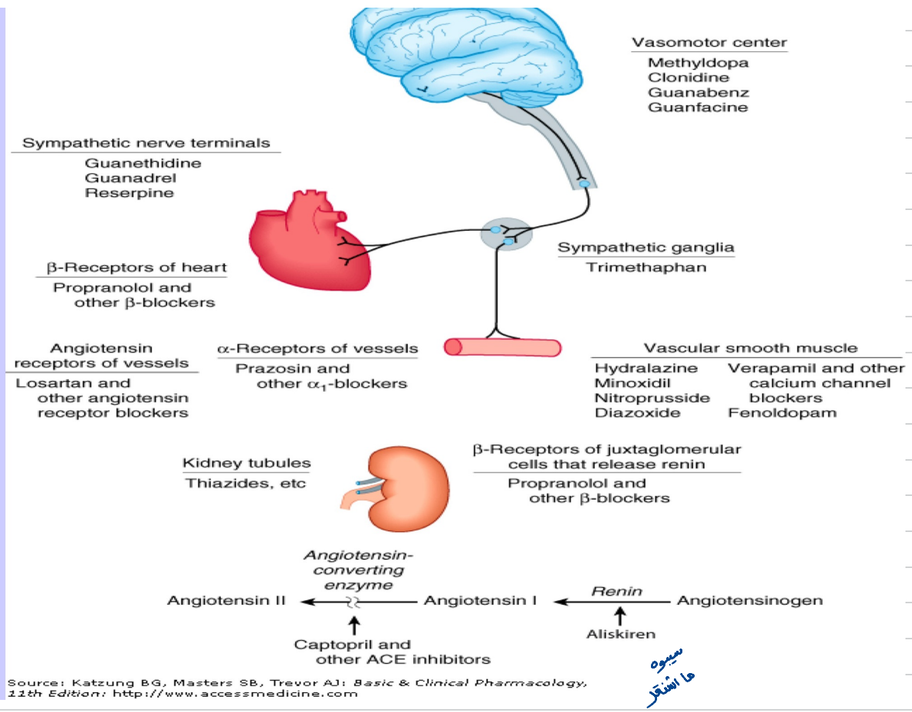
Mechanisms Controlling CO and TPR

1. Neural
SymNS
PSNS

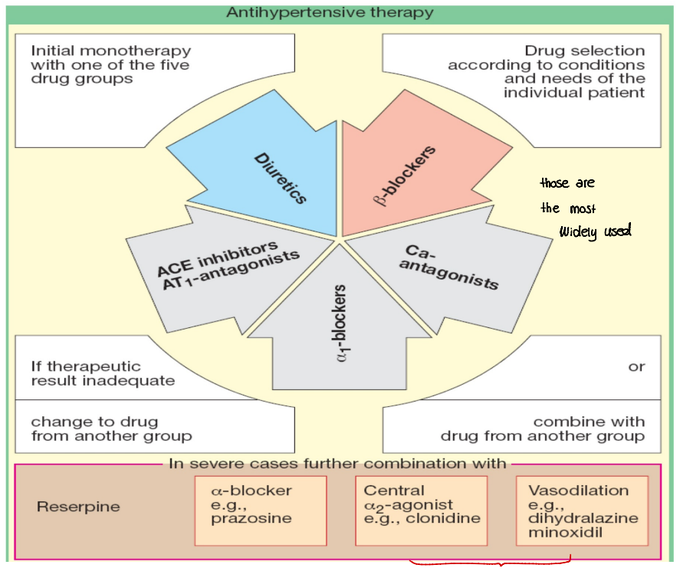


2. Hormonal
Renal
Ang II
Adrenal
Catecholamines
Aldosterone

3. Local Factors



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th Edition*: http://www.accessmedicine.com



→ Some pts take them all
Example pt: With HTN & prostate hypertrophy
↳ already taking α1 blocker
↳ SE ⇒ orthostatic hypertension for sure

صعوبة الحالات الاستعصية
or Black Americans

سيبوه ما الشغر

Centrally acting

Class	Drugs	MOA	uses	SE	notes
Drugs affecting vasomotor center استعماله قليل بس موجود	Methyldopa Clonidine	α2 agonists → sympathetic feedback inhibition → inhibition of α1 & β1 → negative inotropic + chronotropic effect + vasodilation β1 is on SA / AV / Myocytes → -ve {Chrono, Ino}	Methyldopa → drug of choice for gestational hypertension. -No orthostatic hypertension ☺	-sedation	**Rebound hypertension** Clonidine is a direct α2 agonist, over long time of use, α2 receptors get down regulated (desensitization). Increasing the dose of clonidine can overcome desensitization. (tolerance) The problem happens when the pt. suddenly stops the drug. Body has less "anti sympathetic" effect → over activity of sympathetic → rebound hypertension. Does this problem happen with methyldopa? No, different MOA (not a direct α2 agonist) Decrease Nor-epinephrine production
B blockers More to Angina & Heart failure	β1 / cardioselective : metoprolol atenolol B nonselective: propranolol non selective: (β & α1) caridilol / labetalol	Both negative inotropic & chronotropic effect	Labetalol is used in emergency HTN	-fatigue/nightmares - Masking hypoglycemic in awareness symptoms "no tachycardia" -sudden weight gain -irregular heart beat -congestive heart failure -asthma (non selective) -hypoglycemia in DM pts. (non selective)	Use is dose dependent
α1 antagonists	Prazosin	Vasodilation		-orthostatic hypotension -1st dose syncope لازم ياخذه بالمستشفى	
Diuretics (effective in lowering the BP by 10-15 mmHg)	Thiazides -chlorothiazide Orally 1-2 times a day -hydrochlorothiazide 1-2 times a day	Decrease Na+ reabsorption in distal tubules → depletion of body Na+ stores → Acutely : decrease in cardiac output & increase in peripheral resistance (unknown MOA) Chronically (after 6-8 weeks): normal cardiac output & decrease in peripheral resistance → more water excretion & less plasma volume Thiazides bind the Na+ channels from the interior side → they are dependent on a normal glomerular filtration rate to reach their target	-1st line therapy for hypertension. -often provide adequate treatment for mild or moderate essential hypertension. -in more severe hypertension, diuretics are used in combination with sympathoplegic and vasodilator drugs to control the Na+ retention caused by these agents. -decrease BP in supine & standing positions	-hypokalemia: -increased among salt intake (potassium loss is coupled to Na+ reabsorption in GI) -K+ supplementation is Recommended. -well tolerated (but not in chronic arrhythmias & digitalis intake) -hyperglycemia -inhibit the conversion of proinsulin into insulin -hyperuricemia (CI in gout) -result from the inhibition of renal tubular secretion of uric acid. -hypercalcemia no orthostatic hypotension/ no angle edema	-distal tubules are only responsible for a small % of Na+ reabsorption… much more is reabsorbed in loop of henlie. Among use of thiazides → compensation of Na + reabsorption gradually occurs by other channels, meanwhile, the Na+ becomes depleted. Thiazides function in maintaining the depletion, rather than actually inhibiting the reabsorption of Na+. (evidence: effect isn't dose dependent) To maintain the depletion عشان هيك بنحكي للمريض ما تاكل ملح + to prevent hypokalemia exacerbation
Loop diuretics	Furosemide (lasix) Bumetanide Ethacrynic acid	Decrease Na+ reabsorption in loop of henly → less water reabsorption → lower BP Greater diureses, but less anti- hypertensive effect than diuretics	-Pts with low GFR -pts with resistant HTN and evidence of fluid -effective if CrCl < 30 ml/min creatinine clearance	-ototoxic (especially when used with aminoglycosides) mycin family + Amicasin -hyperuricemia -furosemide = Sulfer allergy -Dry mouth -hypocalcemia + Hypo everything	-dose dependent -must be dosed at least twice daily (LASIX = last six hours) -administer AM & lunch time to avoid nocturia
ACE inhibitors	Prils	Prevent the conversion of Ang1 into Ang2 (the strongest vasoconstrictor in the body)		-ACE is also responsible for the breakdown of bradykinin (an inflammatory vasodilator), more bradykinin = 1. more vasodilation (perfecto) 2.more inflammation → angioedema "lieve pts." 3.cough center irritation → dry cough 10% -1st dose syncope	-most widely used بالاردن Ca++ Channels ← هم blockers Drug of Choice for hypertension & heart failure in Jordanians

Renal

Ang2 receptor blockers ARBs	Zartans	Pts who cannot tolerate SE of prils. → zartans have no effect on bradykinin = no cough/ no angioedema			-prils are much better they increase bradykinin → more V.D → Inhibits ADH "Anti diuretic"
Vascular smooth muscle dilators Local	Hydralazine "Drug of Choice for heart failure in blacks" Ca++ Channels blockers الباقي بالصورة Nitroprusside ⇒ Equal effect on arteries & veins				**Black americans** Due to different physiology, they are less affected by prils → direct SM dilators are drugs of choice [Ca++ Channels blockers]

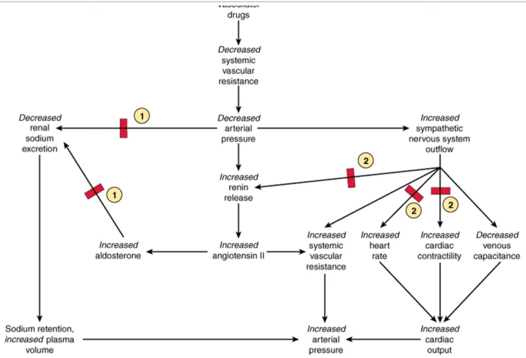
First-dose syncope refers to a sudden, temporary loss of consciousness (fainting) that can happen after taking the first dose of some antihypertensive drugs, particularly **alpha-blockers** (like prazosin) or **ACE inhibitors**.

This reaction occurs because the drug causes a **sudden drop in blood pressure** when it's first introduced to the body. The sudden vasodilation (widening of blood vessels) can cause blood to pool in the lower parts of the body, reducing blood flow to the brain, which leads to fainting.

Doctors often advise taking the first dose at bedtime to reduce the risk, as lying down can help prevent the blood pressure from dropping too low and causing syncope.

vasodilators are the last drugs to use in hypertension treatment ⟹ for resistant HTN
↳ + Drugs of choice in black Americans

General concept to all vasodilators :



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Remember : Blocking one arm is gonna be compensated by overactivity of other arms
∴ we need to block all arms
↳ Block sympathetic by β blockers
↳ Block Renal by Diuretics / loop diuretics

otherwise → sympathetic activation → Reflex tachycardia
→ Baroreceptors activation in the kidney → water retention } Hypertension ما استفدنا اشي

Vasodilators

Drug	MOA	Use	Side effects	Notes
Hydralazine **Ca++ player**	-main effect: decrease the concentration of intracellular Ca++ → **atrio** dilation. How? Decreasing IP3 / working on Ca++ channels -less effect: Increase NO → increase cGMP → dephosphorylation of myosin → dilation	-Oral drug -Drug of choice for black Americans. -Dose = start at 25 mg -Better used in black males (to avoid lupus like S)	-headache (vasodilators) -lupus like syndrome Mechanism: hydralazine is metabolized (detoxified) in the liver by acetylation (a part of phase 2 detoxification system). People can be either fast or slow acetylators. In slow acetylators → accumulation of reactive metabolites of hydralazine → stimulating the immune system → forming anti histone Ab (as in SLE). Time dependent: > 6 months of use Sex dependent: 4:1 more in F Race dependent: Caucasians > blacks Dose dependent: <50 mg = 0% >100 mg = 5% >200 mg = 10%	Combinations: -β blockers -thiazides
Menoxidil **Diazoxide** **K+ player**	Activate ATP dependent K+ channels → increased K+ efflux → hyperpolarization → atrio dilation	-Oral drug -Drug is reserved for severe hypertension & is mostly used in men rather than women (hypertrichosis)	-hypertrichosis (growth of hair) is seen over long time use.	Combinations: -β blockers -loop diuretics (thiazides are not strong enough) ↓ Recall: You need to control hyponatremia/ hypomagnesemia…. Hypocalcemia is controlled by the body
Nitroprusside **NO player**	Increase the production of NO → increase cGMP → dephosphorylation of myosin → dilation Equal effect on arteries & veins (good for angina)	-IV Infusion (continuous delivery) -Used in emergency hypertension (when BP > 210/150) -onset of action = 30 sec -peak = 2 min -clearance (titration) = 3 min after stopping the Infusion → PERFECT FOR EMERGENCY	-cyanide toxicity Cyanide is produced as a byproduct of NO production. Under low doses/ short periods, body can detoxify cyanide by converting it into thiocyanate (a less toxic product). BUT, on long time use (>48 hrs) or high infusion rates (>4 ug/ kg/ day), cyanide accumulates → Inhibiting oxidative phosphorylation & driving the cells into anaerobic metabolism → production of lactic acid → metabolic acidosis (LIFE THREATNING)	No long term use = no need for combinations
Fenoldopam **Dopamine player**	Dopamine 1 receptor agonists → vasodilation Higher effect on arteries Higher effect on RENAL arteries providing more renal blood flow & increasing the GFR	-IV infusion (continuous delivery) -Good drug for pts with kidney impairment -Used in emergency (but not as good as Nitroprusside – harder titration) -onset of action = 5- 10 mins -clearance (titration) = 30-60 mins		

Hypertension emergency

- It is rare but life threatening, in which DBP is > 150 mm Hg with SBP > 210 mm Hg (healthy person), or DBP of > 130 mm Hg in individual with pre-existing complications, such as encephalopathy, cerebral hemorrhage, and left ventricular failure, or aortic stenosis.

- **Sodium nitropresside** (onset 1-2 min), is administered intravenously and causes sudden vasodilation and reflex tachycardia, it is effective in all patients regardless the cause.

  It metabolized rapidly (half life of minutes) and require continuous perfusion. An overdose can cause hypotension.

Hypertension emergency

- **Labetalol** (α and β blocker), (onset 5-10 min) does not induce reflex tachycardia, given intravenous bolus or infusion.

  Have the same β blockers contraindication (Asthma ….) and major limitation of this agent is the long half-life(3-6 hr), that prevent rapid titration.

- **Fenoldopam** (onset 2-5 min), peripheral dopamine 1 receptor agonist that also given as an intravenous infusion.

  It lowers blood pressure through arteriolar vasodilation and also through specific dopamine receptors along the nephron promoting sodium excretion.

Hypertension emergency

may be particularly beneficial in patients with renal insufficiency (maintains or increases renal perfusion).

β blockers
كل بيت فيه بيتا بلوكر

Class	Drugs	Use	SE
β1 selective blockers	Atenolol Metoprolol Esmolol Acebutolol Sotalol	**Generally** They are not 1st line therapies for HTN … use is more oriented to controlling the heart when taking other anti hypertensive drugs, rather than actually lowering the BP (as in vasodilators) **Metoprolol & Atenolol** Most widely used in the treatment of HTN (bc they are cardioselective) **Esmolol** -Has a fast effect: fast onset & short t1/2 (9-10 mins) → constant IV infusions -used for intra or post operative HTN (Keep in mind: other B blockers are contraindicated during anesthesia) -hypertensive emergencies (especially if associated with tachycardia) **Satolol** Drug of choice for arrhythmias in children **Propranolol** Drug of choice for migraine **Timolol** Drug of choice for glaucoma **Acebutolol & Pindolol & penbutolol** & carvidolol Partial agonists = blockers with some sympathomimetic activity → They lower the BP by mainly decreasing vascular resistance & to a lesser extent decreasing CO, HR → perfect for HTN pts with bradyarrhythmias or peripheral vascular disease. -choosing the drug depends on selectivity & contraindications (give Acebutolol for asthmatic) **Labetolol & Carvedilol** -3rd line therapy of emergency HTN (after nitroprusside & fenoldopam) -drugs of choice for pts of pheochromocytoma HTN	**Common** Parasympathetic overactivation → Dizziness, sudden weight gain, irregular heart Beat, congestive heart failure (only at high dose) **For non selective** -exacerbation of asthma (CI) -masking of emergency hypoglycemia in DM pts (masks the tachycardia) **Sudden withdrawal / changing the drug type** Causes rebound hypertension & arrhythmia, due to drug induced β receptors supersensitization → Tapering is the solution **Use in congestive heart failure** Logically, we don't want to exert a negative inotropic/ chronotropic effect on a heart that is already failing to pump. BUT, **small dose** (1/4) can stop the hypertrophy
β non selective blockers	Propranolol Nadolol Timolol Pindolol Penbutolol		
β and α blockers	Carvedilol Labetalol		

- Labetolol is the 2nd drug of choice in pregnancy

Potassium sparing diuretics

Drugs working on RAAS

Drugs	MOA	Use	SE
ACE inhibitors (prils) **-Enalapril** **-lisinopril** **-captopril**	3 effects: 1. inhibiting aldosterone effect → diuretic effect on collective ducts 2. inhibiting Ang2 effect → vasodilators 3.increasing bradykinin activity → vasodilators → notice: no direct effect on CO & HR, they only decrease peripheral resistance.	-treating HTN pts with chronic kidney disease → They increase blood flow to the kidneys, diminish proteinuria -drugs of choice for HTN with DM nephropathy (EVEN IN BLACKS) -kidney disease even in the absence of HTN -heart failure	-SE of bradykinin accumulation → 1. dry cough 2. angioedema -SE of inhibiting aldosterone → hyperkalemia -1st dose syncope -CI in pregnancy (cause fetal renal toxicity)
ARBs (sartans) **-losartan** **-candesartan**	Ang2 receptor blockers → they lack effect on bradykinin		-same SE (except for bradykinin)
Aldosterone inhibitors **-spironolactone** **-eplerenone**	Only diuretic effect		Hyperkalemia

→ note: those drugs cause hyperkalemia

Thiazides cause hypokalemia

Combine to get rid of SE →

-ACEI + Thiazide = BluePress Plus

-ARB + Thiazide = codiovan

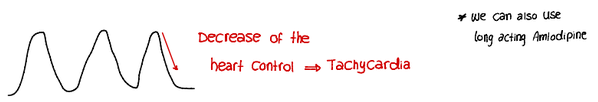
BUT, ACEI/ ARBs/ ALD inhibitors shouldn't be combined to prevent hyperkalemia

EXCEPT in pts with end stage heart failure (where we need complete block of ANG2 effect) →

This is the only case where ACEIs & ARBs are combined (however, you also need to control hyperkalemia)

Note: ACEIs are contraindicated in bilateral renal stenosis, but allowed in unilateral

Ca++ channels blockers

Drugs	MOA	SE & CI	Notes
Dihydropyridines (dipine) -Nifedipine -amlodipine -nimodipine	- L Ca++ channel blockers - mostly specific to arterial channels rather than heart channels → vasodilation effect	- SE of vasodilation → -headache/ flushing/ ankle swelling -reflex tachycardia & orthostatic hypotension are minimal … WHY? 1. the drug affects the arteries more than veins 2.little negative inotropic effect prevents reflex tachycardia	-combination with β blockers is allowed since they have little effect on the heart. Nefidipine has two preparations: 1.short acting (given 3 times a day) 2.sustained release → short acting Nefidipine has a higher risk of reflex tachycardia … WHY? -the drop in its concentration each time = no effect on the heart 
Diphenylalkylamine -varapamil	-L Ca++ channel blockers -mostly specific to heart channels → cardioselective -negative chronotropic & inotropic effect	-strong inotropic effect → - don't combine with β blockers (they also have a negative inotropic effect) -good for arrhythmias -constipation -Gingival hyperplasia —don't give in CHF	
Benzothiazepines -diltiazem	-L Ca++ channel blockers -mostly specific to heart channels → cardioselective -negative chronotropic & inotropic effect		Diltiazem has a weaker effect than verapamil 👉 used instead of verapamil in pts with low ejection fraction

	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	+ +	↔	↔

* and others dihydropyridines
↓ = decrease
↑ = increase
↔ = without change

Adverse effects of calcium channel-blocking agents

Drug	Effect on heart rate	Adverse effects
Nifedipine	↑	Headache, flushing, ankle swelling
Amlodipine	↑	Ankle swelling
Nimodipine	±	Flushing, headache
Diltiazem	±	Generally mild
Verapamil	↓	Constipation, marked negative inotropic action

Calcium channel blockers **do not affect** concentrations of plasma cholesterol or triglycerides, or extracellular calcium homeostasis.

Drugs that affect α receptors

Drugs	MOA & use	SE
Selective α1 blockers (zosin) **-Alfozosin** **-Doxazosin** **-Prazosin** **-Terazosin** **-Silodosin**	-blocking α1 receptors → vasodilation of all vessels (A&V) treatment of urinary retention in men with benign prostatic hyperplasia -Silodosin is specific to urinary retention (given for men with prostate hyperplasia & without hypertension)	-SE related to strong (esp. venous) dilation → Orthostatic hypotension Reflex tachycardia (should be combined with β blockers) 1st dose syncope
α2 agonists **-clonidine** **-methyldopa**	-GRADUAL α2 agonists → sympathetic feedback inhibition → inhibition of α1 & β1 → negative inotropic + chronotropic effect + vavsodilation. -Clonidine → lowers the HR & CO -methyldopa → does not decrease CO → renal blood flow is maitained → useful in the treatment of HTN complicated with renal disease. -methyldopa is the drug of choice for gestational HTN	-since the effect is gradual → no reflex tachycardia water retention more significant (usually combined with diuretics) **clonidine** **-**sedation -dry mouth -dry nasal mucosa **Methyldopa** -sedation & drowziness -remember → rebound hypertension with clonidine

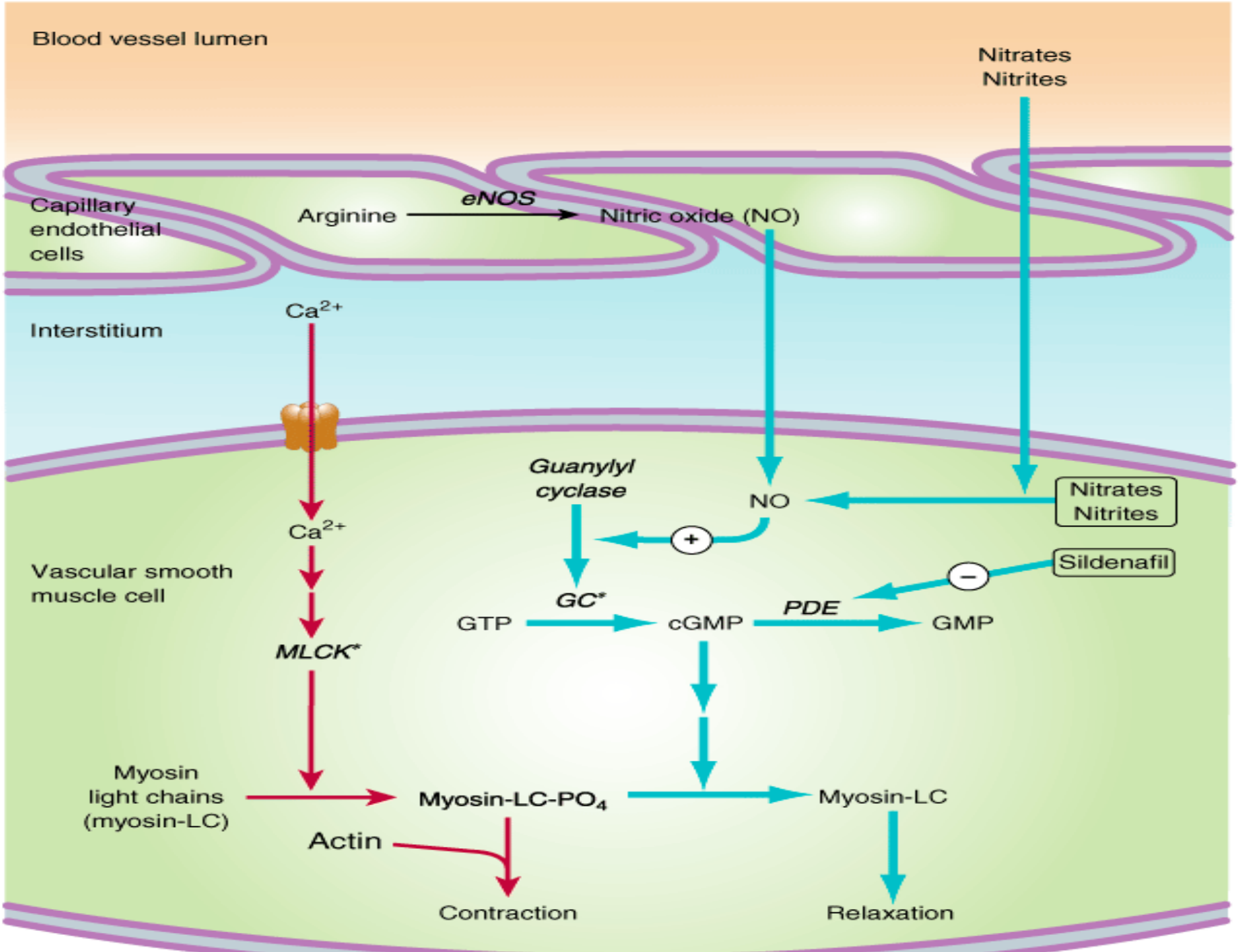
Ghada Barakat

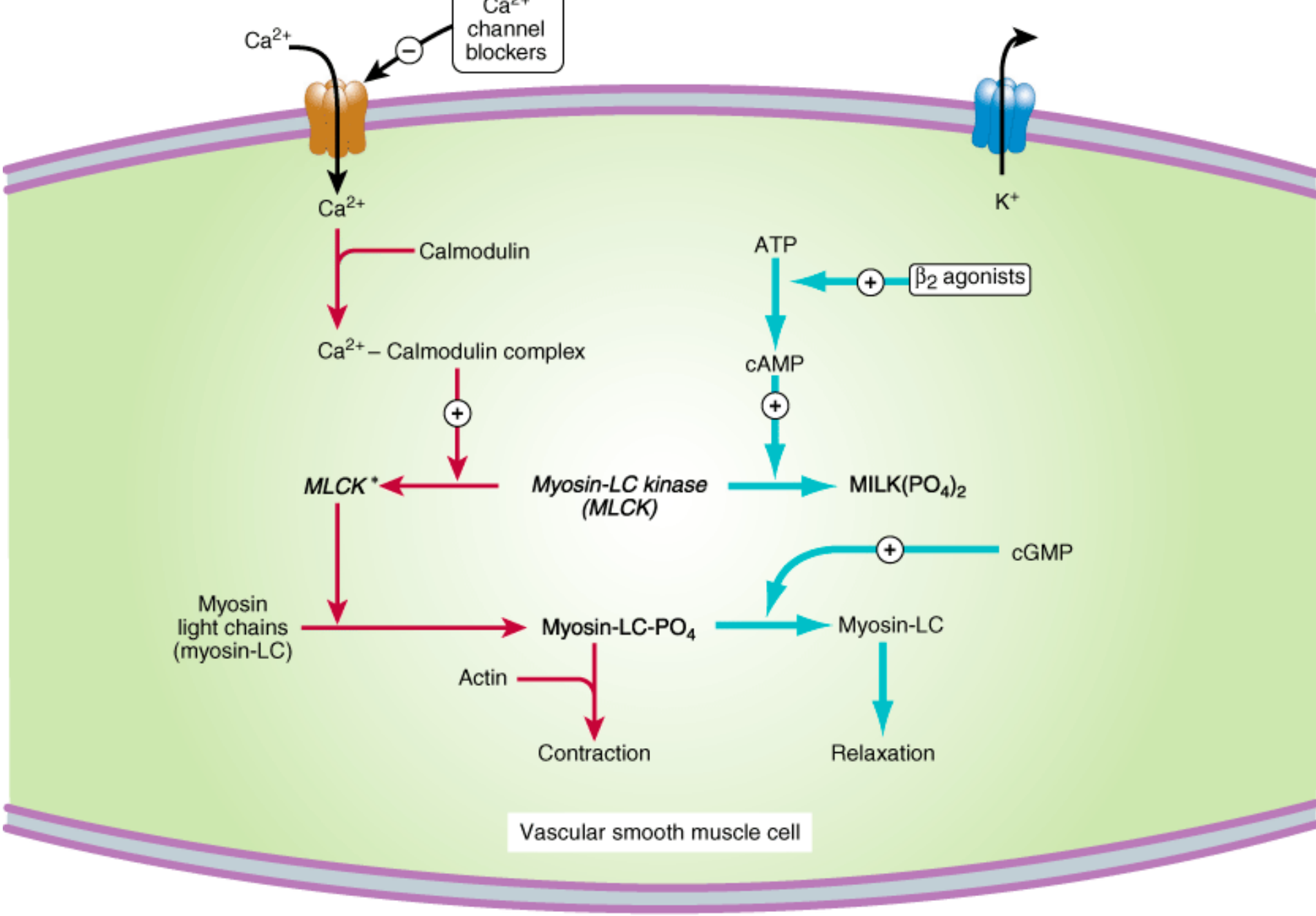
Angina = increased myocardial demand on O2 + decreased perfusion → the lower heart perfusion activates angiogenesis of vessels that bypass the coronary stenosis (collateral blood flow)

Type	Pathophysiology	Drugs
Stable	-the most common -squeezing feeling in the chest -caused by reduction of coronary perfusion due to coronary atherosclerosis → the heart becomes susceptible to ischemia whenever there is increased demand (examples: exercise/ emotional excitement)	-Rest & nitrates (vasodilators) -nitrates are strong vasodilators → reflex tachycardia → we need to control the heart by high dose β1 blockers
Unstable	-lies between stable angina & myocardial infarction -unrelated to exercise … occurs at rest -caused by more severe atherosclerosis → lipid plug might detach (تلولح) & close the coronary artery	-more aggressive therapy (dislipidemias/ antiplatelets…) -nitrates are also used (combined with high dose β1 blockers)
Variant (vasospastic)	-caused by coronary artery spasm due to contraction of the smooth muscles in its wall, rather than directly by atherosclerosis -increased Ca++ influx can be associated	-β1 blockers cant be used … WHY? They have minimal unspecific antagonism on β2 receptors on the coronary artery → causing coronary vasoconstriction (و أنا هاي مشكلتي أصلا) -Ca++ channel blockers are the drug of choice (depines)

Drugs of angina

Drug	MOA	Use	SE	Notes
Organic nitrates **-Nitroglycerine** **-Isosorbide dinitrate** **-Isosorbide mononitrate** Rescue agents	NO → Increase cGMP → Dephosphorylation of myosin + decrease in intracellular Ca++ → vascular smooth muscle relaxation. **Effect** 1. dilation of arteries, including coronary → more perfusion to the heart 2. dilation of large veins → pooling of the blood → decrease preload volume → reduce the load on the heart. 3. decreased ventricular volume/ arterial pressure/ ejection time → decreased O2 demand 4. increased collateral flow -What is the difference between the 3 types of nitrates? -kinetics -selectivity towards arteries or veins (only significant in small doses)	**Nitroglycerine preparations** -undergoes significant 1st bypass metabolism → oral isn't a good choice 1. sublingual 2. transdermal (patch) 3. spray **Isosorbide preparations** -has a long t1/2 && can avoid 1st bypass metabolism → oral -drug of choice for angina attack is sublingual glycerine, WHY? 1. kinetics → OOA= 1min, while its an hour for Isosorbide 2. selectivity → it has higher selectivity towards veins rather than arteries… decreasing the risk of reflex tachycardia when given in small emergent doses without combination with β blockers -how to use ? the pt. is given the drug, if pain doesn't resolve in 10 – 15 min → the drug is given again. You're allowed to give 3 doses. If the pain persists → call 911	-SE of vasodilation →throbbing headache -usually decreases after few weeks due to tolerance -SE of arterial dilation → reflex tachycardia → increased O2 demand -solution: control the heart using high dose β1 blockers -SE of venous dilation → orthostatic hypotension -don't use with slidinafil (viagra) Viagra has a similar effect on increasing cGMP, potentiating nitrates effect → hypotensive shock. → interval of 6 hrs is recommended between the two agents	**Tolerance** -blood vessels become desensitized to nitrates rapidly … WHY ? -depletion of the tissue thiol → inability to release NO -solution: by daily "nitrate free intervals" to restore sensitivity to the drug … the pt. skip the night dose providing a 10-12 hrs interval **volatile Nitroglycerine** -The conventional sublingual tablet form of nitroglycerin may lose potency when stored as a result of volatilization and adsorption to plastic surfaces. Therefore, it should be kept in tightly closed glass containers. The container doesn't need to be dark, Nitroglycerin is not sensitive to light. - spray is equally effective; it has a shelf life of two to three years and does not require refrigeration Monosorbide has the longest t1/2
β blockers Prophylactic	-Negative inotropic & chronotropic effect on the heart → -decrease oxygen demand -undesirable effect → an increase in end diastolic volume & ejection time → increase O2 demand. -this effect can be balanced by concomitant use of nitrates	-combined with nitrates -1st line therapy for stable angina -unstable angina -MI	contraindications→ -variant angina -bronchial asthma -bradycardia	-β1 selective are preferred -avoid intrinsic sympathomimetics
Ca++ channel blockers **-Nifidipine** **-verapamil** **-diltiazem**	Recall -nifidipines effect is directed towards arteries → reduction of afterload coronary artery vasodilation enhancement of collateral flow -verapamil/ diltiazem slow down the conduction & HR→ decrease the O2 demand → good for angina especially in pts with low blood pressure + pts with a history of arrhythmias (they provide am anti arrhythmic effect)	-1st line therapy for variant angina Which one? Verapamil Diltiazem in pts with low ejection fraction		


Blood vessel lumen
Nitrates
Nitrites
Capillary endothelial cells
Arginine
eNOS
Nitric oxide (NO)
Interstitium
Ca2+
Guanylyl cyclase
NO
Nitrates
Nitrites
Ca2+
Vascular smooth muscle cell
Sildenafil
GC*
PDE
GTP
cGMP
GMP
MLCK*
Myosin light chains (myosin-LC)
Myosin-LC-PO4
Myosin-LC
Actin
Contraction
Relaxation



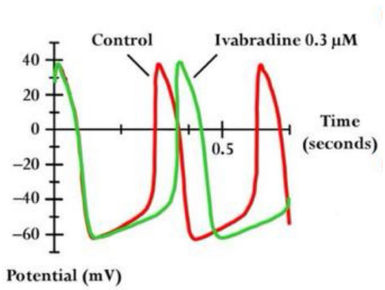
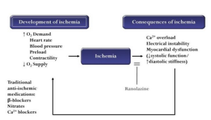
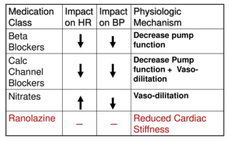
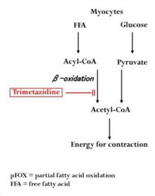
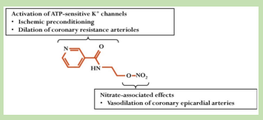
Combination Therapy of Angina

- **Use of more than one class of antianginal agent can reduce specific undesirable effects of single agent therapy**

Effect	Nitrates Alone	Beta-Blockers or Channel Blockers Alone	Nitrates Plus Beta-Blockers or Channel Blockers
Heart Rate	*Reflex Increase*	Decrease*	Decrease
Afterload	Decrease	Decrease	Decrease
Preload	Decrease	*Increase*	None or decrease
Contractility	*Reflex increase*	Decrease*	None
Ejection time	Decrease	*Increase*	None

Undesireable effects are shown in italics

Newer anti angina drugs (remember, we need to decrease the O2 demand)

Drug	MOA	Use	SE/ CI
Ivabradine	-the name (bradine) indicates that the drug will cause bradycardia (decrease HR) HOW? By selectively inhibiting the funny Na+ channels (If) in the SA node → lower pacemaker potential slope → less depolarization frequency → lower HR → less myocardial O2 demand → reduction in angina symptoms -notice: the drug has no effect on blood pressure or myocardial contractility (inotropic effect), effect is only chronotropic. 	**Angina** The drugs lowers the heart rate & myocardial O2 demand **Heart failure with low ejection fraction (<35%)** By lowering the heart rate → heart has longer time to fill → larger end diastolic volume → larger stroke volume. HF pts not sufficiently managed by β blockers can benefit from adding ivabradine & decrease risk for hospitalization. 	**Drug – drug interaction** Ivabradine is metabolized by CYP3A4 CYP3A4 inducers (ex.rifampicin) → decreased activity CYP3A4 inhibitors (ex. Azoles) → increased activity **Contraindications** -don't use with verapamil or diltiazem (strong effect on the heart) … however, β blockers are allowed. **SE** -Luminous phenomena (14.5%) → What is it? Sensation of enhanced brightness in a fully maintained visual field. Why? Due to blockage of Ih ion channels in the retina, Which are very similar to cardiac If channels. -Blurred vision -Bradycardia at high dose (2-5% compared to 4.3% in Atenolol) -Headache (2.6- 4.8%) … although its not a vasodilator
Ronalazine	-selective inhibitor of late Na+ influx in the myocardium → reducing Ca++ overload → attenuating the ischemic abnormalities of ventricular repolarization & the resulting reduced contractility. -Note: late Na+ influx happens during the plateau phase, it increases after ischemia, leading to increased Ca++ overload → increased contractility + diastolic relaxation failure → increased O2 demand → worsens angina & ischemia. Thus, inhibiting late Na+ influx will prevent those consequences, lowering the O2 demand. -Notice: again, there is no effect on blood pressure + no effect on the heart rate again, we are just decreasing the O2 demand -pFOX family (little effect)	-reduces the frequency of Angina episodes -improves the exercise tolerance -improves myocardial ischemia  	-prolonged QT interval → How? By inhibition of Ikr potassium channels, which prolongs the ventricular action potential. QT prolongation is increased in pts with mild or severe liver diseases (contraindicated)
Trimetazidine	-The name (meta) indicates that the drug has a metabolic effect What is it? Switching the energy source from fatty acid oxidation into glucose Result → less O2 demand Drugs that have this effect are classified under the pFOX family (partial FA oxidation) -Notice: limited hemodynamic effect -Note: fatty acid oxygen is increased during ischemia. So preventing it is a part of treating the consequences of ischemia.		-Parkinsonism symptoms (CI in Parkinson pts) -Extrapyramidal (CNS symptoms such as tremor, restless leg syndrome)
Nicorandil 	2 parts → -nitrate part working as a vasodilator -activator of ATP sensitive K+ channels → hyperpolarization → less contractility.	-2nd line option to treat pts with stable angina when they don't tolerate or cant use β blockers or Ca++ channel blockers/ or when they don't respond to them	-Don't use with Nitrates -GI, skin, mucosal ulcerations (especially if used with acetylsalicylic acid or NSAIDs), in this case, drug should be discontinued permanently.

Ghada Barakat