CVS
PHARMACOLOGY

Modified NO: 4

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Color code

Slides

Doctor

Additional info

Important

Calcium channel blockers

- Like ACE Inhibitors, they are recommended agents when the preferred first-line agents are contraindicated or ineffective.

- They are effective in patient with angina and diabetes.

  - They exerts their antihypertensive effect by their vasodilation effect.

Dihydropyridines bind to L type Calcium channels in vessels rather than the cardiac cells while non Dihydropyridines bind toward the cardio cells rather than the vessels and that's explain why verapamil has a strong negative in tropic activity 💔

However don't forget what we talked about the selectivity in the previous lecture

Calcium channel blockers

- They divided into three chemical classes:
  a. Diphenylalkylamines, Varapamil.
  b. Benzothiazepines, Diltiazem
  c. Dihydropyridines, Nifedipine

- Mechanism of action

- Calcium enters muscle cell through special voltage sensitive calcium channel. These agents exert their effect by antagonists block for the inward movement of calcium by binding to the L-type channels in the heart and peripheral vasculature.

	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

- Recap
- Calcium channel blockers are divided into two groups:

1. **Non-cardio-selective (Vessel-selective/Dihydropyridines):** such as: Nifedipine, Amlodipine (characterized by the suffix '-dipine').

• These mainly target peripheral arteries, causing strong vasodilation (4 pluses) which significantly lowers blood pressure (4 pluses).

• Due to this strong vasodilation, **reflex tachycardia** may occur as a compensatory mechanism, potentially leading to side effects like headaches and blood pooling in the lower extremities, particularly in the veins.

• Nifedipine can cause **orthostatic hypotension**, though this is not its primary side effect, as it mainly comes from venous dilation.
• Although it is primarily vessel-selective, it is not absolutely selective and can bind to cardiac cells, resulting in **negative inotropic effects** (reduced heart contractility).
• Increasing in cardiac output due to two factors:
1. Decreasing afterload .
2. Reflex tachycardia compensating for the drop in blood pressure.

2. **Cardio-selective (Non-Dihydropyridines):** such as: Diltiazem, Verapamil.

• These 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). In reality verapamil is anti-arrhythmic drug rather than antihypertensive drug.

• Verapamil used in patients with hypertension and arrhythmia (if is is related to SA node like Atrial fibrillation and atrial flutter).

• Diltiazem (weak antihypertensive and moderate anti arrhythmic action) used in between but more toward the verapamil uses, sometimes the ejection fraction of the patient is low so, we don't use verapamil which has strong negative intropic action.

• Always remember Verapamil is contraindicated 100% in patients with congestive heart failure and never combine it with beta blockers as both have strong negative intropic and chronotropic while Diltiazem is contraindicated in 90%.

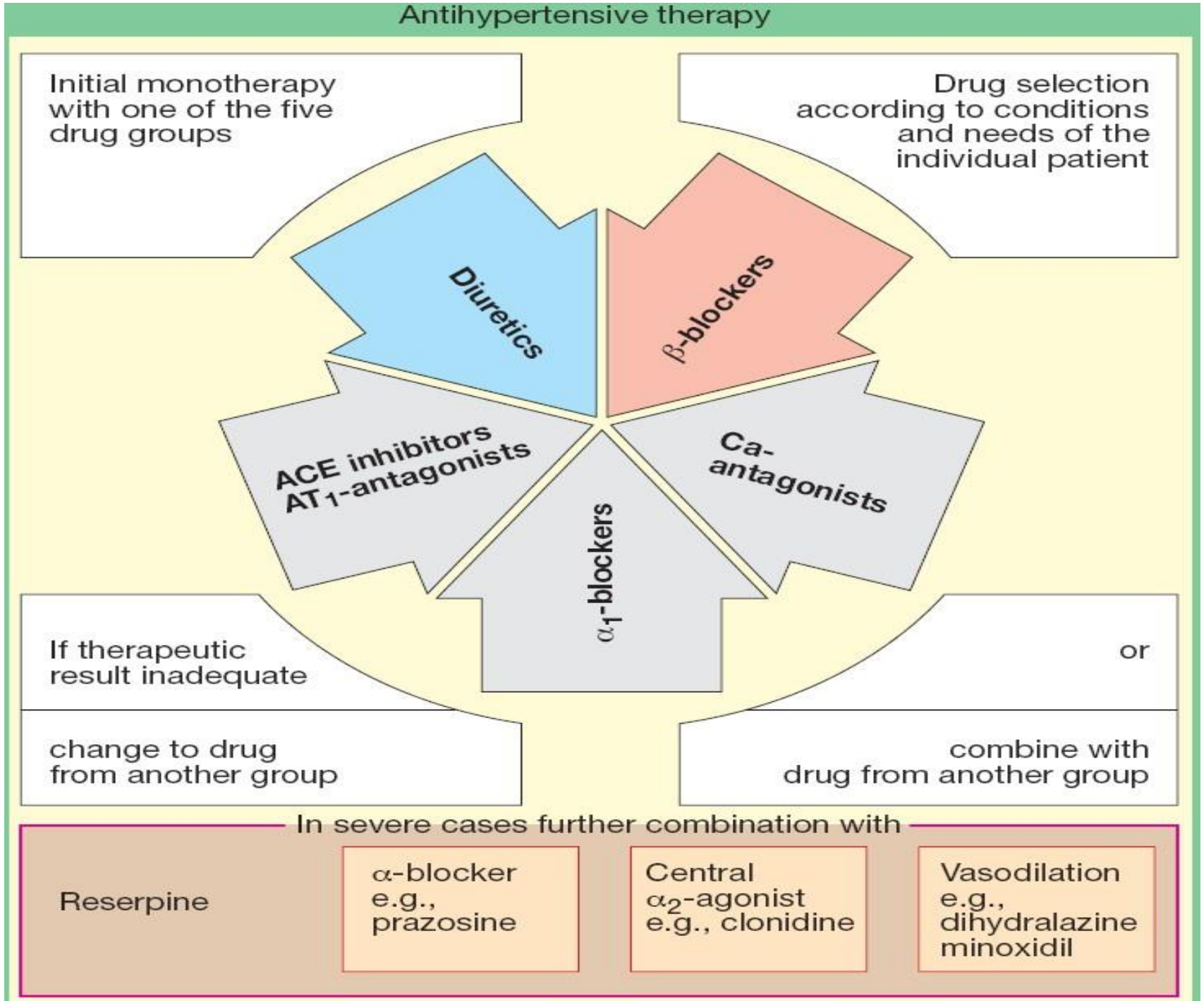
Adverse effects of calcium channel-blocking agents

Drug	Effect on heart rate	Adverse effects
Nifedipine	↑	Headache, flushing, ankle swelling (lower part edema) because of the reduction of blood pressure
Amlodipine	↑	Ankle swelling
Nimodipine	±	Flushing, headache
Diltiazem	±	Generally mild
Verapamil	↓	1. Constipation (because of the binding with the channels that present in GI tract) 2. marked negative inotropic action 3. Gingival hyperplasia.

All "dipine" drugs have the same side effects

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

- There is another drug that can cause gingival hyperplasia we will take about it in CNS that is called phynytoin (antiepileptic drug).


Antihypertensive therapy
Initial monotherapy with one of the five drug groups
Drug selection according to conditions and needs of the individual patient
Diuretics
β-blockers
ACE inhibitors
AT1-antagonists
Ca-antagonists
α1-blockers
If therapeutic result inadequate
or
change to drug from another group
combine with drug from another group
In severe cases further combination with
Reserpine
α-blocker e.g., prazosine
Central α2-agonist e.g., clonidine
Vasodilation e.g., dihydralazine minoxidil

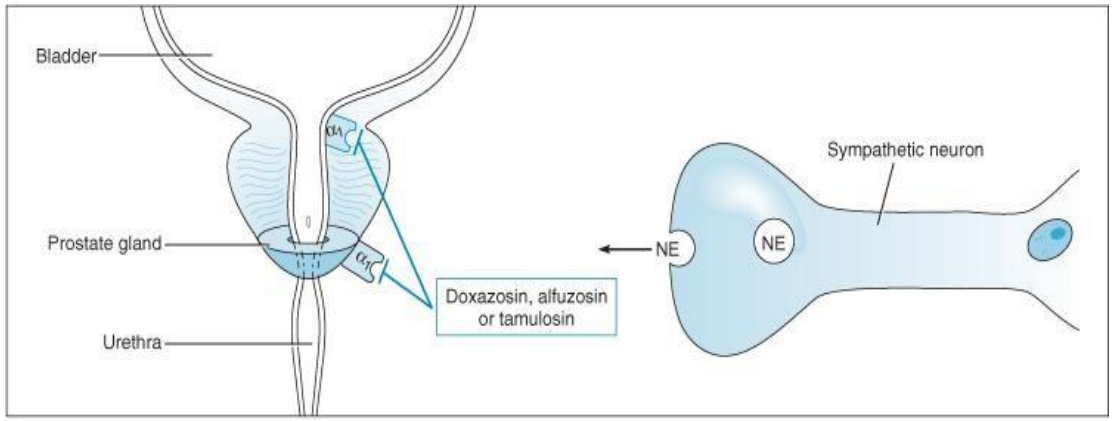
Selective α_1-blockers

- Alpha 1 blockers are used in patients with benign prostate hyperplasia, the alpha1 receptors present on arteries and veins so, be careful they may cause orthostatic hypertension , first dose syncope, reflex tachycardia and retention of water and sodium. It is problematic by its use (not a great drug).

- Selectively block α_1 receptors Alfuzosin, doxazosin, prazosin, terazosin they bind with alpha 1 receptors on vessels and prostate so, we treat the hypertension and the prostate but remember the side effects that we talked about above and there is also headache because of the problem of the perfusion of the blood to the brain.

- **Silodosin is selective to alpha 1 in prostate it has no relation with hypertension.**

- Used in the treatment of chronic hypertension
- Also used to treat urinary retention in men with benign prostatic hyperplasia



❗Slides from 10-24, the doctor explained them before in online and in-person lectures (read them quickly).

Centrally acting adrenergic drugs

- **Clonidine**, an $\alpha 2$ agonist diminishes central adrenergic outflow.

- Used to treat mild to moderate hypertension that has not responded adequately to treatment with diuretics alone.

- Does not decrease renal blood flow, thus it is useful in the treatment of the hypertension complicated with renal disease.

- Nonetheless it does produce sodium and water retention, and so usually administered in combination with a diuretics

Centrally acting

- Methyldopa and clonidine produce slightly different hemodynamic effects: clonidine lowers heart rate and cardiac output more than does methyldopa.

- Withdrawal of clonidine after protracted use, particularly with high dosages (more than 1 mg/d), can result in life-threatening hypertensive crisis mediated by increased sympathetic nervous activity. Patients exhibit nervousness, tachycardia, headache, and sweating after omitting one or two doses of the drug.

- all patients who take clonidine should be warned of the possibility. If the drug must be stopped, it should be done gradually while other antihypertensive agents are being substituted. Treatment of the hypertensive crisis consists of reinstitution of clonidine therapy or administration of - and - adrenoceptor–blocking agents.

Clonidine

- Adverse effects
  - effects include dry mouth, sedation and drying of the nasal mucosa.
  - Rebound hypertension occur following sudden withdrawal, so should withdraw slowly.

Methyldopa

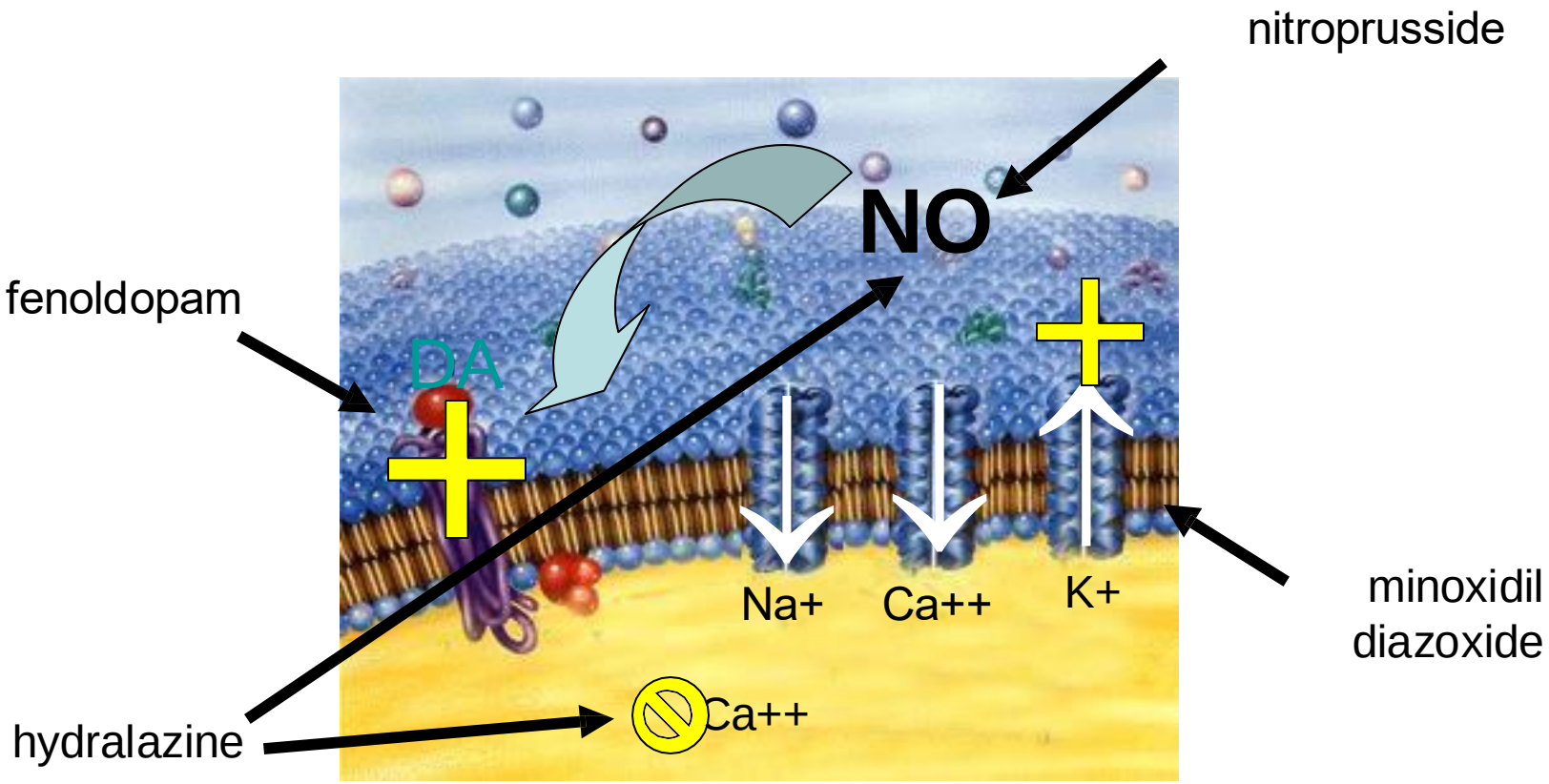
- α2 agonist that converted to methylnorepinihrine centrally to diminish the adrenergic outflow from the CNS,
- Which lead to reduced the peripheral resistance and decreased blood pressure.
- Cardiac output is not decreased, and so the blood supply to the vital organs, such as kidney, which make
- Methyldopa especially valuable in treating hypertension with renal insufficiency. (cause reduction in renal vascular resistance)
- used primarily for hypertension during pregnancy
- The Most common side effect are sedation and drowsiness.

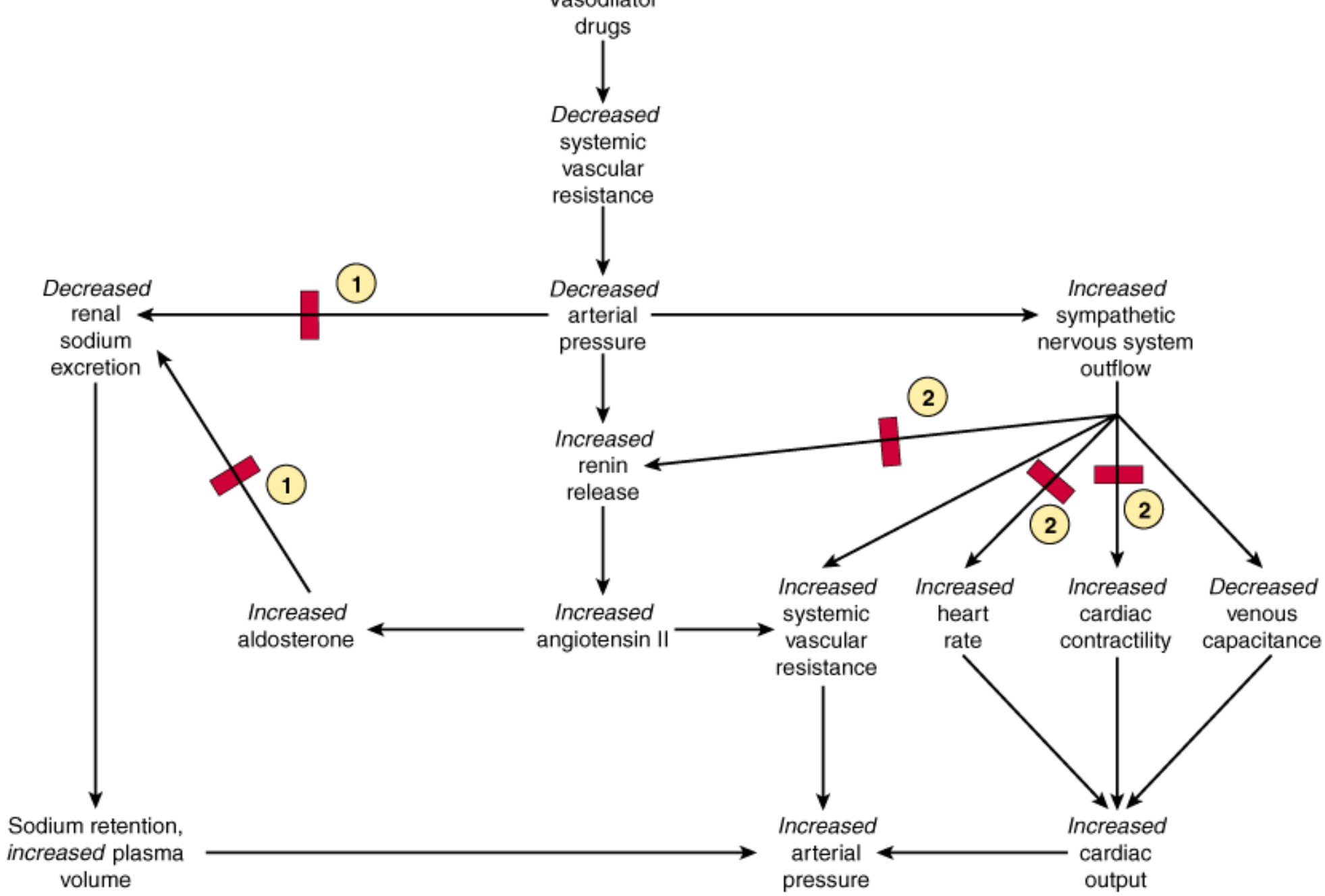
Vasodilator

- These agents are a smooth muscle relaxants, such as Hydralazine and minoxidil.
- They produce reflex stimulation of the heart resulting in increasing the myocardiac contractibility, heart rate, and oxygen consumption, so they may prompt angina, Myocardiac Infarction in predisposed individuals .
- They increase plasma renin concentration, which resulting in sodium and water retention.
- These unwanted effects can be blocked by the combination with a diuretics and a β blocker.

Vasodilators

Hydralazine ; Minoxidil;
Nitroprusside; Diazoxide;
Fenoldopam





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

Hydralazine

- Used to treat moderately severe hypertension, combine with diuretic (sodium and water retention) and β blocker (reflex tachycardia).
- Hydralazine monotherapy is accepted method of controlling blood pressure in pregnancy-induced hypertension.
- Main side effects are arrhythmia, precipitation of angina. Lupus-like syndrome can occur with high doses, but it is reversible on stopping the therapy.

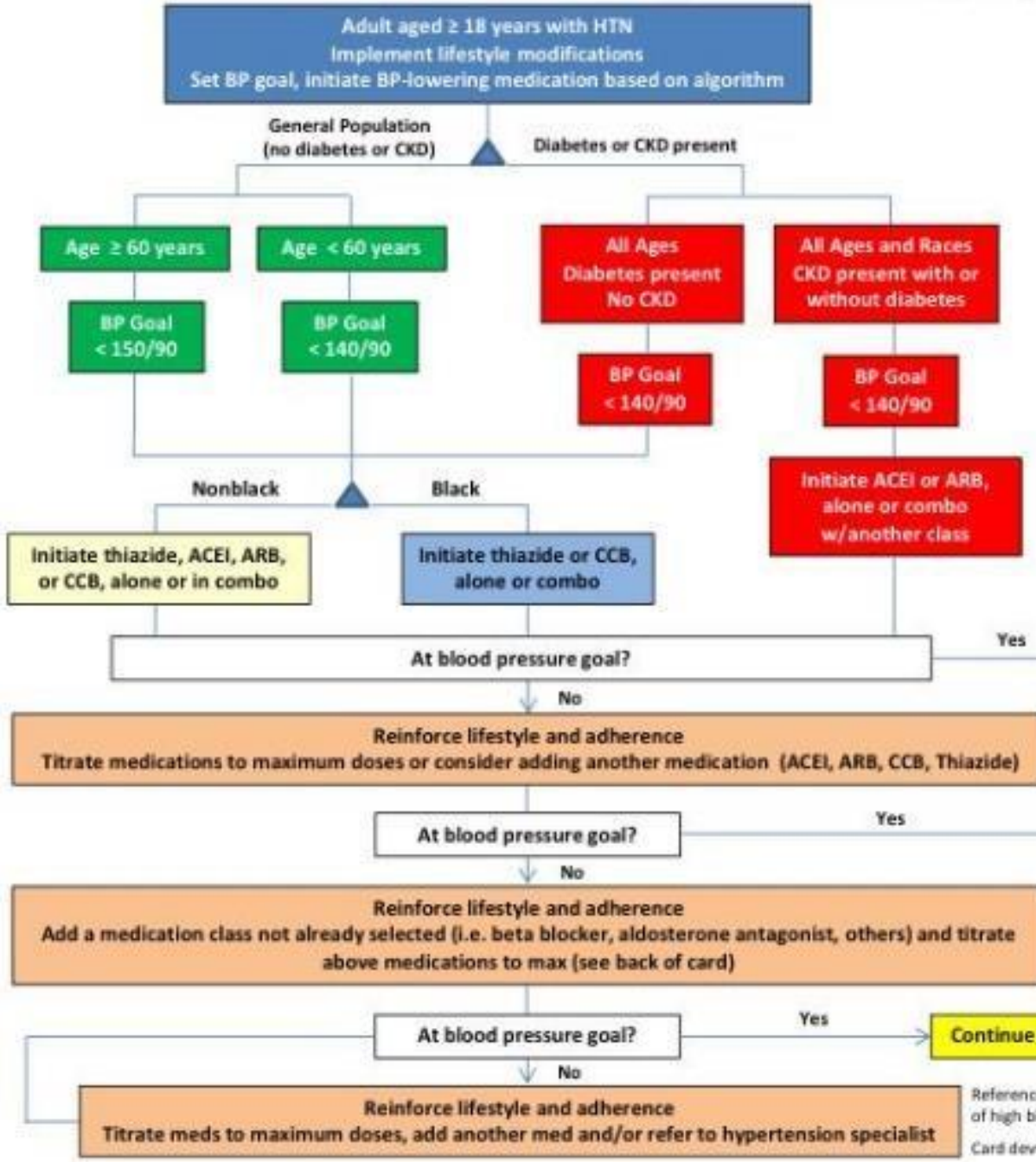
Hypertension emergency

- 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.

JNC 8 Hypertension Guideline Algorithm



Initial Drugs of Choice for Hypertension

- ACE inhibitor (ACEI)
- Angiotensin receptor blocker (ARB)
- Thiazide diuretic
- Calcium channel blocker (CCB)

Strategy	Description
A	Start one drug, titrate to maximum dose, and then add a second drug.
B	Start one drug, then add a second drug before achieving max dose of first
C	Begin 2 drugs at same time, as separate pills or combination pill. **Initial combination therapy is recommended if BP is greater than 20/10mm Hg above goal**

Lifestyle changes:

- Smoking Cessation
- Control blood glucose and lipids
- Diet
  - ✓Eat healthy (i.e., DASH diet)
  - ✓Moderate alcohol consumption
  - ✓Reduce sodium intake to no more than 2,400 mg/day
- Physical activity
  - ✓Moderate-to-vigorous activity 3-4 days a week averaging 40 min per session.

Reference: James PA, Ortiz E, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: (JNC8). JAMA. 2014 Feb 5;311(5):507-20

Card developed by Cole Gleen, Pharm.D. & James L Taylor, Pharm.D.

Table 1. Interactions between antihypertensive and other drugs

Drugs (class)	Interaction with	Mechanism	Effect
β-Blockers	verapamil diltiazem	Additive effects	A-V conduction impaired; risk of A-V block
	oral antidiabetics	β_2-receptor blockade	symptoms of hypoglycaemia are suppressed
	broncho-spasmolytic agents	β_2-receptor blockade	suppression of the bronchospasmolytic effect
	dobutamine	β_1-receptor antagonism	the inotropic action of dobutamine is inhibited
Thiazid diuretics	digoxin	Hypokalaemia	digoxin becomes more toxic (arrhythmogenic)
	lithium ions	renal excretion of lithium ions impaired	accumulation of lithium ions
α-Blockers	noradrenaline	α_1-receptor blockade	noradrenaline shows less vasoconstrictor activity
Calcium antagonists			
Verapamil, diltiazem	β-Blocker	additive effect	A-V conduction impaired; risk of A-V block
	digoxin	renal excretion of digoxin	digoxin may accumulate; arrhythmogenic effect
	protease inhibitors (HIV-treatment)	inhibition of hepatic degradation	accumulation of verapamil or diltiazem
	cimetidine	ibid.	ibid.
DihydropyridineCa-antagonists	β-blocker	β-receptor blockade	suppression of reflex tachycardia (favourable)
Felodipine	Grapefruit Juice	Enzymic inhibition (Cyt.L450 system)	accumulation of felodipine
ACE-inhibitors	diuretics (thiazide)	additive effect	strong hypotensive action
	Diuretics (K^+-sparing)	reduced renal excretion of K^+	hyperkalemia
	NSAID´-s including high dose ASA	retention of Na^+ and H_2O	reduced antihypertensive effects
	lithium ions	Reduced excretion of lithium ions	lithium ions accumulate

Table 1. Interactions between antihypertensive and other drugs

Drugs (class)	Interaction with	Mechanism	Effect
AT_1-receptor antagonists	virtually the same as ACE-inhibitors	interactions as ACEi-s (see above)	described before
Centrally acting antihypertensives			
α-methyl-DOPA	Fe^{2+}-ions	enteral absorption of α-methyl-DOPA	reduced antihypertensive action
clonidine	tricyclic antidepressants	antagonism of central α_2-adrenoceptors	Ibid.
	β-blockers	unknown	the clonidine rebound phenomenon is more frequent
both clonidine and α-methyl-DOPA	centrally acting depressant agents (hypnotics, tranquillizers, neuroleptics, anti-epileptics, some anti-depressants, H1-anti-histaminic agents, alcohol)	additive effect, non-specific	sedation,fatigue

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).

Types of angina

- **Angina** is the partial closure (60–70%) of coronary arteries that supply the heart. This closure is caused by plaque buildup due to atherosclerosis.

- Angina has three overlapping patterns, which are caused by varying combination of increased myocardial demand and decreased myocardial perfusion.

A. Stable angina, the most common form, and characterized by a burning heavy or squeezing feeling in the chest.

Caused by reduction of coronary perfusion due to coronary atherosclerosis. So the heart become susceptible to ischemia whenever there is demand, such as exercise, emotional excitement.

This type is rapidly relieved by rest or nitroglycerin.

Types of angina

B. Unstable angina, lies between stable angina and myocardial infarction, Often unrelated to exercise.

The symptoms are not relieved by rest or nitroglycerin.

unstable angina require more aggressive therapy, for example treatments of dyslipidemias, hypertension, anti-platelets.

C. Variant angina, occurs at rest and caused by coronary artery spasm (i.e. caused by contraction of the smooth muscle tissue in the vessel walls rather than directly by atherosclerosis)

Generally, this type rapidly responds to nitroglycerin and calcium channel blockers.

- **Types of Angina:**

1. **Stable Angina:**

• Occurs during physical activity or stress (“exercise angina”).

• Caused by the narrowing of coronary arteries due to plaque buildup. This leads to reduced blood supply to the heart, while oxygen demand increases (e.g., during sympathetic activation, positive inotropic, or chronotropic effects), the angina attack occurs when oxygen demand exceeds supply.

2. **Transient Angina (Vasospastic Angina):**

• Caused by sudden vasospasm of coronary arteries, unrelated to plaque or atherosclerosis.

• Common in cocaine or certain drug addictions.

• It typically occurs in the morning and is not exercise-related.

3. **Unstable Angina:**

• Caused by the rupture of a plaque in the arterial wall, forming a flap fissure (بتلولح).

• The flap can intermittently move, causing varying degrees of occlusion, which leads to angina attacks.

• The fissure is unstable (hence the name “unstable angina”) and is often associated with platelet aggregation.

• Treatment involves anticoagulants like **heparin** to dissolve clots and prevent complete occlusion, as well as **warfarin** and **antiplatelet drugs** to reduce the risk of myocardial infarction (MI).

• A complete occlusion can cause myocardial cell death, leading to heart failure or death due to hypoxia-induced apoptosis.

Extra image

TYPES

STABLE ANGINA / CLASSIC ANGINA

Atherosclerosis

Occurs with exertion or exercise

Relieved by rest or antianginals

VARIANT ANGINA / PRINZMETAL ANGINA

Coronary Spasm

Typically at rest during night or early morning hours

Relieved by anti - angina drugs (Nitroglycerin)

UNSTABLE ANGINA / CRESCENDO ANGINA

Atherosclerosis with blood clot

Severe pain often occurs at rest or minimal exertion

Not relieved by rest or medication

1. β-adrenergic blocking agents

- They suppress the heart by blocking β1 receptors, 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.
- The cardioselective β1 agents, such as acebutolol and atenolol and metoprolol are preferred.
- They combined with nitrates to increase exercise duration and tolerance.

Beta-Blockers

- Decrease myocardial oxygen consumption
- Blunt exercise response
- Try to avoid drugs with intrinsic sympathomimetic activity
- First line therapy in all patients with stable angina

- The first treatment of angina due to holding the heart back (decreasing the attack).
- Beta blockers are used as prophylactic (not a treatment) for attack in stable and unstable angina, prophylactic for emotional stress, emotional happens, movement, exercise and any things can cause increase in heart rate
- Never give a beta blockers for patients with vasospastic angina (variant angina) because they have a relation with beta 2
- The coronary artery has two receptors : 1. alpha 1 receptor that makes constriction. 2. beta 2 makes dilation.
- In vasospastic angina 10% of absolute selective beta blockers such as atenolol metoprolol will bind with beta 2 therefore, blocking beta 2 increasing the vasospasm.

- The dose is not constant, it increases whenever the patient has attack.
- In congestive heart failure we start with bisoprolol 2.5 mg, here we start with 10 mg (the initial dose is 4x than congestive heart failure) and then we increase the dose.

! Don't use acebutolol as it has an intrinsic sympathomimetic activity, it is relative contraindicated because there is no point of giving positive inotropic activity to hold the heart back).

Undesirable effects

- **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.**

- **These deleterious effects of beta -blocking agents can be balanced by the concomitant use of nitrates.**

- In beta blockers, perfusion time is increased, but there is a decrease in supply. The deleterious effects of beta blockers are counteracted by nitrates, and the deleterious effects of nitrates are counteracted by beta blockers. like hypo and hyperkalemia in thiazide with ACEIs.

β-adrenergic blocking agents

2.clinical uses:

stable and unstable angina.

myocardia infarction.

3.contraindication

Variant angina,

bronchial asthma,

bradycardia,

- Beta blockers have no relation with peptic ulcer.
- Beta blockers are contraindicated in asthma, COPD.

2. Organic nitrates

- More selective toward veins rather than arteries.
- It can affect preload and afterload (primarily decreasing preload).

- These compounds cause a rapid reduction in the myocardial oxygen demand, and so provide a rapid relief for the angina symptoms.They are vasodilators, so they have significant activity on the coronary arteries, causing dilation.

- Their mechanism of action summarized in a decrease coronary spasm or vasoconstruction and in an increase perfusion of the myocardial by relaxing the coronary arteries.

- Members of this group include: isosorbide dinitrate, isosorbide mononitrate (longer activity than dinitrate) , and Nitroglycerine.

- The main mechanism that differentiates organic nitrates from calcium channel inhibitors is their greater activity on veins.

- Let's talk about Nitroglycerine:
- It is given sublingual or as patches because:

1- Its first-pass metabolism is 90%, making oral administration ineffective, as only 7%-8% of the drug will enter systemic circulation. We learned this concept with doctor suhail xD

2- When Nitroglycerin is taken sublingually, the rich perfusion under the tongue facilitates rapid absorption, delivering the drug directly to the heart to relieve the attack.

- It is a **Rescue Agent** drug **(emergency drug)** will obviously not be administered orally (unlike beta blockers or calcium channel inhibitors), as its purpose is to rescue the patient from an attack, whether it is stable or unstable.

- We give it to patient sublingually and wait for 5 minutes. If there is no effect, we repeat the dose. If it still doesn't work, we try a third time. If there is no response after the third dose, the patient must be hospitalized, as this indicates unstable angina.

- This drug decreases preload and afterload while increasing perfusion toward the heart. By doing so, it reduces the oxygen demand and increases the oxygen supply, helping to relieve an angina pectoris attack, especially in the case of stable angina.

- It might work on unstable angina, but it depends on the degree of occlusion.

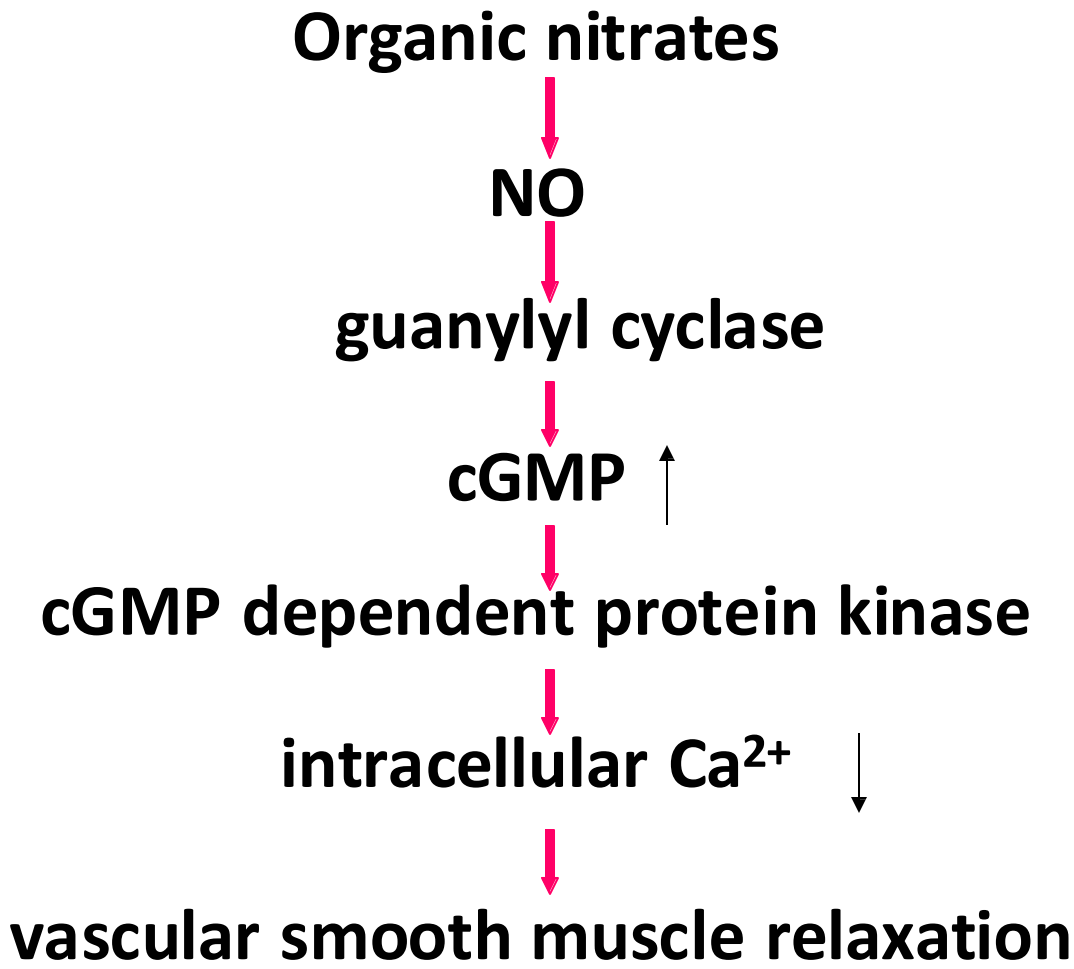
- Nitroglycerine work fast and has a weak t1/2.

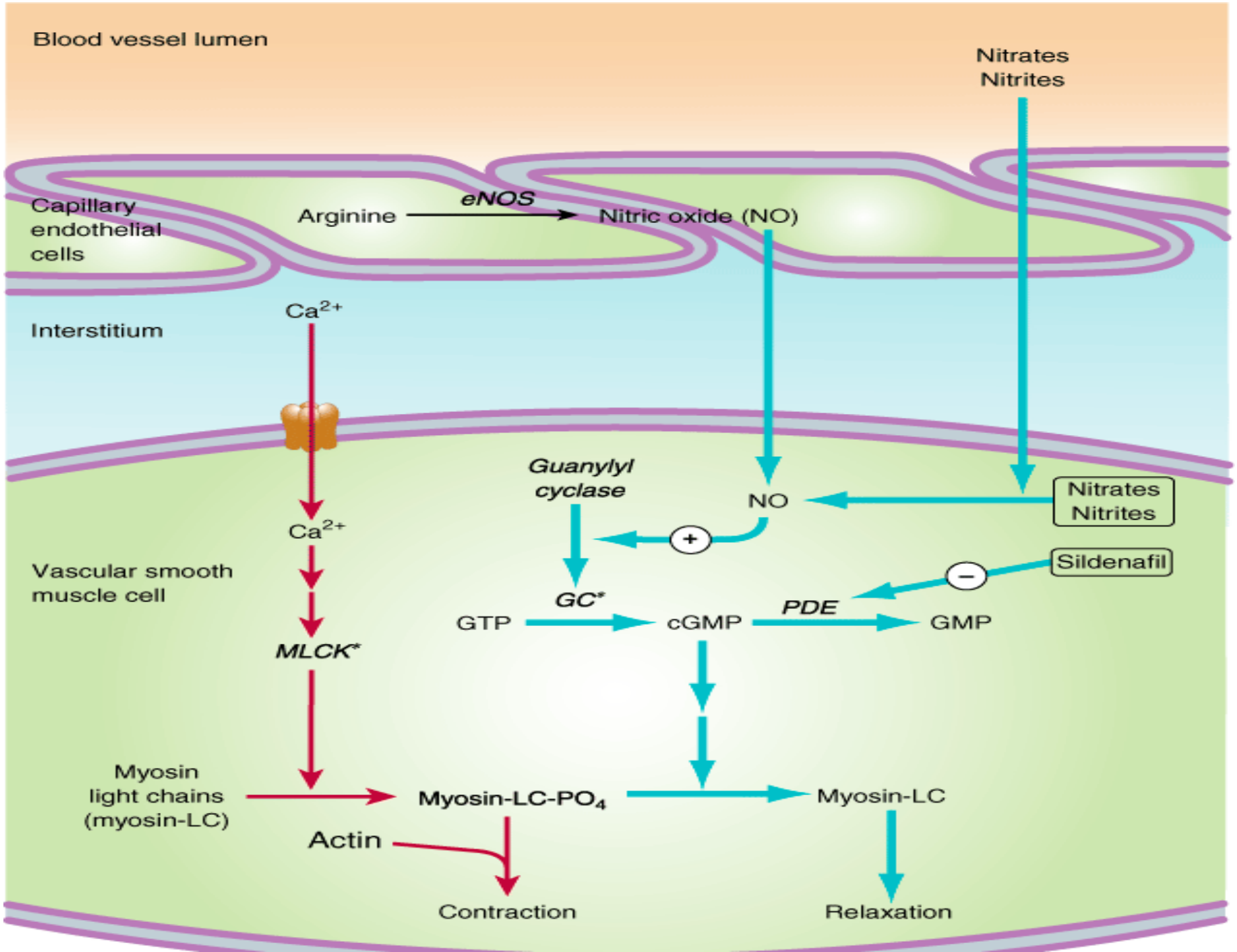
- What is the difference between Nitroglycerine and isosorbide dinitrate and isosorbide mononitrate?

- 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).

- isosorbide mononitrate --> twice a day
- isosorbide dinitrate --> 3 times a day

2.Pharmacological mechanism




Blood vessel lumen
Nitrates
Nitrites
Capillary endothelial cells
Arginine
eNOS
Nitric oxide (NO)
Interstitium
Ca^{2+}
Ca^{2+}
Vascular smooth muscle cell
Guanylyl cyclase
NO
Nitrates
Nitrites
+
Sildenafil
−
GC*
PDE
GTP
cGMP
GMP
MLCK*
Myosin light chains (myosin-LC)
Myosin-LC-PO_4
Myosin-LC
Actin
Contraction
Relaxation

- The two previous slides are sufficient to understand how the drug works, but we will repeat the key points here and also discuss drug-drug interactions. 😉

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.

- **Organic nitrates are contraindicated with Sildenafil (Viagra)** as it used for pulmonary hypertension, it has so bad drug-drug interaction as it can lead to death.

- It inhibits PDE (phosphodiesterase), an enzyme which its inhibition can lead to increase cGMP.

- Imagine that 70s old patient that has angina and taking nitrates take this drug (Sildenafil) this will cause hypotension shock --> death.

Organic nitrates

- All of the three agents are effective but they differ in the onset and duration of action.

- For rapid relief of an ongoing attack that precipitate by exercise and emotional stress, sublingual nitroglycerine is the drug of choice.

- At therapeutics dose nitroglycerine has two major effects:

  a. dilation of the large veins, resulting in pooling of blood in the veins (diminish preload and reduce the work of heart). orthostatic hypotension and syncope.

  b. dilates the coronary arteries.

Beneficial and Deleterious Effects of Nitrates in the Treatment of Angina

	Result
1. Potential beneficial effects	
Decreased ventricular volume Decreased arterial pressure Decreased ejection time	Decreased myocardial oxygen requirement
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
Increased collateral flow	Improved perfusion to ischemic myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
2. Potential deleterious effects	
Reflex tachycardia	Increased myocardial oxygen requirement
Reflex increase in contractility	
Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

This can be fixed by giving beta blockers

Organic nitrates

- The time to onset the action varies from 1 min for nitroglycerine to 1 hr for isosorbide mononitrate .

- Significant first pass metabolism of nitroglycerine occurs so it administrated sublingually or transdermally (patch).

- Isosorbide mononitrate has long duration of action due to its ability to avoid first pass effect (so it is administrated orally).

Organic nitrates

- Adverse effect:

  a. headache (throbbing headach) is a common early side effect of nitrates, which is usually decrease after the first few days (patient develop tolerance).

b. high doses can cause postural hypotension syncope, also can result and tachycardia.

- Sildinafil (Viagra) potentiates the action of nitrates, and to avoid the dangerous hypotension, an interval of six hour between the two agents is recommended.

Tolerance

The main problem with using nitrates is that desensitization of the enzyme may occur, or depletion of NO levels in the body. Ultimately, desensitization will happen.

- When you keep your patient on nitrates, body will try to protect itself since nitrates cause pulling down of the blood, reduction of blood pressure and so for so on. So, the body will tolerate with it.
- Tolerance to the action of the nitrates develops rapidly, the blood vessels become desensitized to the vasodilation.
- Why????? diminished release of nitric oxide resulting from depletion of tissue thiol compounds may be partly responsible for tolerance to nitroglycerin. Mechanism is not important (biochem) just know that there is depletion of nitric oxide level
- The tolerance can be overcame by providing a daily “nitrate free intervals” to restore sensitivity to the drug (this interval are usually 10 – 12 hr at night)

Good story to understand how we deal with nitrates tolerance !😁

- In TNT (trinitrotoluene) factories, nitrates were used, and these nitrates were volatile. Workers exposed to the nitrate when they returned on Mondays would experience symptoms such as orthostatic hypotension, blood pooling, and a characteristic throbbing headache. On the first day (Monday), they would experience these symptoms, and by Tuesday, the symptoms would persist but at a reduced intensity. By Wednesday, the symptoms would typically subside, and by Thursday, there would be no symptoms. On Saturday and Sunday, when the workers were off, there would be no exposure or symptoms. However, when they returned on Monday, the symptoms would recur, and the cycle would repeat, with symptoms diminishing after the second day of exposure.

- The idea here is that the workers were initially exposed to nitrates and experienced symptoms, but over time, they developed tolerance, causing the symptoms to subside. From observing these workers, the concept of resisting nitrate tolerance was developed.

- The tolerance can be overcome by providing a daily "nitrate free intervals" to restore sensitivity to the drug (this interval are usually 10 – 12 hr at night). In workers case, they are free of nitrates in off days.

- If we are giving Isosorbide mononitrate --> one pill a day.

- So, remember this story if you are going to work in TNT factor xD (might doctor ask about it in exam? IDK 😆)

Important notes to your patient

- 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. Nitroglycerin is not sensitive to light.

نقاط هاي السلايد:

-1المحافظة على تسكير العلبة بعد الاستعمال مهم، بكون مكتوب على العلبة سنتين بس احنا بنحكي بنقول للدكاترة اعتمدوه 6اشهر، لانه بعرفش اذا كان بحافظ على تسكير العلبة .

-2احيانا المريضين)خصوصا كبار السن (بشتروا كياس بلاستكية صغيرة بنحط فيها الجرع اليومية، وبفرغوا الادوية فيها، اذا عملت هيك لل nitrates)غالبا بكون (isosorbide mononitrateبعد فترة راح تفقد فعاليتها، وبتصير عالفاضي، عشان هيك بيجي ختيار صار معاه جلطة وهو بقلك كنت اخذ كل الادوية 😔

- spray is equally effective; it has a shelf life of two to three years and does not require refrigeration

3. Calcium channel blockers

We will talk about Prinzmetal angina and what's the relation of calcium channel inhibitors with it.

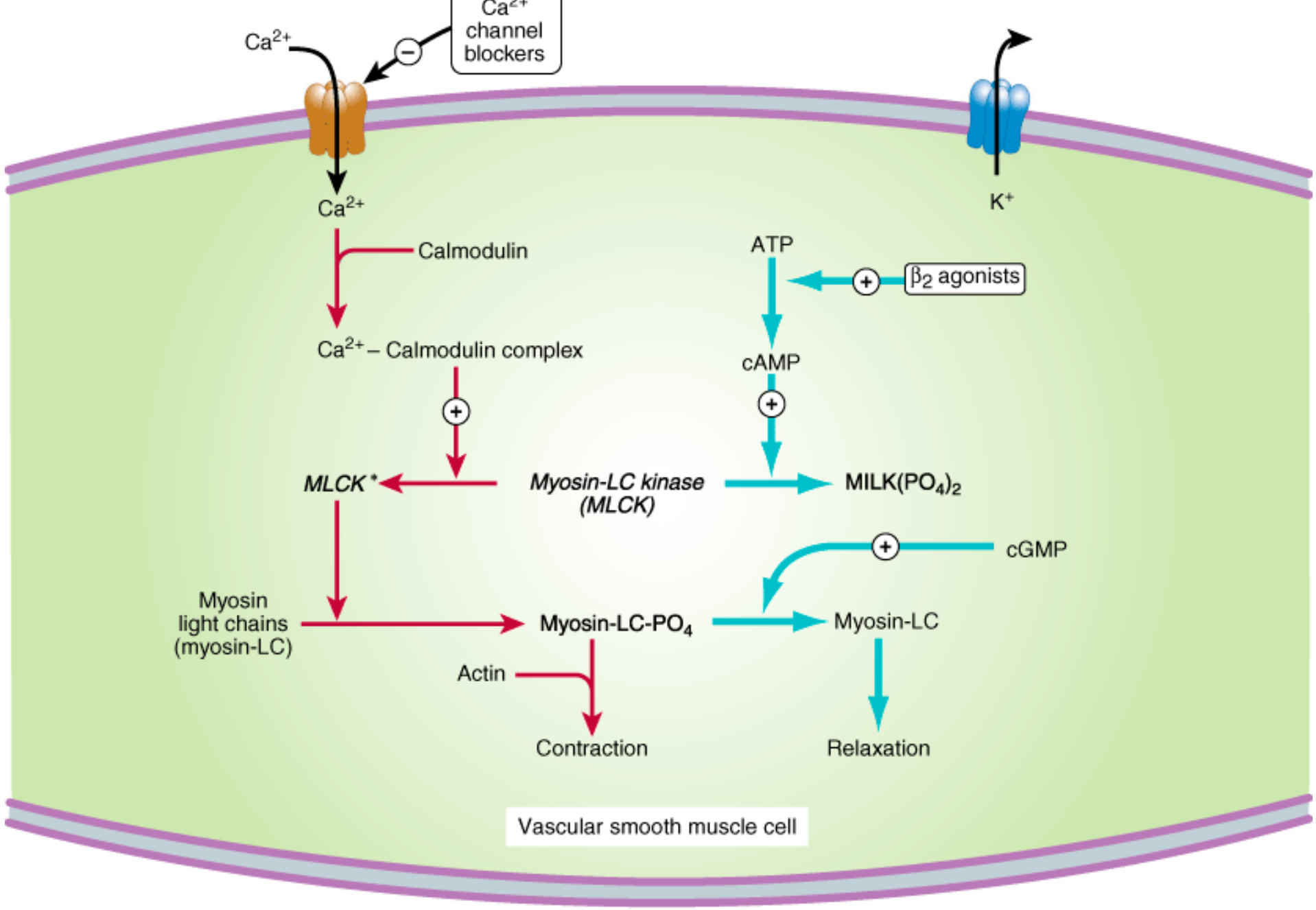
- Inhibiting the entrance of calcium into cardiac and smooth muscles cells of the coronary arteries and so they lower blood pressure.

A. Nifidipine, arterioles vasodilation effect with minimal effect on the heart, and is useful in the treatments of angina caused by spontaneous coronary spasm (Variant angina).

B. Verapamil, slow cardiac conduction directly, and thus decrease oxygen demand, so should be avoided with patient with a congestive heart failure due to its negative inotropic effect on the heart.

C. Diltiazem has similar effect on the heart to Verapamil.

- We have vasospastic (تشنج وعائي) , we need to relax the coronary arteries, which can be achieved using Nifedipine, Verapamil, or Diltiazem.
- Think with me, for Prinzmetal angina, what is the best drug to use between these? It's Verapamil 😱
- Why? because Verapamil reduces the heart's pumping force (negative inotropic effect) and dilates the coronary arteries.
- Nifedipine will cause afterload reduction, reflex tachycardia خربت بيت المريض (If I have to give Nifedipine, I must combine it with Beta blocker).
- Drugs of choice in treating of Prinzmetal angina are diltiazem, verapamil.
- Studies have shown that African Americans may have a higher prevalence of this condition compared to other populations.



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

Mechanisms of Action

- Arterial dilation/after-load reduction more in dipines
- Coronary arterial vasodilation
- Prevention of coronary vasoconstriction
- Enhancement of coronary collateral flow
- Improved subendocardial perfusion التروية عن طريق الشعيرات
- Slowing of heart rate with diltiazem, verapamil

- All have the same effect on coronary artery dilation, Verapamil has higher negative inotropic effect than Diltiazem, so here we look at the ejection fraction in patient.

- Verapamil has a stronger negative inotropic effect (reduces the heart's pumping force) compared to diltiazem.
- In patients with already reduced EF, verapamil could further impair cardiac output, worsening heart failure symptoms. Therefore, it should be used cautiously or avoided in these patients.

- Diltiazem has a weaker negative inotropic effect compared to verapamil, making it a safer option in patients with mildly reduced EF.

- Be aware when using Dipine because it can cause reflex tachycardia.

	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	+ +	↔	↔

Calcium channel blockers

- 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 effects.

- Side-effects are also concentration-dependent, and mainly related to the arterial vasodilator responses (headache, flushing and ankle oedema);

  these effects are more pronounced with dihydropyridine CCB's.

- Never ever give these patients short acting Nifedipine, even if you are using beta blockers.
- Beta blockers are contraindicated with Verapamil (both have negative inotropic activity)
- If you can't give Verapamil or Diltiazem because the heart of the patient is very weak, you can give sustained release dipine with beta blocker to hold back the reflex tachycardia.

Verapamil and Diltiazem

- **In patients with relatively low blood pressure, dihydropyridines can cause further deleterious lowering of pressure.**

Verapamil and diltiazem appear to produce less hypotension and may be better tolerated in these circumstances.

- **In patients with a history of atrial tachycardia, flutter, and fibrillation, verapamil and diltiazem provide a distinct advantage because of their antiarrhythmic effects.**

😬😑 الدكتور قال اعتبروني شرحته

Comparison

- It is just a comparison between giving nitrates or calcium channel inhibitors to a patient with prinzmetal angina.
- Prinzmetal angina --> Calcium Channel Inhibitors are better
- Stable angina --> Nitrates are better (Number 1)

- Meta-analyses comparing effects of beta-blockers and CCB's in stable angina pectoris indicate that:

beta-blockers are more effective than CCB's in reducing anginal episodes,

but that effects on exercise tolerance and ischemia of the two drug classes are similar

- However, CCB's are especially effective in patients with vasospastic (Prinzmetal) angina

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

Recommendations for pharmacological therapy of vasospastic angina

- Treatment with calcium antagonists and if necessary nitrates in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.

- Decrease vasospasm of coronary vessels (calcium channel blockers are efficacious in >70% of patients; *increase oxygen delivery*)

وَمَا لَنَآ أَلَّا نَتَوَكَّلَ عَلَى ٱللَّهِ وَقَدْ هَدَىٰنَا سُبُلَنَا وَلَنَصْبِرَنَّ عَلَىٰ مَآ ءَاذَيْتُمُونَا وَعَلَى ٱللَّهِ فَلْيَتَوَكَّلِ ٱلْمُتَوَكِّلُونَ

﴿ الآية ١٢ ﴾

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!