CVS
PHARMACOLOGY

Modified NO: 3

كتابة: عمر صمادي وإسماعيل العارضة

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Today we are going to talk about :

1. Beta blockers
2. ACE inhibitors (Angiotensin converting enzyme inhibitors)
3. Angiotensin II antagonists/blockers
4. Calcium channel inhibitors

Color code

Slides
Doctor
Additional info
Important

β-adrenergic blocking agents

- **The various β blockers all appear to be equally effective for the treatments of hypertension.**
- **Propranolol, Timolol, Nadolol, Pindolol, Penbutolol, carvedilol, are nonselective,**
- **while Metoprolol, Acebutolol, and Atenolol, Esmolol are Cardioselective, sotalol.**

  This drug is used in arrythmia, will be discussed later
- **Adverse effects,**

  Dizziness, sudden weight gain , irregular heartbeat. Congestive heart failure, asthma (non-selective), hypoglycemia (non-selective) in patient with diabetes mellitus.

We use beta blockers in hypertensive patients to decrease their cardiac output.
We have two main types of β blockers:

1. Non-selective β blockers, they don't discriminate between β1 and β2 receptors, contraindicated in patients with : Asthma, COPD, and other illnesses that are worsened with β2 antagonism.
2. Cardioselective, they bind more (almost exclusively) to β1 receptors.

The problem that not all hypertensive patients are the same, they might have bradycardia or tachycardia, for example, it's not wise to give a patient with bradycardia a β blocker of any type because it will worsen the bradycardia and might a collapse in circulation.

Beta blockers

- Metoprolol and atenolol, which are cardioselective, are the most widely used blockers in the treatment of hypertension.

- Pindolol, acebutolol (important), and penbutolol are partial agonists, ie, blockers with some intrinsic sympathomimetic activity. They lower blood pressure by decreasing vascular resistance and appear to depress cardiac output or heart rate less than other blockers. this may be particularly beneficial for patients with bradyarrhythmias or peripheral vascular disease.
- Labetalol, Carvedilol cause of its combined - and -blocking activity, labetalol is useful in treating the hypertension of pheochromocytoma and hypertensive emergencies. (they are used in emergency situations though they are not the first choice, another thing is that we use Labetalol more than Carvedilol)

These were color coded green in the first slide

These are 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**. Also contraindicated in patients with : Asthma, COPD, and other illnesses that are worsened with beta2 antagonism.

- We have a special type of β blockers called **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 we imply a weaker signal, so the overall effect is antagonism.

- These drugs are Pindolol, penbutolol (non-selective), and acebutolol (β1 selective).
- These partial agonists could also be called drugs with intrinsic sympathomimetic activity (ISA).

- Labetalol and carvedilol are totally non-selective blockers as we said in the previous slide.
- For hypertension we mainly use labetalol and avoid carvedilol, though carvedilol is used more for heart failure, will be explained later when we learn about heart failure.
- 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.
- β blockers are contraindicated in heart failure because they worsen the hypertrophy that comes with heart failure, but the other problem is the compensatory increase in heart rate and force of contraction that leads the heart to even more failure. We found out that a low dose of these drugs is a good solution.

The drug of choice intra operational is Esmolol (for pharmacokinetic reasons)

Esmolol

- Esmolol has a short half-life (9–10 minutes) and is administered by constant intravenous infusion.

- Esmolol is used for management of intraoperative and postoperative hypertension,
- and sometimes for hypertensive emergencies, particularly when hypertension is associated with tachycardia.

Esmolol is a special β blocker because of its very short half life, it is used in titration (usually in operations) because it is fast acting and has fast resolution, so we can easily control the duration of the β blocking effect.
For example, if a patient had tachycardia mid operation, we give them an Esmolol titration, once the tachycardia risk resolutes, we take them off the titration.
In these situations, why don't we just administer the usual long-acting drugs?
Because anesthesia has a hypotensive effect, so if the tachycardia resolves but the drug is still acting the patient will go into a hypotensive shock.

Indications for beta blockers include

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

β-adrenergic blocking agents

- **Sudden withdrawal may cause rebound hypertension,**
- The withdrawal syndrome may involve up-regulation
  or supersensitivity of beta receptor adrenoceptors.
- So, the removal should therefore be gradual to avoid precipitation of arrhythmia

- 🚨 After administering β blockers for a while, β receptors will be hypersensitized, so stopping the drug abruptly or even changing the brand of the drug will have a very strong adrenergic effect that could be dangerous, so stopping the drug should be with tapering (to become progressively smaller toward one end).
- This also applies to α2 agonists where desensitization happens

ACE Inhibitors

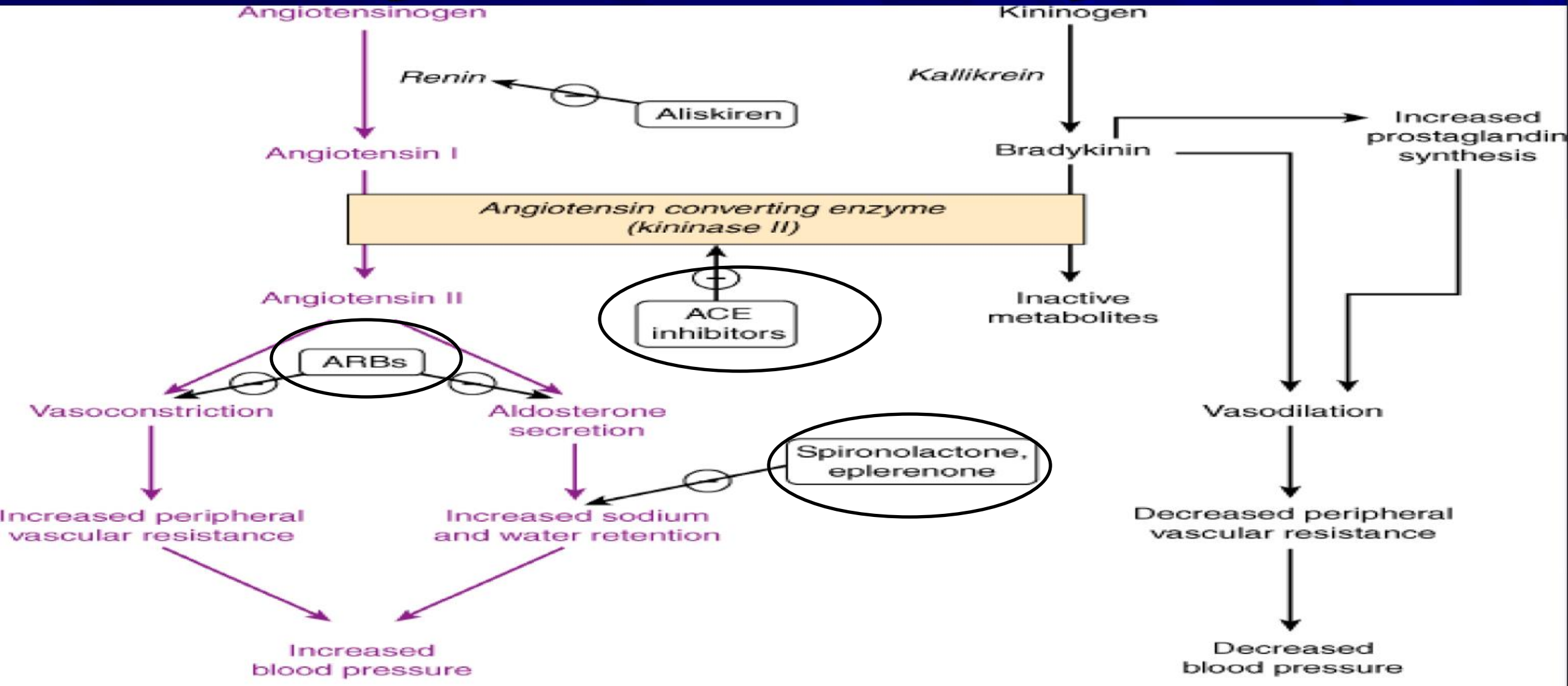
- **ACE Inhibitors, such as Enalapril, Lisinopril, and Captopril are recommended when the preferred first line agents (diuretics or β blockers) are contraindicated or ineffective.**

- **They lower the blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output.**

- **The block the ACE that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. Moreover, ACE is also responsible for the breakdown bradykinin (endogenous vasodilator).**

- **Benazepril, fosinopril, moexipril, perindopril, quinapril, ramipril,** and **trandolapril**

Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system.



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

- **Where does the aldosterone come from?🤔**

Angiotensin II binds to receptors in the adrenal cortex, leading to the production of aldosterone.

"Prils" (ACE inhibitors) and "sartans" (ARBs) cause a decrease in aldosterone-mediated sodium and water retention, as well as a reduction in vasoconstriction, which lowers blood pressure.
In addition to these effects, **ACE inhibitors** inhibit the breakdown of bradykinin. However, this can lead to side effects such as **cough, angioedema**, and **syncope**, especially at the beginning of treatment. Similar to alpha-1 blockers, patients starting ACEIs should be monitored under medical supervision.

If aldosterone secretion is inhibited, the effects are **similar to diuretics**, but with a key difference:
sodium (Na^+) is exchanged for potassium (K^+). Normally, Na^+ is reabsorbed, and K^+ is excreted. However, when using ACEIs, ARBs, potassium-sparing diuretics like spironolactone or eplerenone, Na^+ is excreted, and K^+ is reabsorbed, potentially causing **hyperkalemia** instead of hypokalemia.
To mitigate hyperkalemia, **thiazide diuretics** are often prescribed. The most common combination for treating hypertension is **an ACEI or ARB with thiazides**, a combination marketed as **Co-Diovan**.

ACEIs, ARBs, spironolactone, and eplerenone act as **aldosterone antagonists**, promoting sodium excretion (Na^+ out) and potassium retention (K^+ in).
It is crucial **not** to combine ACEIs with ARBs, ACEIs with spironolactone or eplerenone, or ARBs with spironolactone or eplerenone, as these combinations can lead to excessive **hyperkalemia**.

ACE Inhibitors

-Dry cough occurs in 10% of patients and thought to be due to increase level of bradykinin in the pulmonary tree.

-Potassium level should be monitored, and spironolactone (Prevent potassium secretion) is contraindicated.

-Angioedema is rare but a potential life-threading reaction (may be caused by bradykinin).

-Because of the risk of first-dose syncope because the angiotensin receptors present in arteries and veins**, and the angioedema ACE inhibitors are first administrated under the doctor observation.**

- ⛔ Contraindications pregnancy because of gestational hypertension

The ACEIs and ARBs are the drugs of choice in Jordan ⛔ except in pregnancy, cuz these drugs are teratogenic

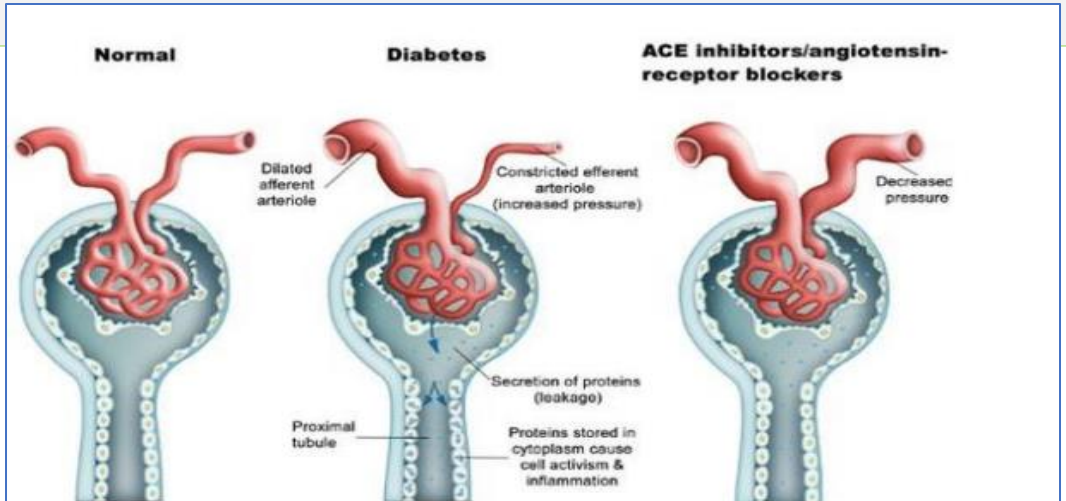
- **ACE inhibitors have a particularly useful role in treating patients with chronic kidney disease because they diminish proteinuria and stabilize renal function (even in the absence of lowering of blood pressure).**

- **This effect is particularly valuable in diabetes, and these drugs are now recommended in diabetes even in the absence of hypertension.**

ACE inhibitors are particularly beneficial in cases of **kidney failure** because angiotensin II receptors are present throughout the body, including in the **efferent arterioles** of the kidneys.
When angiotensin II levels increase, it causes **constriction of the efferent arterioles**, which raises pressure in the glomerulus and increases **glomerular filtration pressure**. While this initially helps maintain filtration, prolonged high pressure can damage the glomerulus, leading to **proteinuria** (protein leakage into the urine).
To prevent this damage, **ACEIs** are used to inhibit the synthesis of angiotensin II, thereby reducing vasoconstriction. Alternatively, **angiotensin receptor blockers (ARBs)** can be prescribed. ARBs bind to angiotensin II receptors, preventing angiotensin II from exerting its effects, including the constriction of efferent arterioles. By reducing this constriction, both ACEIs and ARBs help lower glomerular pressure, which protects the kidneys and reduces the risk of proteinuria.

ACE inhibitors have a particularly useful role in treating patients with chronic kidney disease (CKD) because they reduce proteinuria and stabilize renal function, even in the absence of blood pressure lowering.
Anyways, guidelines change for Black Americans in this context. Typically, Black Americans are recommended to start treatment with calcium channel blockers for hypertension. However, if they have hypertension with kidney impairment, the treatment should start with ACE inhibitors.
The effect of ACE inhibitors is particularly valuable in diabetes, and these drugs are now recommended for diabetic patients, even in the absence of hypertension.

This recommendation is because Black Americans tend to respond better to calcium channel blockers for hypertension. However, in cases of kidney impairment, ACE inhibitors are preferred because they protect kidney function by reducing proteinuria and stabilizing renal function, which is crucial for managing chronic kidney disease.
-Another extra info: In diabetes, high blood sugar levels can damage the kidneys' filtering units (glomeruli), leading to protein leakage in the urine (proteinuria) and progressive kidney disease. ACE inhibitors can prevent tis damage, look at this extra pic



ACEI

- These benefits probably result from improved intrarenal hemodynamics, with decreased glomerular efferent arteriolar resistance and a resulting reduction of intraglomerular capillary pressure.

- ACE inhibitors have also proved to be extremely useful in the treatment of heart failure, and after myocardial infarction.

The doctor skipped this slide

Angiotensin II-receptors antagonists

- These agents are alternatives to the ACE Inhibitors, and can be used in patient who cannot tolerate ACE Inhibitors. **Losartan** being the prototype.
- Their pharmacologic effects are Similar to ACE Inhibitors (vasodilation, block aldesterone secretion), however they do not increase the bardykinin levels.
- Their adverse effect are similar to ACE Inhibitor, although the risks of cough and angioedema are significantly decreased.
- **Candesartan, eprosartan, irbesartan,telmisartan, and olmesartan**

The doctor skipped this slide as well

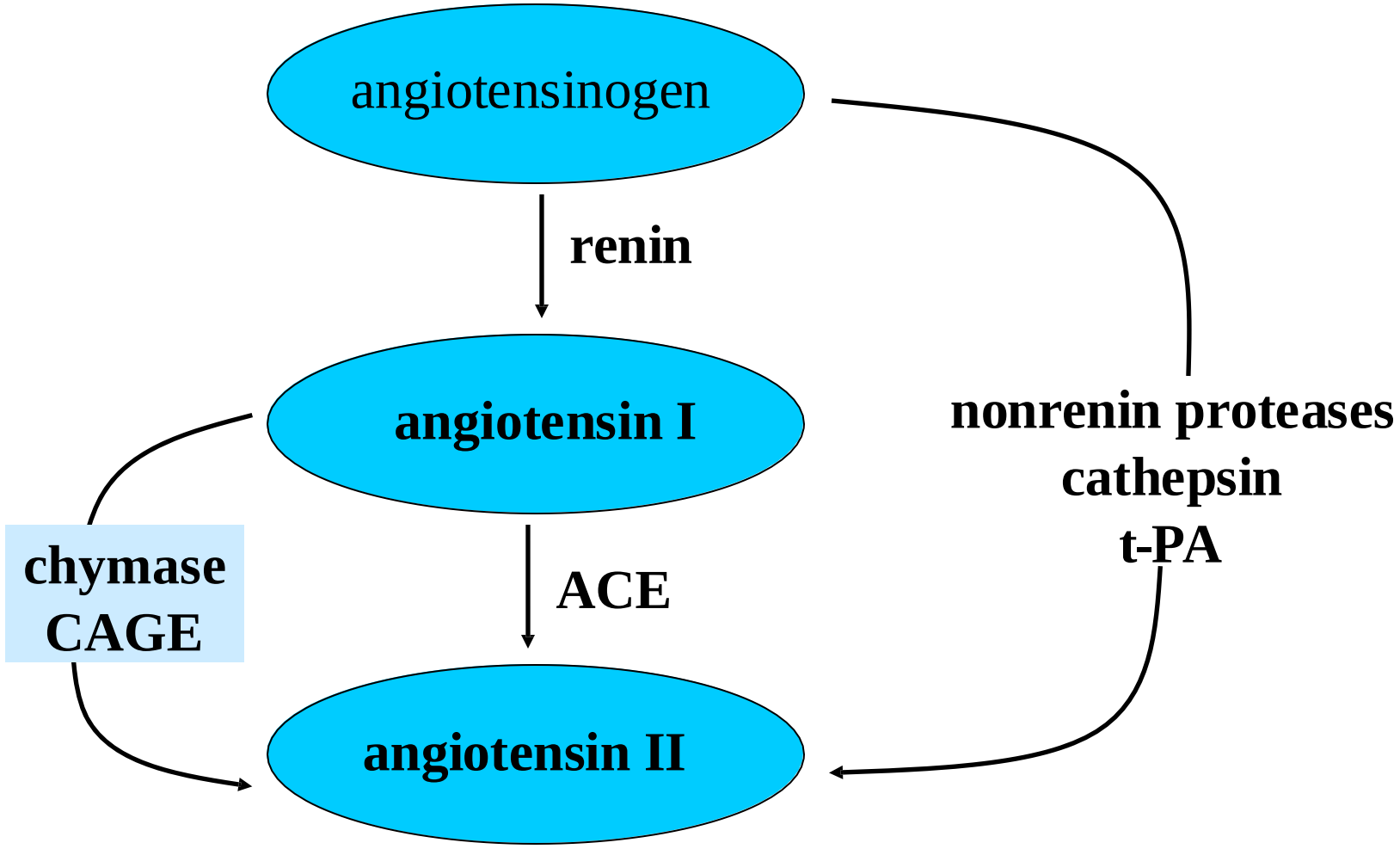
-these drugs lower blood pressure as the ACE inhibitors and have the **advantage** of much lower incidence of adverse effects resulting from

accumulation of bradykinin (cough, angioneurotic oedema)

- they **cause fetal** renal toxicity (like that of the ACE inhibitors)

-these drugs reduce aldosterone levels and cause **potassium accumulation** (attainment of toxic levels - hazardous in patients with renal impairment).

Will be discussed in heart failure



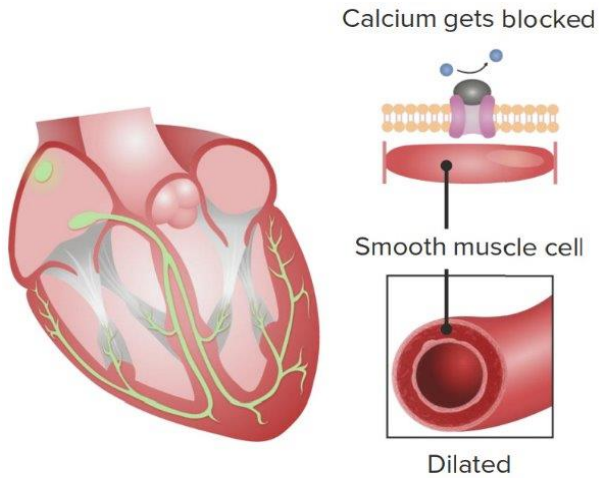
Calcium channel blockers

- 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.

Extra pic



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.
If vasodilation occurs in veins, it may lead to orthostatic hypotension (pooling of blood in the lower body).
It is important to note that calcium channel blockers target the heart and arteries -and to a lesser extent, the veins. Regarding selectivity, calcium channel blockers are more selective for vessels. These drugs, which belong to the antihypertensive class ending with the suffix “DIPINE,” cause peripheral arterial dilation (4 pluses, as highlighted in the red circle) and significantly lower blood pressure (also 4 pluses ++++, specific to “Dipine”). They also exhibit slight negative inotropic activity (one plus) and increase cardiac output. **Why**? Because vessel dilation reduces resistance against blood flow. Another reason is reflex tachycardia.
However, this reflex tachycardia is limited. How is it limited? By a slight negative inotropic activity. There’s just a small effect.

as a result, reduction in BP

	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

Calcium channel blockers

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

- Mechanism of action

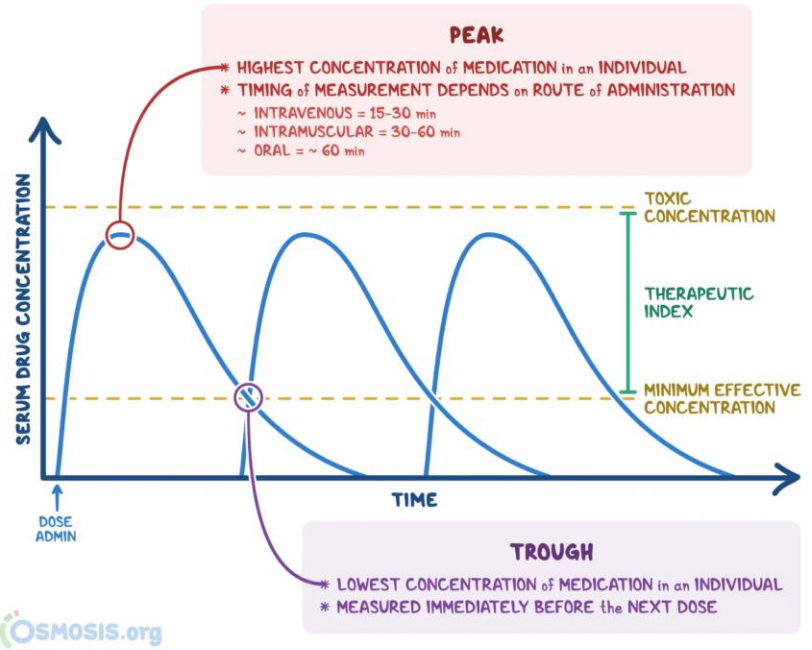
- Calcium enters muscle cell through special voltage sensitive calcium channel. These agents exert their effect by antagonists block for the inward movement of calcium by binding to the L-type channels in the heart and peripheral vasculature.

Important note: There is no such thing as complete selectivity. When we say a drug is a selective β1 receptor agonist, it does **not** mean it doesn't bind to β2 receptors. Similarly, if there is a β2 agonist like salbutamol (a drug for asthma), it doesn't mean it doesn't bind to β1 receptors. In the second example, 90–95% of the drug binds to β2 receptors, but a small portion binds to β1 due to the homology between receptors.

•Similarly, as mentioned earlier, 99% of a drug may bind to L-type calcium channels in the vessels, but a small portion binds to the heart, causing a slight inotropic effect. This is generally not a concern for heart rate unless dealing with a drug with a short half-life, like nifedipine. Why? When the dose peaks at Cmax and then begins to decline toward the next dose (the trough, or the concentration of the drug before the next dose), the binding becomes weaker. In the past, nifedipine was given three times a day, but this issue was addressed by developing sustained-release formulations (nifedipine XR), which maintain consistent drug levels throughout the day and prevent the trough effect.

•We prefer sustained release formulations to avoid the loss of selectivity at the trough. Although nifedipine is cheaper, it is generally not recommended due to its association with reflex tachycardia.

Additional picture:



	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

Then, we move to verapamil and diltiazem, which are selective toward the heart and exhibit significant negative inotropic activity (3 pluses) and SA node depression (2 pluses++). These drugs are primarily used for **arrhythmias** because they act on the AV node (3 and 4 pluses) and the SA node (2 and 2 pluses). **Nifedipine**, on the other hand, is **not** used in such conditions because it increases heart rate. - look at the circle -

Verapamil and diltiazem possess strong negative inotropic effects and are **contraindicated** in congestive heart failure, similar to high doses of beta-blockers. They are suitable for patients with arrhythmias and hypertension but without heart failure.

As a summary: "Dipine" drugs are generally the best option for Black Americans, except for those with renal impairment, where ACE inhibitors are preferred.

ACE inhibitors can be combined with "Dipine" drugs because there is no direct interaction between them. However, side effects must be monitored, and this is managed by adjusting the dose.

	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

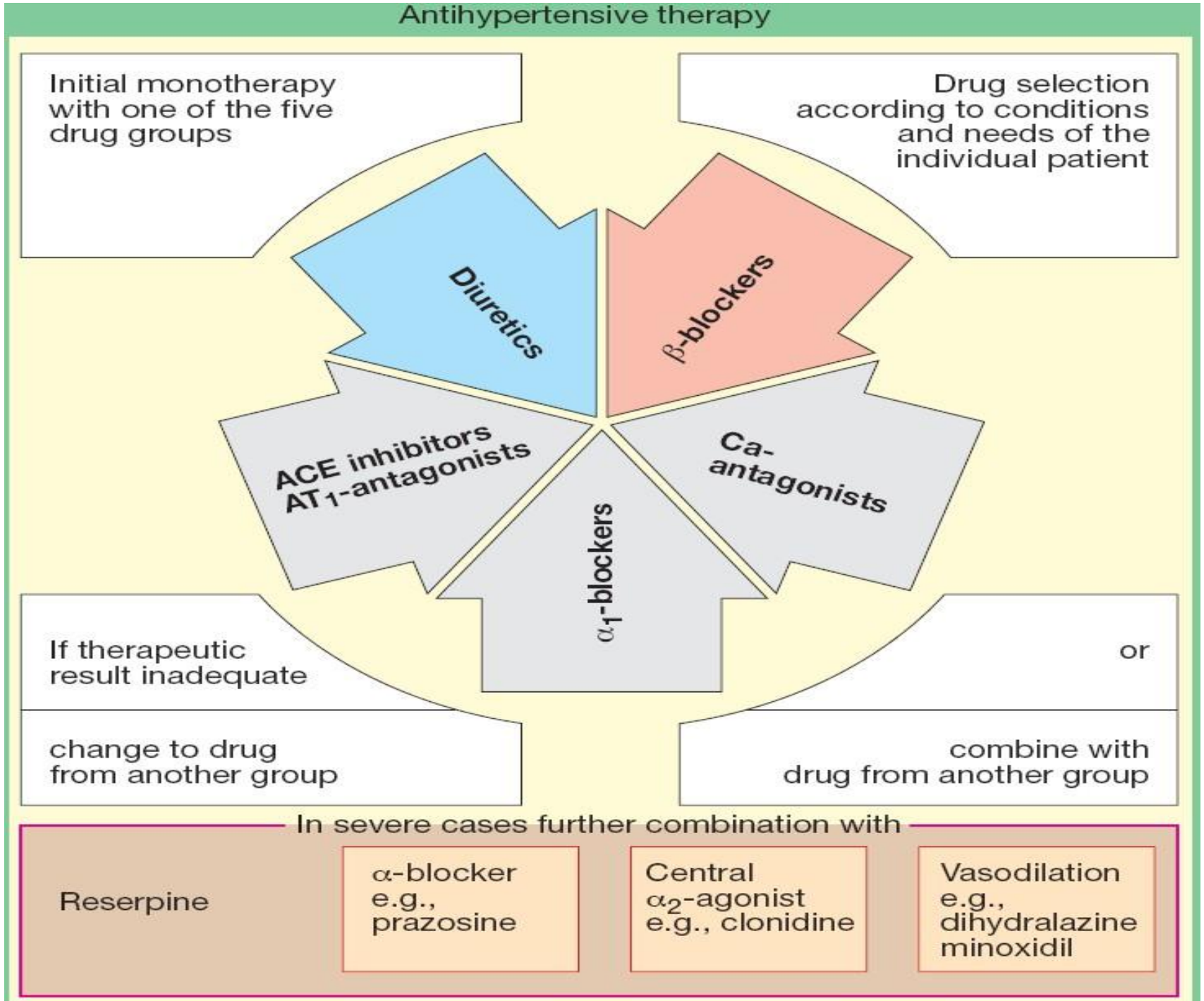
Drug	Effect on heart rate	Adverse effects
Nifedipine	↑	Headache, flushing, ankle swelling
Amlodipine	↑	Ankle swelling
Nimodipine	±	Flushing, headache
Diltiazem	±	Generally mild
Verapamil	↓	Constipation, marked negative inotropic action

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

-Direct Vasodilator=headache ,orthostatic hypotension and edema.

- We should know from this slide that they cause edema, headache and flushing as well as constipation in verapamil (especially) because it has a little bind with GIT.

We shouldn't combine verapamil with B blocker because both has negative inotropic activity and both work in SA and AV nodes


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

فَنَادَىٰ فِي الظُّلُمَاتِ أَن لَّا إِلَٰهَ إِلَّا أَنتَ سُبْحَانَكَ إِنِّي كُنتُ مِنَ الظَّالِمِينَ ❤️

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

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!