Doctor.021
no. 4

CVS
PHARMACOLOGY

Writer: Abdelwahab hamzeh

Corrector: Layan Daoud

Doctor: Malik zihlif

You can enhance your learning experience by accessing my comprehensive Notion document. It offers a wide range of educational resources, including this lecture and much more. Inside, you will find the modified slide content, thought-provoking questions, and informative videos from various reliable sources. With all these valuable materials at your disposal, you can delve deeper into the subject matter and broaden your knowledge. I am certain that you will appreciate the depth and breadth of information provided in this wonderful Notion document. (:

Abdelwahab's Notion....Click Here !

Vasodilator

- Vasodilators, such as Hydralazine and minoxidil, are smooth muscle relaxants.
- They produce reflex stimulation of the heart resulting in increasing the myocardial contractibility, heart rate, and oxygen consumption, so they may prompt angina and myocardial infarction in predisposed individuals.
- They increase plasma renin concentration, which results in sodium and water retention. (which is an unwanted side effect.)
- These unwanted effects can be blocked by the **combination** of diuretics and a blocker. (solution of the side effect).

Notes from the doctor.

Resistant hypertension can occur after the treatment using first-line therapy (diuretics and beta blockers) and second-line therapy (ACE inhibitor, angiotensin receptor blocker (ARBs), calcium channel blocker, clonidine, and methyldopa), in this case, we might go toward the vasodilators which is the topic of our lecture.

Minoxidil and hydralazine are oral drugs.

Vasodilators come in four types:

Fenoldopam and nitroprusside given by infusion.

1- Activation of Calcium like : **Hydralazine**

2- More efflux of K+ like : **Minoxidil**, **Diazoxide**

3- producers of NO like : **Nitroprusside**

4- Agonist for dopamine 1 receptors : **Fenoldopam**

Notes from the doctor.

- As a side effect for **ALL** vasodilators: they can cause reflex tachycardia, and they have an effect on sodium and water retention. which needs to be controlled

- Vasodilators increase plasma renin levels as a side effect through two mechanisms:

1.Direct effect on the kidney.
2.Indirect effect via the baroreceptor reflex and activation of Beta 1 receptors, which stimulates renin production.

- This is a negative feedback mechanism that helps to maintain blood pressure homeostasis.

To avoid this feedback when using vasodilators, they are often combined with diuretics (such as thiazides) and beta blockers.

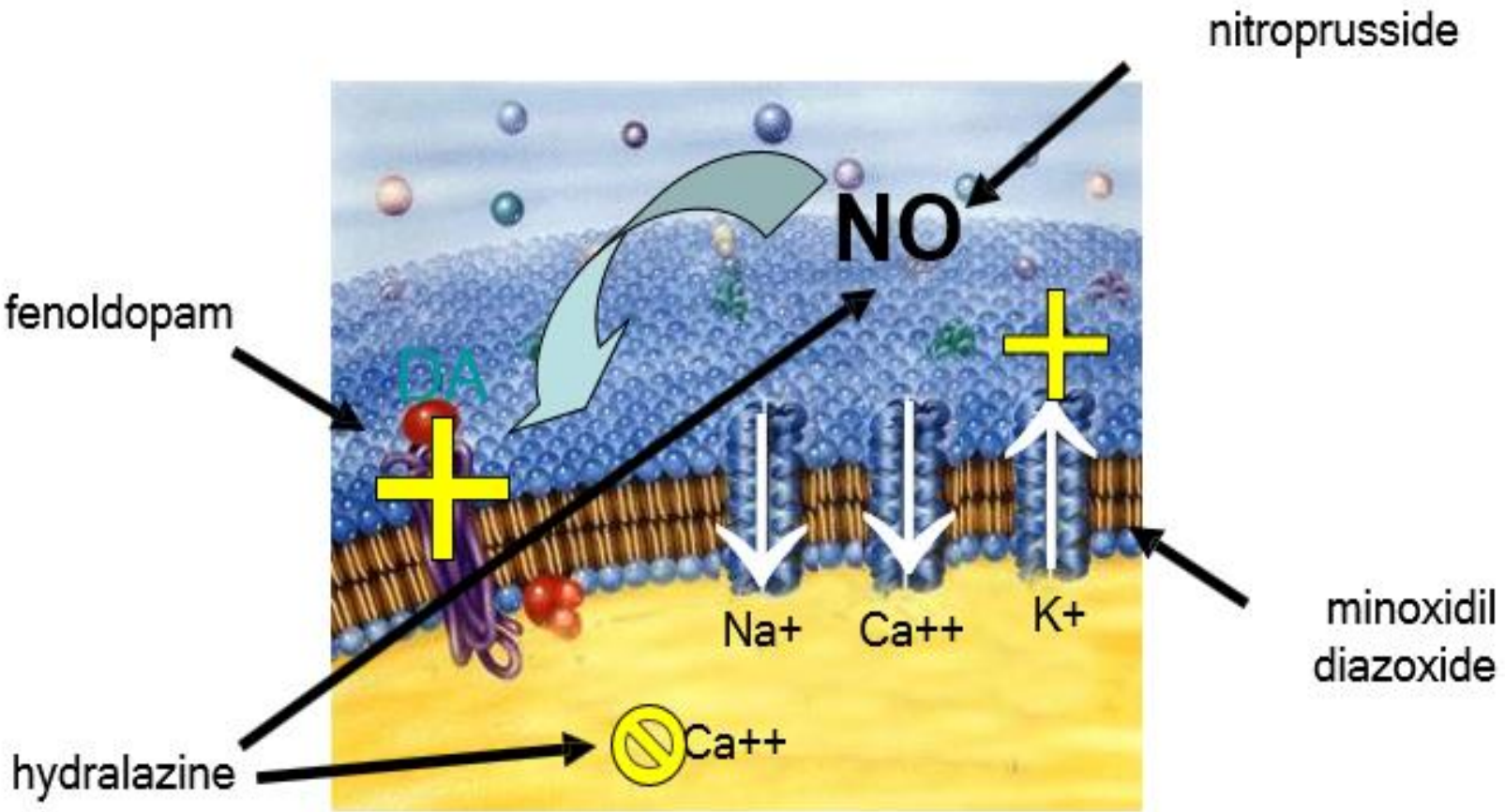
Notes from the doctor.

Hydralazine needs β blocker + Thiazide.

Minoxidil needs β blocker + loop diuretic (not thiazide because the profound retention).

- Remember the side effects of loop diuretics: hypokalemia, hyponatremia, hypovolemia, hypomagnesemia.
- Also, there is hypocalcemia as a side effect of loop diuretic but don't worry because calcium is controlled by other mechanisms.

Main drugs that cause vasodilation



1-Hydralazine

- Hydralazine is used to treat moderately severe hypertension. It is often combined with a **diuretic** to prevent sodium and water retention, as well as a **β blocker** to counteract 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 (special side effect) can occur with high doses, but it is reversible on stopping the therapy.**

Notes from the doctor

Hydralazine has a special place in the treatment of black individuals. Black patients have a problem with their response **to ACE inhibitors**, so we use other options. In heart failure, we use a combination of Hydralazine and isosorbide dinitrate.

- It is important to remember that hydralazine needs to be used in combination with a beta blocker and thiazide. We mentioned earlier that hydralazine is used as a **monotherapy** in pregnancy-induced hypertension.

- Hydralazine has two effects: one toward the Nitric oxide and the other is **reduce the level of calcium within smooth muscles**(most important effect of hydralazine).

- Nitric oxide will have an activity toward dilation and increase the cGMP and dephosphorylate the myosin and relaxes smooth muscles.

Notes from the doctor

As a side effect of hydralazine, we can experience reflex tachycardia and sodium water retention. To address this issue, we use β blockers and thiazide.

- Some evidence suggests that hydralazine inhibits IP3, which triggers the release of calcium from intracellular storage sites, leading to a decrease in their concentration within smooth muscles..

- Another piece of evidence indicates that hydralazine promotes arterial dilation by opening **low** conductance calcium-activated potassium channels.

Most importantly, hydralazine reduces the concentration of intracellular calcium, resulting in **arteriodilation** rather than venous dilation. This arteriodilation induces the reflex release of renin, both directly and indirectly.

Hydralazine

side effects of hydralazine :

1. headache.
2. Sodium and water retention.
3. Reflux tachycardia .
4. Lupus-like syndrome (Special side effect)→ This disease goes toward the acetylation that induces cytotoxicity for hydralazine. This type of side effect is related to the time, if you use this drug for more than six months you may have lupus.

remember the phases of drug metabolism. Phase I includes oxidation, reduction, and hydrolysis mediated by cytochrome P450, but phase II depends on conjugation reactions including glucuronidation, sulfation, acetylation, methylation, and glutathione conjugation.

Lupus is related in women four times more than in men this means **white** ladies have more chance of getting lupus because estrogen will increase the activity of T cells and produce autoimmune disease. The using of hydralazine is dose dependent if the dose of 50 mg it will not produce lupus means more than this amount may produce lupus.

10% of white ladies can get lupus if they use more than 50 mg of hydralazine.
We start with patients by 25 mg if there is no response, we increase the dose.

2- Minoxidil

Mechanism of action.

The opening of ATP undulated potassium channels results in the efflux of K+ ions and **hyperpolarization**, ultimately leading to muscle relaxation. This relaxation affects the arteries.

Additionally, there is sodium water retention, activation of renin, and activation of baroreceptors, which results in reflex tachycardia.

- To decrease water retention, loop diuretics (not thiazides) are used.
- To decrease reflex tachycardia, β blockers are used.

Sodium water retention may be profound (significant) in patients taking minoxidil, so they may require a larger amount of loop diuretic to prevent edema formation.

2- Minoxidil

- the consequences of baroreceptors mediated activation of sympathetic nervous system during minoxidil therapy are similar to those seen with hydralazine.

- Increase in the heart rate, myocadiac contractability and oxygen consumption, so we use Beta blocker as a combination.

- The main side effect is hypertrichosis, occurred in patients who received minoxidil for extended period. (consequence of K+ channel activation).

- Hair growth occurs on the face, back, arms and legs. This side effect usually problematic for women..

2- Minoxidil

- Rogaine is a brand name for minoxidil, a drug used mainly to treat hair loss and promote hair growth.

- It is an over-the-counter drug used by both genders, but it may pose a problem for women due to its side effects.

In general, minoxidil is best reserved for treating severe hypertension in **male patients** with **renal insufficiency** if other drugs are not effective.

Additionally, minoxidil is often administered alongside other medications, such as loop diuretics and beta blockers, to prevent or minimize these side effects.

3- Nitroprusside.

Mechanism of action.

- Nitroprusside produces **nitric oxide(NO)**, which increases cGMP. This leads to the dephosphorylation of myosin and results in the relaxation of smooth muscles.

- the effect of Nitroprusside is on **Both** veins and arteries.

- reduces constriction in veins and arteries, decreases preload and afterload, and increases perfusion toward coronary arteries.

- There may be reflex tachycardia, but it is not as pronounced (marked) as what occurs with hydralazine and minoxidil..

- Used for short term, so no long term control.

3-Nitroprusside

Important side effect for nitroprusside.

- nitroprusside contains cyanide, and when combined with thiol group causes thio-cyanosis.

- this toxicity occurs if we used nitroprusside more than(24-48 h) and if the infusion rate is high (5mg/kg/day). Sometime even low dose can cause this toxic effect.

- the result of thio-cyanosis is lactic acidosis which cause other problems.

4- Fenoldopam

- Dopamine 1 receptor agonist, dopamine receptor present on arteries and its activation leads to arterial dilation.

-Dopamine receptors also present in the kidney, so fenoldopam is a good drug for patient with kidney problem and emergency hypertension .

-Fenoldopam is given by infusion not orally.

Fenoldopam works quickly, typically within 5-10 minutes, and has a half-life of 30-60 minutes. However, **it is not ideal for titration** due to its long half-life. In comparison, **nitroprusside** is a better drug for titration and is therefore more commonly used in cases of emergency hypertension.

Hypertension emergency

- it is rare but life-threatening when the diastolic blood pressure (DBP) is greater than 150 mmHg and the systolic blood pressure (SBP) is greater than 210 mmHg **in a healthy person**, **OR** when the DBP is greater than 130 mmHg in individuals with pre-existing complications such as encephalopathy, cerebral hemorrhage, left ventricular failure, or aortic stenosis

Here are some drugs used in emergency hypertension:

- **1-Sodium nitroprusside** (onset 1-2 min), is administered intravenously and causes sudden vasodilation and reflex tachycardia, it is effective in ALL patients regardless the cause. (Nitroprusside is the first choice in hypertension emergency)

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

Hypertension emergency

- **2- Fenoldopam** (onset 2-5 min), peripheral dopamine 1 receptor agonist that also given as an intravenous infusion. (not available in all hospitals).

It may be particularly beneficial for patients with renal insufficiency as it helps maintain or increase renal perfusion.

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

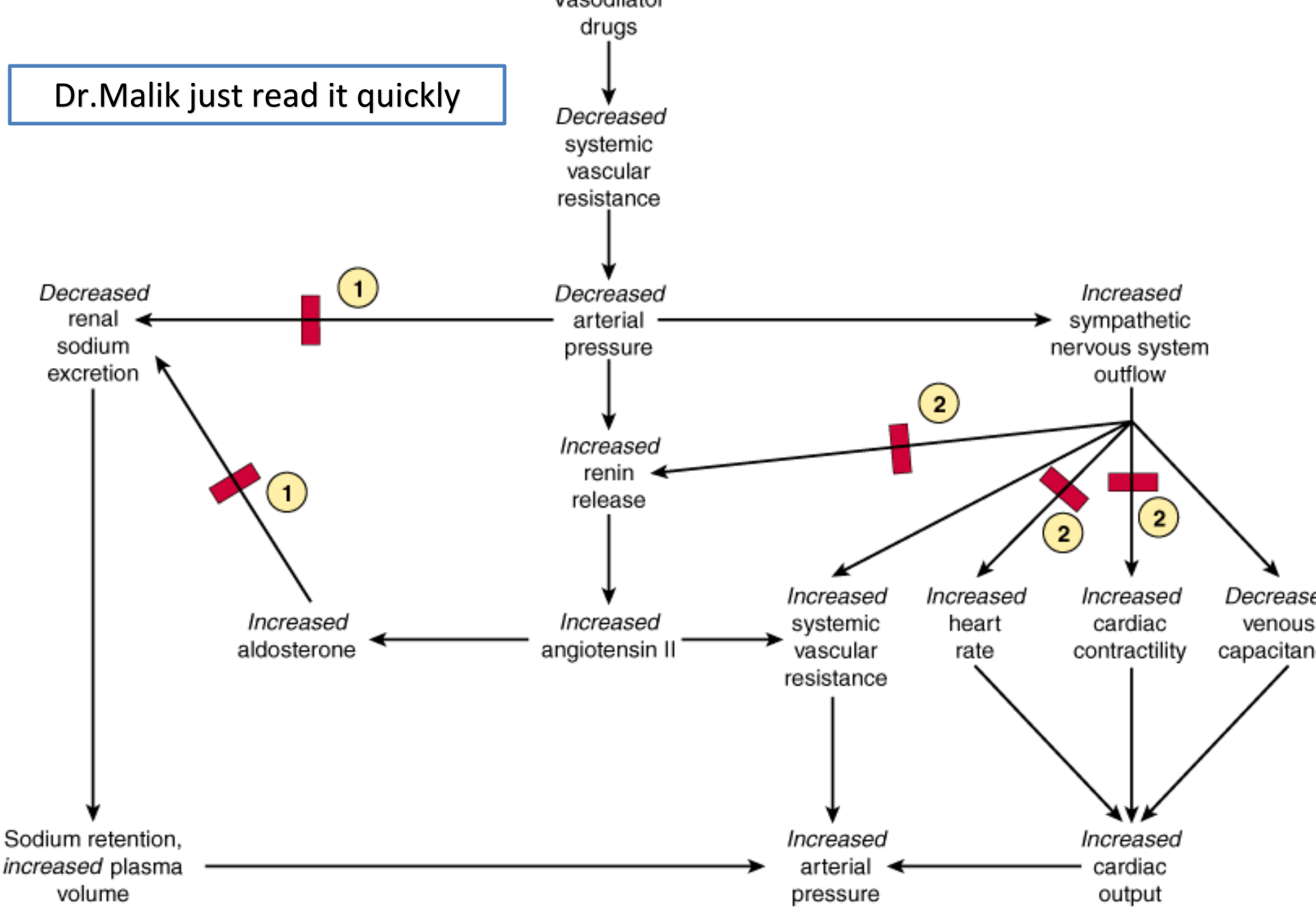
Hypertension emergency

- **3-Labetalol** (α and β blocker), with an onset of 5-10 minutes, **does not induce reflex tachycardia** when given as an intravenous bolus or infusion. It shares the same β blocker contraindication (asthma...) and its major limitation is its long half-life (3-6 hours), **which prevents rapid titration**.

Therefore, for titration purposes, the best drug is **nitroprusside** (with a short half-life), followed by **fenoldopam**, and lastly **labetalol** (with a long half-life).

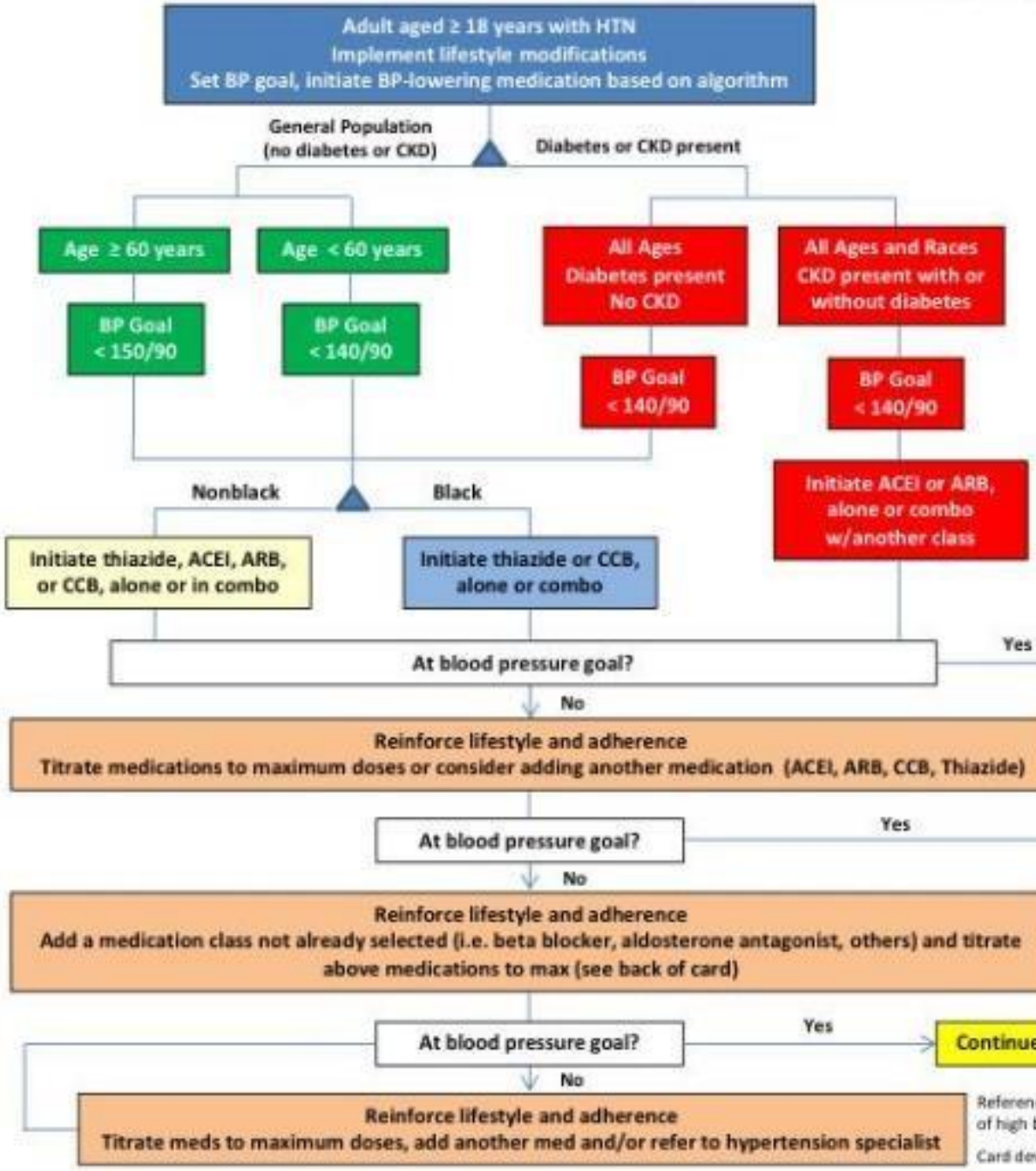
Drugs with a short half-life allow for better titration and are more commonly used in emergency hypertension, such as nitroprusside.

Dr.Malik just read it quickly



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

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.

تمام أعزائي بالنّسبة للسلايد اللّي قبل الدكتور ما شرحها, رح أحاول أشرحلكم إياها وعلى راحتكم إذا حابّيين تدرسوها أو لا, شوف الجدول وتبّع مع كلامي رح تشوفه كثيير سهل, شكرًا شكرًا

The flowchart is divided into three columns: A, B, and C. Each column represents a different group of patients with hypertension, based on their age and whether they have diabetes or chronic kidney disease (CKD)

Column A is for adults aged 21 years or older with hypertension, who do not have diabetes or CKD. Their BP goal is less than 140/90 mmHg. The initial drugs to use are thiazide-type diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs). The drugs should be titrated every month until the BP goal is reached. If the BP is not controlled with one drug, another drug from a different class should be added. If the BP is still not controlled with two drugs, a third drug from a different class should be added. The patient should be followed up every month until the BP goal is reached, and then every 3 to 6 months thereafter. And every time we should take lifestyle modification into consideration along the drug therapy.

Column B is for adults aged 60 years or older with hypertension, who do not have diabetes or CKD. Their BP goal is less than 150/90 mmHg. The initial drugs to use are the same as column A, except that ACEIs and ARBs should be avoided in black patients. The titration, addition, and follow-up steps are the same as column A.

Column C is for adults with diabetes or CKD, regardless of their age. Their BP goal is less than 140/90 mmHg. The initial drugs to use are ACEIs or ARBs, which have additional benefits for these patients. If the BP is not controlled with one drug, another drug from a different class should be added. The preferred classes are CCBs or thiazide-type diuretics. The titration, addition, and follow-up steps are the same as column A.

Thank you !

اللهم كن مع اهلنا واخواننا في غزة, يا رب أيدهم بجنود من عندك واستعملنا في نصرة دينك اللهم اكرمنا كما اكرمتهم !
اللهم استعملنا ولا تستبدلنا, اللهم استعملنا ولا تستبدلنا, اللهم استعملنا ولا تستبدلنا

Don’t panic, the drugs that aren’t mentioned the previous lectures are not required, you have to memorize only the drugs that are discussed in the lectures فقط عليكم دراسة ما تمَّ ذِكره بالمحاضرات السّابقة من هذه الجدوال أنتم لستم مطالبين بغير ذلك

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

Slide 10 isosorbide dinitrate. (not mono).

Slide 12 : white lady (not black)

V3: Slides 23, 27 &28 are required, and see what is written about them.