Antihypertensive drugs

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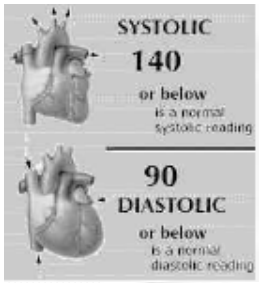
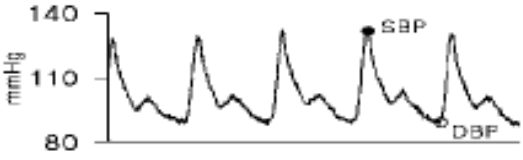
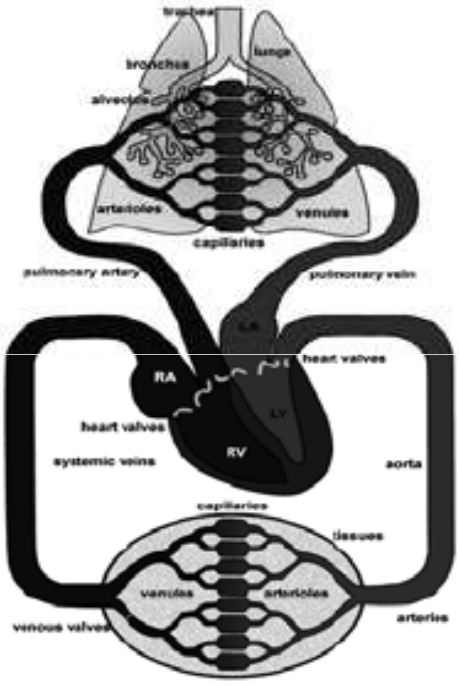
Systolic – Diastolic Blood Pressure







Diastolic: the minimum arterial pressure during relaxation and dilatation of the ventricles of the heart

Systolic: The blood pressure when the heart is contracting.

Regulation of Arterial Pressure

• Arterial pressure = cardiac output X peripheral resistance

• Arterial pressure affected by:

– the autonomic nervous system (fast)

– the renin-angiotensin system (hours or days)

– the kidneys (days)

Cardiovascular Pharmacology

Definition of Hypertension (HT)

- Sustained elevation of systolic and/or diastolic BP above an arbitrarily .defined level

• systolic >139 mmHg and/or diastolic >89 mmHg.

-General population (15-20%) hypertensive.

Primary (essential) HT (90%): is a lifelong disease, longterm control & treatment, cause unknown.

Secondary HT (10%): can be cured by surgical procedures (early diagnosis of cause, ie renal stenosis, pheochromocytoma).

• Renal artery stenosis (narrowing) is a decrease in the diameter of the renal arteries. The resulting restriction of blood flow to the kidneys may lead to impaired kidney function (renal failure) and high blood pressure (hypertension), referred to as renovascular hypertension.
• pheochromocytoma is a neuroendocrine tumor of the medulla of the adrenal glands.

Hypertension (HT)

Secondary HTs (10%)

- neurogenic HT caused by brain damage
- cortisol overproduction: hypophysis or adrenal gland tumor
- aldosterone overproduction: adrenal gland tumor hyperplasia
- renal artery stenosis or occlusion
- adrenal medulla tumor: pheochromocytoma

Primary (essential) HTs (90%)

- primary cause(s) unknown, possibly multi-factorial defects
- genetics - smoking - stress
- salt intake - obesity - age
-alcohol - caffeine – others

Hypertension consequences:

Heart failure, kidney damage, stroke, blindness …

Hypertension (HT)

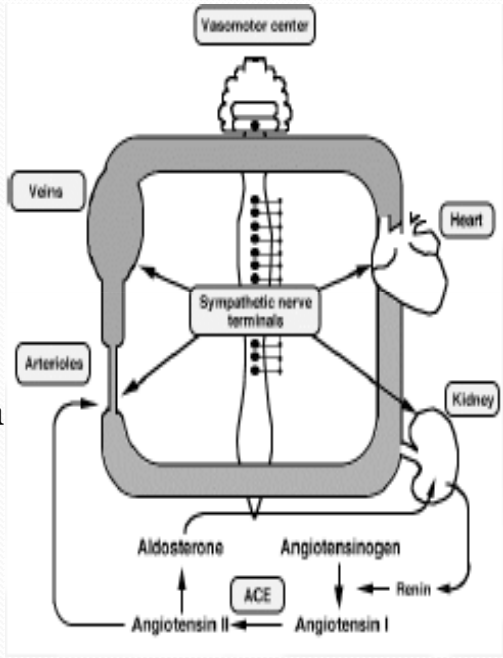
New Blood Pressure Classification

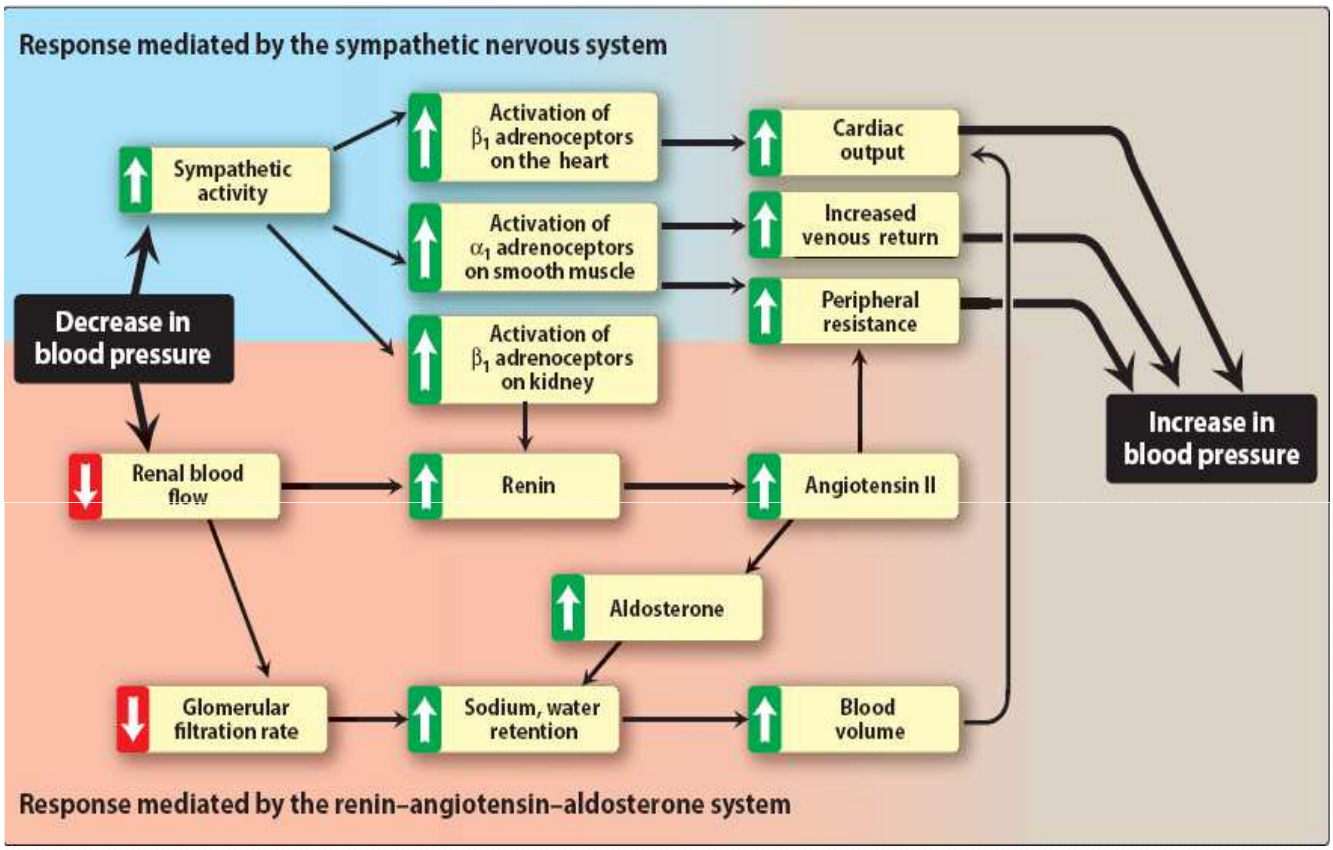
BP Classification	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Pre-hypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥160	or	≥100

Antihypertensive Drugs

Potential drug targets:

- CNS, ANS: decrease sympathetic tone
- Heart: decrease cardiac output
- Veins: dilate ⇨ decrease preload
- Arterioles: dilate ⇨ decrease afterload
- Kidneys: increase diuresis; inhibit RAA system





Response of the autonomic nervous system and the renin–angiotensin–aldosterone system to a decrease in blood pressure

Antihypertensive Drugs

DIURETICS

Amiloride MIDAMOR
Bumetanide BUMEX
Chlorthalidone HYGROTON
Eplerenone INSPRA
Ethacrynic acid EDECRIN
Furosemide LASIX
Hydrochlorothiazide MICROZIDE
Indapamide LOZOL
Metolazone MYKROX, ZAROXOLYN
Spironolactone ALDACTONE
Triamterene DYRENIUM
Torsemide DEMADEX

β-BLOCKERS

Acebutolol SECTRAL
Atenolol TENORMIN
Betaxolol KERLONE
Bisoprolol ZEBETA
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Penbutolol LEVATOL
Pindolol VISKEN
Propranolol INDERAL LA, INNOPRAN XL
Timolol BLOCADREN

ACE INHIBITORS

Benazepril LOTENSIN
Captopril CAPOTEN
Enalapril VASOTEC
Fosinopril MONOPRIL
Lisinopril PRINIVIL, ZESTRIL
Moexipril UNIVASC
Quinapril ACCUPRIL
Perindopril ACEON
Ramipril ALTACE
Trandolapril MAVIK

ANGIOTENSIN II RECEPTOR BLOCKERS

Azilsartan medoxomil EDARBI
Candesartan ATACAND
Eprosartan TEVETEN
Irbesartan AVAPRO
Losartan COZAAR
Olmesartan BENICAR
Telmisartan MICARDIS
Valsartan DIOVAN

RENIN INHIBITORS

Aliskiren TEKTURNA

CALCIUM CHANNEL BLOCKERS

Amlodipine NORVASC
Clevidipine CLEVIPREX
Diltiazem CARDIZEM, CARTIA, DILACOR
Felodipine PLENDIL
Isradipine DYNACIRC CR
Nicardipine CARDENE
Nifedipine ADALAT, NIFEDIAC, PROCARDIA
Nisoldipine SULAR
Verapamil CALAN, ISOPTIN, VERELAN

α-BLOCKERS

Doxazosin CARDURA
Prazosin MINIPRESS
Terazosin HYTRIN

OTHERS

Clonidine CATAPRES, DURACLON
Fenoldopam CORLOPAM
Hydralazine APRESOLINE
Methyldopa ALDOMET
Minoxidil LONITEN
Nitroprusside NITROPRESS

TREATMENT STRATEGIES

- Mild hypertension can sometimes be controlled with monotherapy, but most patients require more than one drug to achieve blood pressure control.

- Current recommendations are to initiate therapy with a thiazide diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker (CCBs).

- Patients with systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100 mm Hg should be started on two antihypertensives simultaneously.

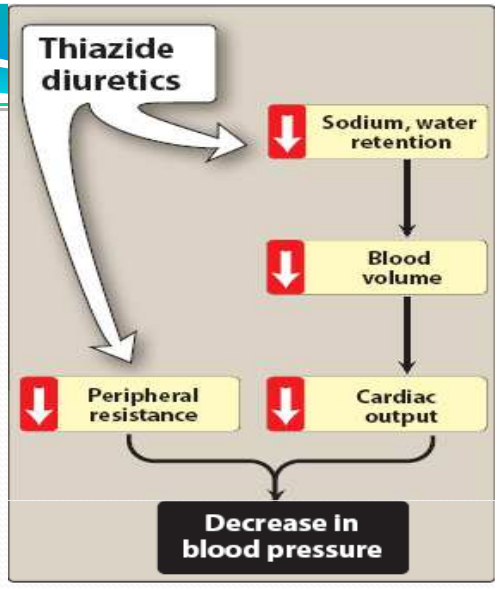
1. DIURETICS

➢ Initial mechanism of action : ⬇ blood volume ⇨ ⬇ blood pressure.

➢ Thiazide diuretics can be used as initial drug therapy for hypertension (unless there are compelling reasons to choose another agent).

➢ Routine serum electrolyte monitoring should be done for all patients receiving diuretics.

A. Thiazide diuretics



➢ Useful in combination therapy (with β-blockers, ACE inhibitors, ARBs, and K-sparing diuretics).

➢ Not effective in patients with inadequate kidney function. (SOLUTION= Loop diuretics).

➢ Can induce hypokalemia, hyperuricemia, and hyperglycemia.

B. Loop diuretics

- *Act by blocking sodium and chloride reabsorption* in the kidneys, (even in patients with poor renal function or not responded to thiazide diuretics).
- Cause decreased renal vascular resistance and increased renal blood flow.
- Rarely used alone to treat hypertension.
- Like thiazides, they can cause hypokalemia.

C. Potassium-sparing diuretics

- Reduce potassium loss in the urine.
- Sometimes used in combination with loop diuretics and thiazides
- *Amiloride and triamterene : inhibitors* of epithelial sodium transport at the late distal and collecting ducts
- *Spironolactone and eplerenone :* aldosterone receptor antagonists

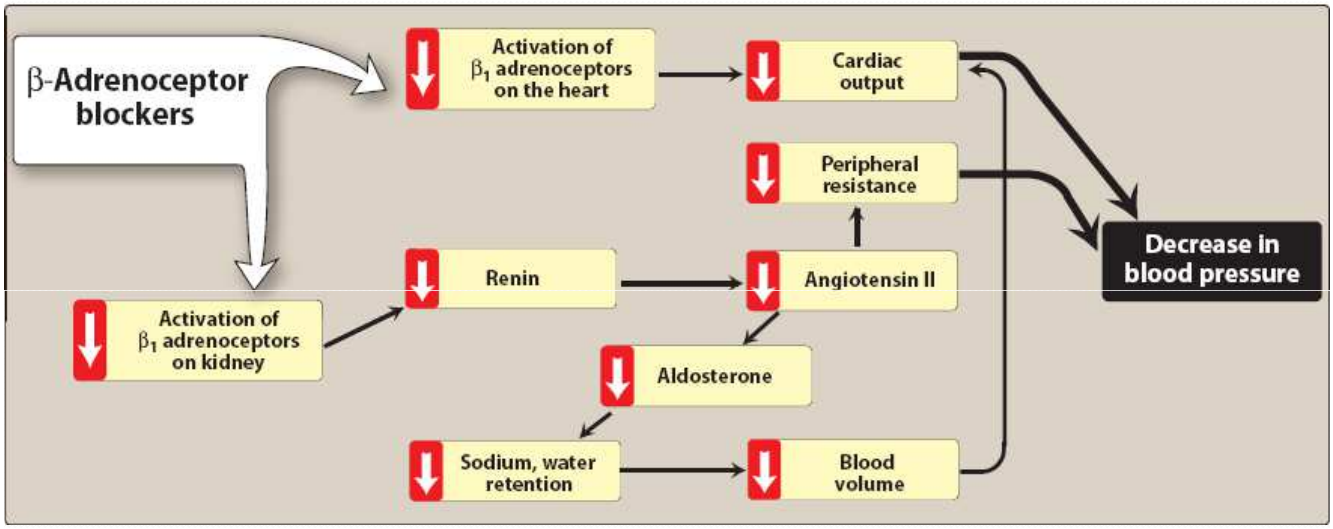
2- β-ADRENOCEPTOR–BLOCKING AGENTS

- β-Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure

A. Actions

- Selective β1 blockers (*metoprolol ,atenolol) = most commonly prescribed* β-blockers.
- *Nebivolol is a selective β1 blocker, which also* increases the production of nitric oxide, leading to vasodilation.

- The selective β-blockers may be administered cautiously to hypertensive patients who also have asthma.
- The nonselective β-blockers (*propranolol and nadolol) are contraindicated in patients with asthma*.



Actions of β-adrenoceptor–blocking agents.

B. Therapeutic uses

- In hypertensive patients with concomitant heart disease

(previous myocardial infarction, angina pectoris, and chronic heart failure).

- Conditions that discourage the use of β-blockers include:

asthma and severe peripheral vascular disease.

C. Pharmacokinetics

- Orally active for the treatment of hypertension (may take several weeks to develop their full effects).

- *Esmolol, metoprolol, and propranolol are available in intravenous* formulations.

- *Propranolol undergoes extensive and highly first-pass* metabolism.

D. Adverse effects

1. **Common effects:**

- The β-blockers may cause bradycardia, hypotension, and CNS side effects such as fatigue, lethargy, and insomnia.
- The β-blockers may decrease libido and cause erectile dysfunction, which can severely reduce patient compliance.

2. **Alterations in serum lipid patterns:**

- Nonselective β-blockers may decrease HDL cholesterol and increase TG.

3. Drug withdrawal:

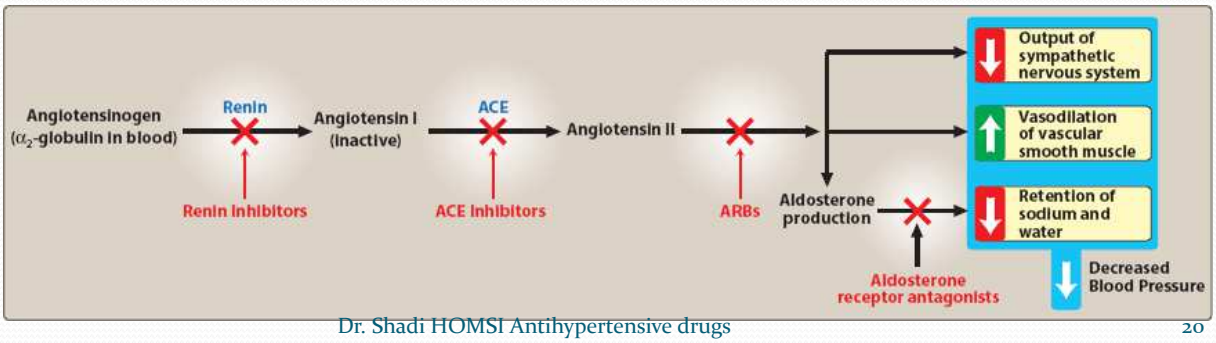
- Abrupt withdrawal may induce angina, myocardial infarction, and even sudden death in patients with ischemic heart disease.

3- ACE INHIBITORS

- The ACE inhibitors, such as *enalapril and lisinopril* , are recommended as **first-line treatment** of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease.

A. Actions

- The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility.



B. Therapeutic uses

- Slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy.

- ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction.

- ACE inhibitors are first-line drugs for treating heart failure, hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease.

C. Pharmacokinetics

- Orally bioavailable as a drug or prodrug.
- All but *captopril and lisinopril undergo hepatic conversion* to active metabolites.
- *Fosinopril is the only one* not eliminated primarily by the kidneys.
- *Enalaprilat* is the only drug in this class available intravenously.

D. Adverse effects

- Common side effects: dry cough, rash, fever, altered taste, hypotension and hyperkalemia.
- Angioedema is a rare but potentially life-threatening reaction.
- ACE inhibitors can induce fetal malformations and should not be used by pregnant women.

4- ANGIOTENSIN II RECEPTOR BLOCKERS

- The ARBs, such as *losartan and irbesartan:* alternatives to the ACE inhibitors.
- Block the AT2 receptors, ↓ ↓ the activation of AT2 receptors by angiotensin II.
- Their pharmacologic effects are similar to those of ACE inhibitors.
- They may be used as first-line agents for the treatment of HT, especially in patients with diabetes, heart failure, or chronic kidney disease.
- Adverse effects are similar to those of ACE inhibitors with decreased risks of cough and angioedema (ARBs do not increase bradykinin levels).
- **ARBs should not be combined with an ACE inhibitor**.
- These agents are also teratogenic and should not be used by pregnant women.

5- RENIN INHIBITOR

- *Aliskiren (*selective renin inhibitor) *directly inhibits renin and, thus, acts* earlier in the RAAS than ACE inhibitors or ARBs.
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- *Aliskiren should not be* combined with an ACE inhibitor or ARB.
- *Aliskiren can cause diarrhea,* especially at higher doses, and can also cause cough and angioedema, but probably less often than ACE inhibitors.
- *Aliskiren is contraindicated during pregnancy.*
- *Aliskiren is metabolized* by CYP 3A4.

6- CALCIUM CHANNEL BLOCKERS

- Recommended treatment option in HT patients with diabetes or angina.

A. Classes of calcium channel blockers

1. **Diphenylalkylamines (***Verapamil* **):**

- *Verapamil is* the least selective of any CCBs and has significant effects on both cardiac and vascular smooth muscle cells.
- It is also used to treat angina and supraventricular tachyarrhythmias and to prevent migraine.

2. Benzothiazepines (*Diltiazem* **):**

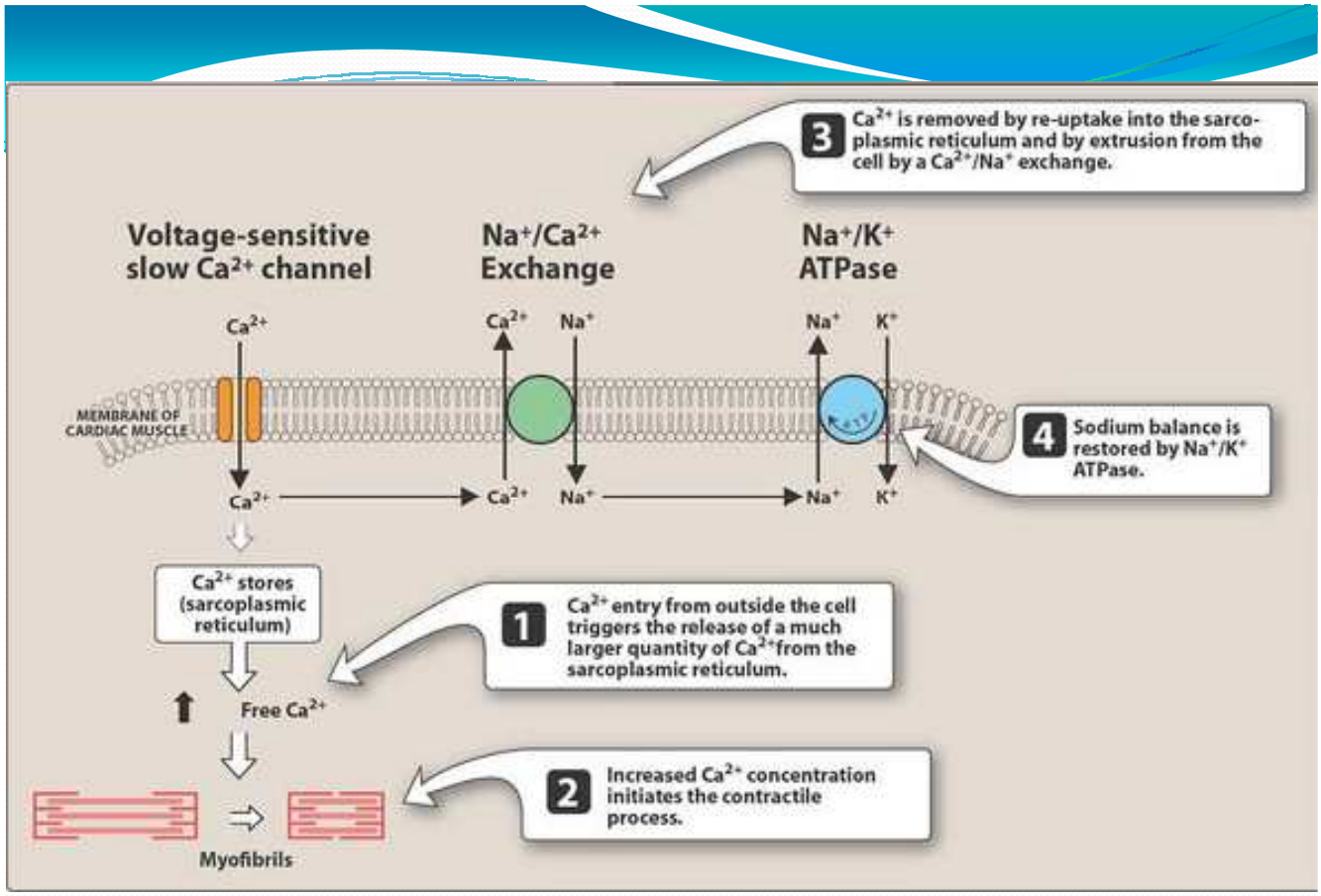
- *Diltiazem affects both cardiac and vascular smooth* muscle cells.
- *Diltiazem has a favorable* side effect profile.

3. Dihydropyridines:

- Includes *nifedipine (the prototype), amlodipine, felodipine, isradipine, nicardipine, and nisoldipine.*
- Differ in pharmacokinetics, approved uses, and drug interactions.
- All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart (particularly beneficial in treating hypertension).
- Show little interaction with other cardiovascular drugs, such as *digoxin or warfarin, (which are often used concomitantly with* CCBs).

B. Actions

- The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium.
- Calcium enters muscle cells through special voltage sensitive calcium channels. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium.
- CCBs block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles.
- **Calcium channel blockers do not dilate veins.**



C. Therapeutic uses

- In the management of HT, CCBs may be used as an initial therapy or as add-on therapy.
- Useful in the treatment of HT patients who also have asthma, diabetes, and/or peripheral vascular disease.
- All CCBs are useful in the treatment of angina.

D. Pharmacokinetics

- Most of these agents have short half-lives (3 to 8 hours) following an oral dose.
- Sustained-release preparations are available and permit once-daily dosing.
- *Amlodipine has a very long half-life and does not* require a sustained-release formulation.

E. Adverse effects

- First-degree atrioventricular block and constipation are common dose dependent side effects of *verapamil*.
- *Verapamil and diltiazem should* be avoided in patients with heart failure or with atrioventricular block due to their negative inotropic (force of cardiac muscle contraction) and dromotropic (velocity of conduction) effects.
- Dizziness, headache, Peripheral edema, and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines.

7- α-ADRENOCEPTOR–BLOCKING AGENTS

- *Prazosin, doxazosin, and terazosin* produce a competitive block of α1-adrenoceptors.
- They decrease peripheral vascular resistance and lower arterial BP by causing relaxation of both arterial and venous smooth muscle.
- These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.
- Reflex tachycardia and postural hypotension often occur at the onset of treatment.
- Due to weaker outcome data and their side effect profile, α-blockers are no longer recommended as initial treatment for hypertension.

8- α-/β-ADRENOCEPTOR–BLOCKING AGENTS

- *Labetalol and carvedilol block α1, β1, and β2* receptors.

- *Carvedilol, although an effective antihypertensive, is mainly* used in the treatment of heart failure.

- *Labetalol is used in the management* of gestational hypertension and hypertensive emergencies.

9- CENTRALLY ACTING ADRENERGIC DRUGS

A. Clonidine

- ***α2 agonist*** → inhibition of sympathetic vasomotor centers → ↓ sympathetic outflow to the periphery → ↓ TPR and ↓ blood pressure.

- *T*reatment of HT that has not responded to treatment with two or more drugs.

- *Clonidine does not decrease* renal blood flow or glomerular filtration ⇨ useful in the treatment of hypertension complicated by renal disease.

- *Clonidine is* absorbed well after *oral* administration and is excreted by the kidney.
- It is also available in a transdermal patch.
- Adverse effects include sedation, dry mouth, and constipation.
- Rebound hypertension occurs following abrupt withdrawal of *clonidine.*

B. Methyldopa

- *α2 agonist , converted to* methylnorepinephrine centrally → ↓ adrenergic outflow from the CNS.
- The most common side effects : *sedation* and drowsiness.
- Its use is limited due to adverse effects and the need for multiple daily doses.
- It is mainly used for management of hypertension in pregnancy, where it has a record of safety.

10- VASODILATORS

- The direct-acting smooth muscle relaxants, (*hydralazine* and *minoxidil), are not used as primary* drugs to treat hypertension.
- Act by producing relaxation of vascular smooth muscle, primarily in arteries and arterioles ⇨ ↓TPR ⇨ ↓ BP.
- Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals.

10- VASODILATORS

- *Hydralazine* is accepted to use for management of HT in pregnancy.
- Adverse effects of *hydralazine include headache,* tachycardia, nausea, sweating, arrhythmia, and precipitation of angina.
- *Minoxidil treatment causes hypertrichosis* (the growth of body hair). This drug is used topically to treat male pattern baldness.

HYPERTENSIVE EMERGENCY

- Hypertensive emergency is a rare but life-threatening situation characterized by:
  - severe elevations in BP (systolic > 180 mm Hg or diastolic > 120 mm Hg)
  - with evidence of progressive target organ damage (ex. stroke, myocardial infarction).
- Hypertensive emergencies require :
  - timely blood pressure reduction
  - with treatment administered IV to prevent or limit target organ damage.
- A variety of medications are used, including:
  - calcium channel blockers (*nicardipine and clevidipine),*
  - *nitric oxide vasodilators (nitroprusside* and *nitroglycerin),*
  - *adrenergic receptor antagonists (phentolamine, esmolol, and labetalol),*
  - *the vasodilator hydralazine,*
  - *and the dopamine* agonist *fenoldopam.*

RESISTANT HYPERTENSION

- Resistant hypertension is defined as blood pressure that remains elevated (above goal) despite administration of an optimal three-drug regimen that includes a diuretic.

- The most common causes of resistant hypertension are:
  - poor compliance,
  - excessive ethanol intake,
  - concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome),
  - concomitant medications (sympathomimetics, NSAIDs, or antidepressants)
  - insufficient dose and/or drugs, and use of drugs with similar mechanisms of action.

XVII. COMBINATION THERAPY

- Combination therapy with separate agents or a fixed-dose combination pill may lower blood pressure more quickly with minimal adverse effects.

- Initiating therapy with two antihypertensive drugs should be considered in patients with blood pressures that are more than 20/10 mm Hg above the goal.