

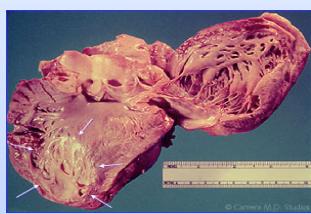
Antihypertensive Drugs

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Hypertension: The Silent Killer



Heart Attack



Stroke



Kidney Failure

CRITICAL POINT!

Hypertension- asymptomatic

Morbidity and mortality due to end organ damage

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Hypertension

- Rise in BP than normal value (120/80)
- Defined as SBP \geq 140 mmHg and/ or DBP \geq 90 mmHg averaged over 2 readings as measured at each of 2+ separate clinic visits.

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Classification

Severity

Normal:	SBP<120 and DBP<80
Prehypertension:	SBP 120-139 or DBP 80-89
Hypertension	
Stage I:	SBP 140-159 or DBP 90-99
Stage II:	SBP \geq 160 or DBP \geq 100

Etiology

Primary:	Unknown cause 90-95% essential or idiopathic
Secondary:	~10% Known cause (pre-eclampsia, renal artery disease, pheochromocytoma)

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Classification

(Hypertensive crisis)

Sever
HTN

+

No symptoms and
no acute end organ
dysfunction

=

Hypertensive
Urgency

Sever
HTN

+

symptoms and /or
acute end organ
dysfunction

=

Hypertensive
emergency

Sever
HTN

+

Retinal
hemorrhages and
or papilledema

=

Hypertensive
malignant

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Risk factor for Primary Hypertension

- Obesity
- Smoking
- Sedentary lifestyle
- Excessive dietary sodium intake
- Excessive alcohol intake
- Low dietary potassium intake (??)
- Family history

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Pathogenesis of Primary Hypertension

Major physiologic system responsible for hypertension:

- Renin-angiotensin-aldosterone system (RAAS)
- Sympathetic Nervous System

Others probable contributors:

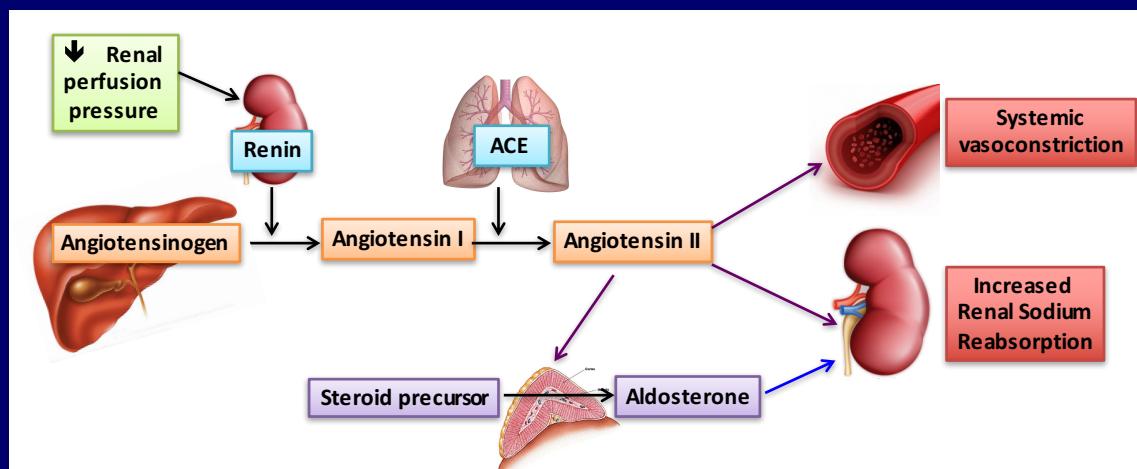
- Endothelial dysfunction (endothelin 1 dysfunction, impairment of Nitric Oxide Synthesis)
- Cytokine dysregulation

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Renin Angiotensin Aldosterone System

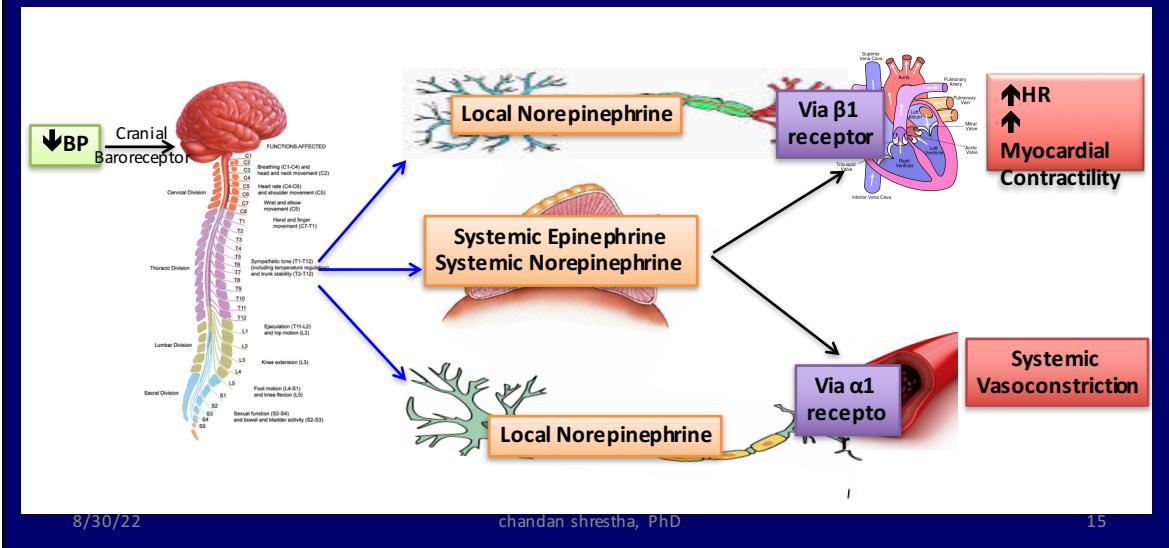


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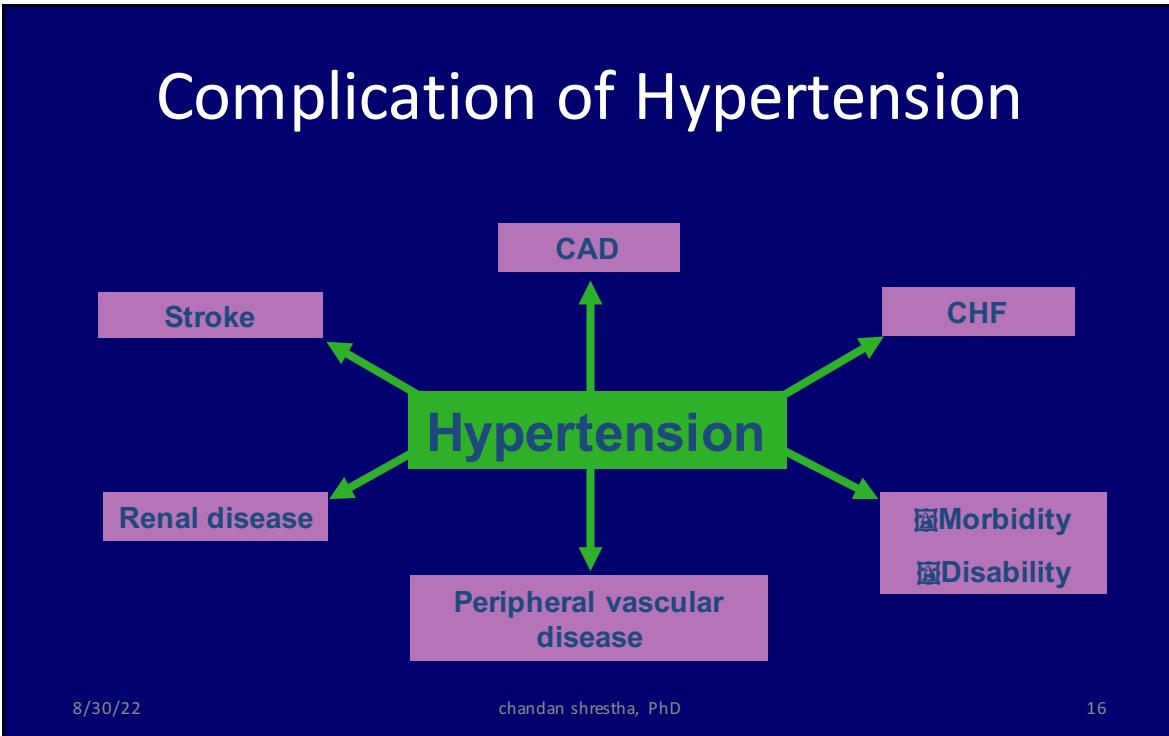
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Sympathetic Nervous System



Complication of Hypertension



Management of HTN

A. Non-pharmacological

- decrease of salt intake
- reduction of body weight
- restriction of smoking and drinking excessive amounts of alcohol
- regular physical activity and relaxation, lack of stress
- increased intake of Mg²⁺, K⁺, Ca²⁺ - fruit, vegetables

B. Pharmacological

Non compliance??

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Antihypertensive Drugs



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Antihypertensive Drugs

1. **Diuretics**
 - a. Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide
 - b. High ceiling: Furosemide
 - c. K⁺ Sparing: Spironolactone, Amiloride
2. **ACE inhibitors:** Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril
3. **Angiotensin (A T₁ receptor) blockers:** Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan, Olmesartan
4. **Calcium channel blockers:** Verapamil, Diltiazem, Nifedipine, Felodipine, Cilnidipine, Amlodipine, Nitrendipine, Lacidipine.
5. **β Adrenergic blockers:** Propranolol, Metoprolol, Atenolol
6. **β + α Adrenergic blockers:** Labetalol, Carvedilol
7. **α Adrenergic blockers:** Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine
8. **Central sympatholytics:** Clonidine, Methylldopa
9. **Vasodilators**
Arteriolar: Hydralazine, Minoxidil, Diazoxide
Arteriolar + venous: Sodium nitroprusside

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ACE Inhibitors Drug (Suffix- Pril)

- Captopril
- Enalapril (2.5~20mg)
- Lisinopril
- Perindopril
- Ramipril

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ACE Inhibitors (Angiotensin Converting Enzyme Inhibitor)

MOA: inhibit enzyme ACE that convert Angiotensin I to Angiotensin II.

Clinical Application

- Young
- Decrease morbidity and mortality
- 1. Hypertension, especially in diabetes
- 1. Non hypertensive conditions
 - Diabetic nephropathy
 - Post MI
 - Prophylaxis in high cardiovascular risk patients

A/E of ACE Inhibitors

- **Dry Cough ($\geq 20\%$)**
- Angioedema (very rare; ACE-I >> ARB)
- Orthostatic hypotension
- Hyperkalemia, hyponatremia
- Increased serum creatinine
- Renal impairment (esp with bilateral renal artery stenosis)
- Teratogenicity
- Headache, Dizziness, fatigue, Nausea, skin rash

ARB Drug (Suffix- sartan)

- Losartan
- Telmisartan
- Valsartan
- Candesartan

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ARBs (Angiotensin Receptor Blockers)

MOA: blocks binding of angiotensin II to its receptor (AT₁R) on target tissues.

- Lowers BP in a similar fashion as ACE-I
- Alternate to ACE-I.

Clinical Application

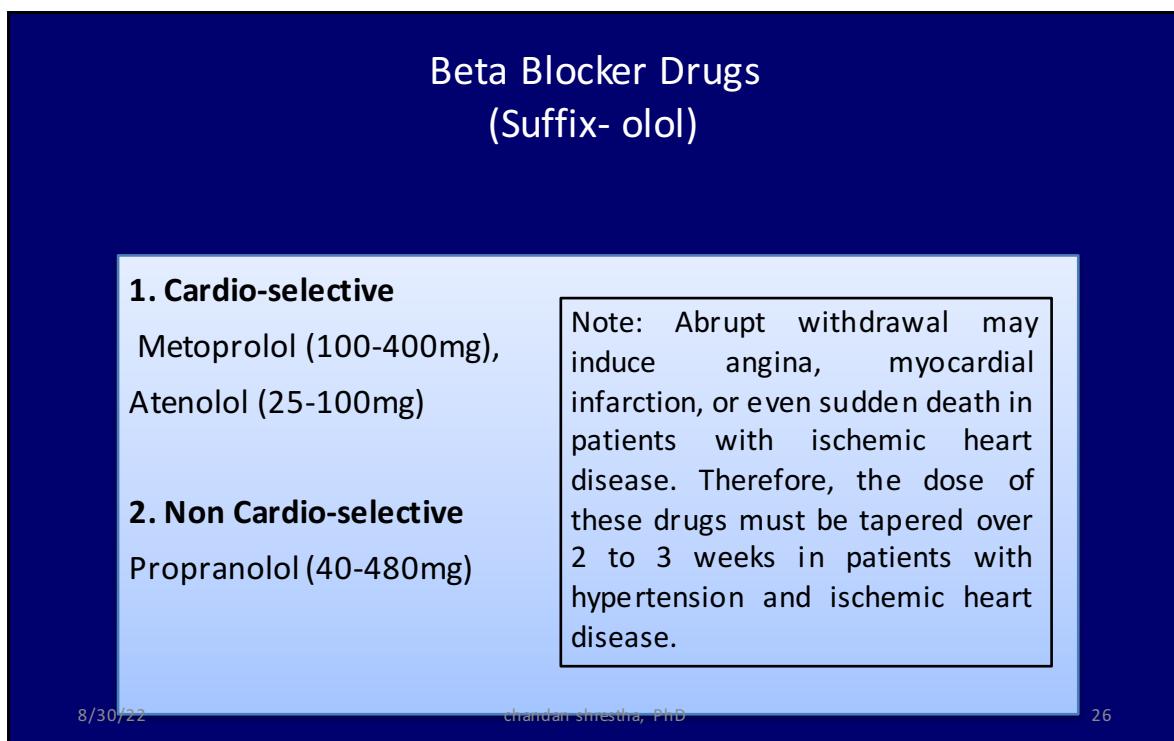
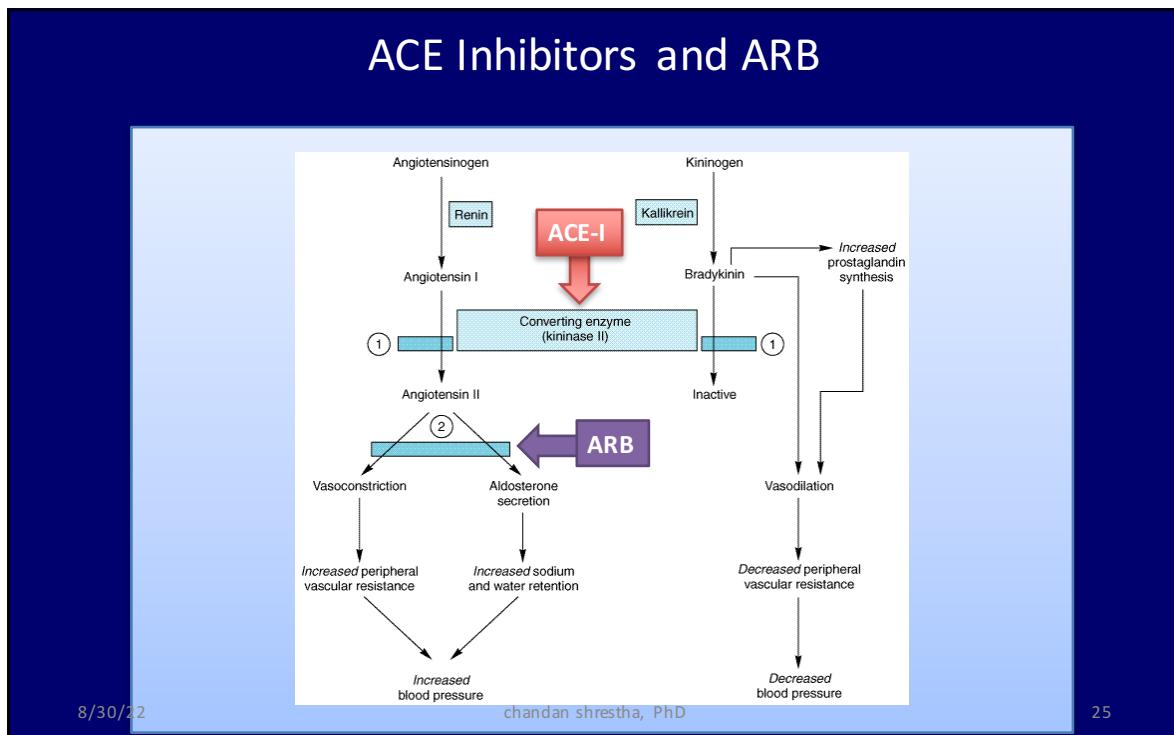
1. Hypertension, especially in diabetes
2. CHF

A/E: Similar to ACE-I; but no cough.

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Beta-Blockers

- These are the drugs that block the action of catecholamine (epinephrine and norepinephrine) on **beta adrenergic receptors.**
- **Three types of Beta Receptor**
 1. **β_1 : Heart and Kidney**
 2. **β_2 : Internal organ** (Lungs, GIT, Liver, Uterus, smooth muscle, skeletal muscles)
 3. **β_3 : Fat cells**

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Effects of Beta-Adrenergic Receptor Stimulation

β_1 Stimulation

Heart

- Positive chronotropic (increasing HR)
- Inotropic (increasing the strength of contraction)
- Increases cardiac conduction velocity

Kidney: release renin

β_2 Stimulation

- Smooth muscle relaxation
- Tremor in skeletal muscle
- Glycogenolysis

β_3 Stimulation

- Induce lipolysis

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Beta-Blockers

Clinical Application

- Young, non obese hypertensive patients.
- Reduced morbidity and mortality
- 1. Angina
- 2. Arrhythmias
- 3. Hypertension (don't reduce blood pressure in normotensive)
- 4. Post MI

Note: Diuretics and Beta blocker used for HTN **increases the risk of Diabetes** while ACE-I and ARB decreases the risk.

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Beta-Blockers

Other considerations

- Beta blockers can impair the relaxation of bronchial muscle-**should be avoided by asthmatics**
- Topically-used to treat glaucoma-decrease IOP by lowering aqueous humor secretion. But diffuses into blood stream and has systemic effects.
- **Miss use by athletes to enhance performances** as they lower HR and reduce tremor.

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A/E of Beta Blockers

- **Bradycardia**
- **orthostatic hypotension**
- **Fatigue and Dizziness**
- **Insomnia and nightmares**
- **Clinical depression**
- **Sexual dysfunction**
- **Increase lipid cholesterol**

Others

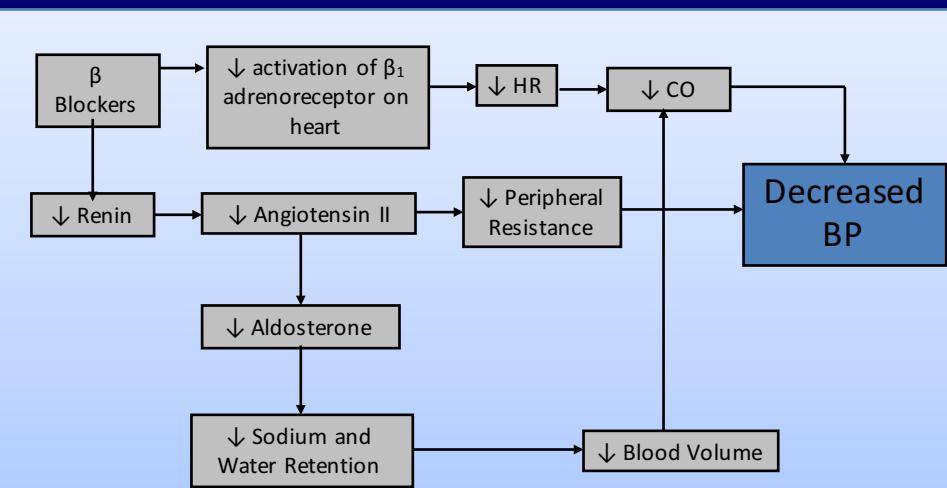
Nausea, Diarrhea, bronchospasm, dyspnea, HF, heart block, abnormal vision, hallucinations.

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Mechanism of action



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CCBs Drugs

Dihydropyridine (Suffix “pine”)

- Nifedipine (5-20mg BD-TDS)
- Amlodipine (5-10 mg OD)

Non-Dihydropyridine

- Phenylalkylamine (verapamil: 40-160 mg TDS)
- Benzothiazepine (diltiazem: 30-60 mg TDS-QID)

Calcium Channel Blockers (CCBs)

MOA: Blocks voltage-dependent, L-type Ca⁺⁺ channels in the heart and in the blood vessels.

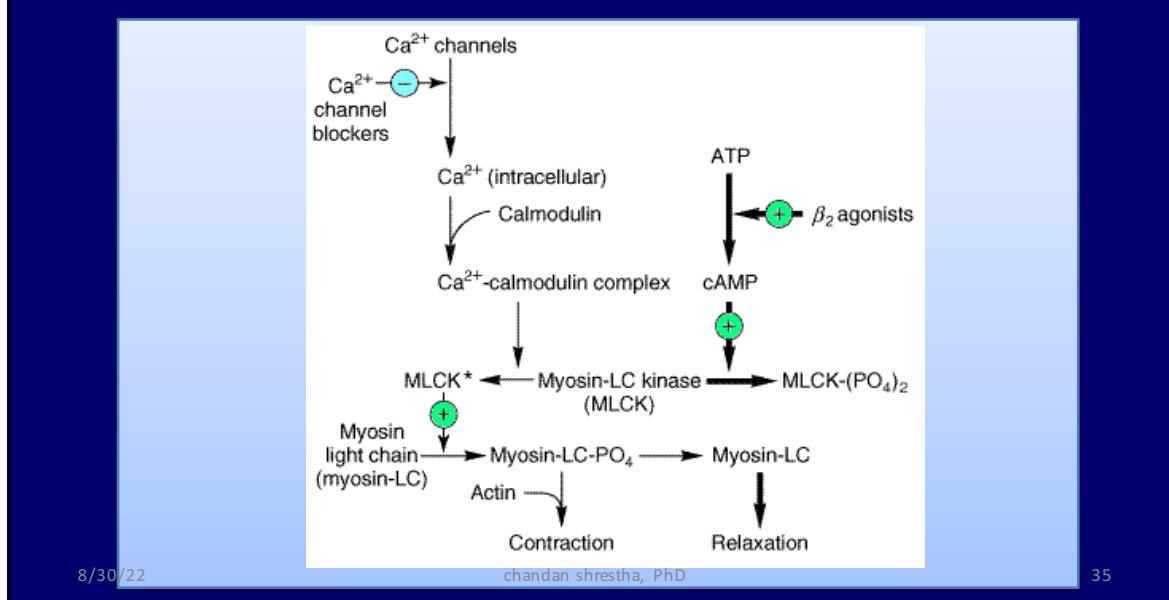
- decrease contraction of heart
- dilated the arteries and
- slow down the conduction of electrical activity

Clinical Application

Elderly patients

- Hypertension
- Angina
- Arrhythmias

Mechanism of action



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A/E of CCBs

Common

- Fatigue
- Swelling of the abdomen, ankles or feet
- Heartburn
- Flushing

Less common

- Numbness or tingling in the hands or feet
- Very fast or very slow heartbeat
- Dizziness
- Upset stomach
- Constipation (especially when taking verapamil)

Rare

- Headache, Chest pain, Fever, Rash

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Diuretics

- First Line Drug Therapy
- Elevate rate of urination and water loss → reduces blood volume → reduces systolic and diastolic pressure → less total pressure in systems
- Do not lower BP in normotensives.
- Thiazides, Loop Diuretics and Potassium sparing Diuretics

Clinical Application

Elderly

- HTN, HF, Liver cirrhosis, Certain kidney diseases

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Thiazides

Hydrochlorothiazide, Chlorthalidone, Indapamide

- Most common

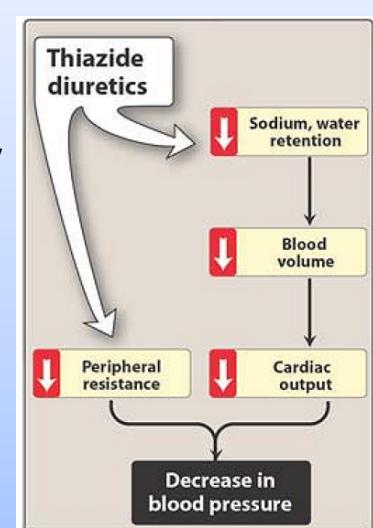
MOA: inhibit sodium reabsorption by blocking Na/Cl transporter in DCT

A/E

- Hypokalemia
- Hyperuricemia
- Hyperglycemia
- Hypomagnesemia

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Loop Diuretics

Furosemide

- Useful in hypertensive patient with moderate or severe renal impairment.
- Used in HTN if response to thiazides is inadequate

MOA: : inhibit sodium reabsorption by blocking $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ transporter in DCT

A/E

- Hypokalemia
- Hyperuricemia

Potassium Sparing Drugs

Spironolactone, Amiloride, Triamterene

- Mild diuresis, lower BP slightly
- Used in combination with other diuretics to prevent potassium loss and augment the antihypertensive action

β and α Adrenergic blockers

Labetalol and Carvedilol

- Blocks both alpha-1 & beta-1 receptors
- Block alpha-1 = dilation of arterioles & veins
- Block beta-1 lead to decreased HR & contractility
- Large doses could block beta-2 receptors → increase in air way resistance - **Do not give to severe asthmatics.**
- A/E : Orthostatic Hypotension, GI upset, nervousness, dry mouth & fatigue
- Labetelol is useful in treatment of hypertension of pheochromocytoma, in pregnant women and hypertensive emergencies.
- Carvedilol: CHF

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Alpha-Adrenergic Blockers

Prazosin

- Blocks α_1 adrenergic receptors → vasodilatation & a decrease in BP
- Minimal effect in cardiac output, renal blood flow, and glomerular filtration rate.
- Useful in clients with lipid abnormalities – decreases VLDL & LDL - responsible for build-up of fatty plaques in arteries & increases HDL (friendly)
- Safe for diabetics (improves carbohydrates metabolism)
- **First Dose Hypotension “Bed Time”**

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Alpha-Adrenergic Blockers

Prazosin

Clinical Application

- Used in HTN, refractory CHF, Benign prostatic hypertrophy (BPH)

A/E

- dizziness, drowsiness, **impotence**, **vertigo**, urinary frequency, tinnitus, dry mouth
- Orthostatic hypotension**, palpitations, **tachycardia**
- Can cause Na & H₂O retention - diuretics may be added
- When taken with ETOH or other antihypertensive agent → severe hypotension

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Centrally Acting Sympatholytics

Clonidine

- Alpha-2 agonist action
- block sympathetic activity within the brain
- Bind and activate alpha₂ (α_2)-adrenoceptors → ↓sympathetic activity → ↓ HR and contractility
- limited use** in the treatment of hypertension.

Clonidine: ↓ NA release

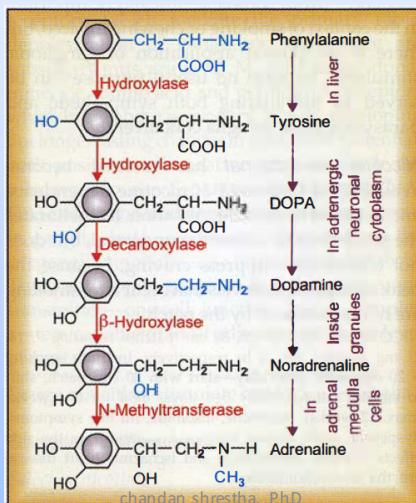
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Centrally Acting Sympatholytics Methyldopa

Methyldopa: false transmitter



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Centrally Acting Sympatholytics Clonidine, Methyldopa

A/E

- Sedation, dry mouth and nasal mucosa, bradycardia, orthostatic hypotension, and impotence.
- Constipation, nausea and gastric upset
- Fluid retention and edema
- Rebound hypertension

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Vasodilator dilate blood vessels (and decrease peripheral vascular resistance) by acting on smooth muscle cells through non-autonomic mechanisms:

* *release of nitric oxide*

(NO stimulates guanylyl cyclase and increase cGMP in smooth muscles → reduction of cytoplasmic Ca^{2+} by causing Ca^{2+} sequestration in the endoplasmic reticulum → relaxation of both Arterioles and venous capacitance vessels, lowering peripheral vascular resistance and reducing cardiac pre- as well as afterload)

* *opening of potassium channels*

(leads to hyperpolarization and relaxation of vascular smooth muscle)

* *blockade of calcium channels*

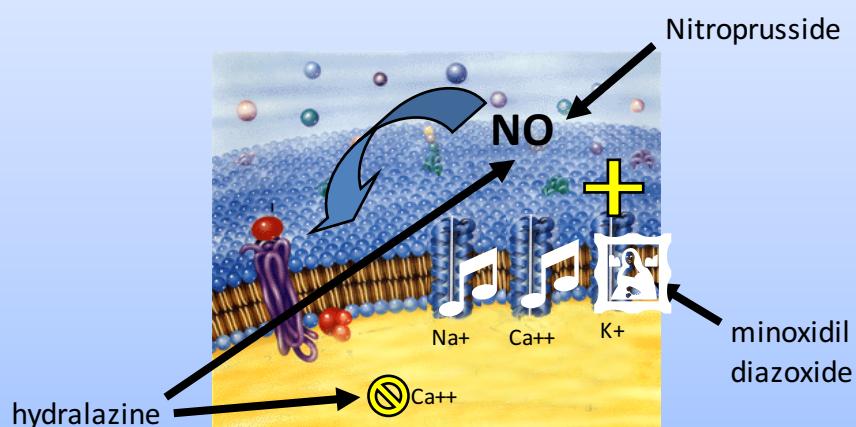
(reduce intracellular calcium concentration → relax arterial smooth muscle, reduce peripheral vascular resistance)

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Vasodilators

- Vasodilators act by producing relaxation of vascular smooth muscle, which decreases resistance and, therefore, BP.



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Renin inhibitor

- A new class of drugs that inhibit action of renin on angiotensinogen, preventing conversion to angiotensin I.
- Act earlier in the RAAS than do ACE-I or ARBs.
- Examples: Aliskiren, Remikiren

A/E

- Angioedema, Hyperkalemia, Hypotension
- Diarrhea and other GI symptoms
- Rash
- Elevated uric acid and gout
- Kidney stones

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Order Treatment

Hypertensive Emergencies

Options	Advantages	Particularly Good For	Disadvantages	Particularly Bad For
Nitroprusside (IV infusion)	Extremely effective Rapid titration	Just about any critically ill patient	Cyanide toxicity Requires unusually close monitoring	Nothing
Nitroglycerin (IV infusion)	Venodilator → ↓ preload Coronary vasodilator	Angina Pulmonary edema	Side effect = headache	Neurologic indications
Labetalol (IV infusion or bolus)	Mixed α and β blockade	Angina	Non-cardioselective ↓ contractility and HR	Pulmonary edema Comorbid asthma/COPD
Esmolol (IV infusion)	↓ contractility and HR Rapid titration	Angina Aortic dissection	↓ contractility and HR (Reflex ↑ SVR)	Pulmonary edema Any condition characterized by primary ↑ in SVR (e.g. pheochromocytoma, autonomic dysreflexia)
Nicardipine (IV infusion)	Prevents cerebral vasospasm	Intracranial hemorrhage Acute ischemic stroke Hypertensive encephalopathy	Possible reflex ↑ HR Possible neg. inotropy	Coronary ischemia? Congestive heart failure?

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Order Treatment

Hypertensive Urgency

Options	Advantages	Particularly Good For	Disadvantages	Particularly Bad For
Hydralazine (IV bolus, or PO)	Nothing specific	Nothing specific	Reflex tachycardia	Aortic dissection Coronary ischemia
Labetalol (IV bolus, or PO)	Mixed alpha and beta blockade	Angina	Non-cardioselective ↓ contractility and HR	Pulmonary edema Comorbid asthma/COPD
Metoprolol (IV bolus, or PO)	↓ contractility and HR	Angina	↓ contractility and HR (Reflex ↑ in SVR)	Pulmonary edema Any condition characterized by primary ↑ in SVR
Clonidine (PO)	Relatively rapid onset for an oral agent (<60 min)	No IV access	Less predictable effect	Hypertensive emergency
Captopril (PO or SL)	Relatively rapid onset for oral agent (<60 min)	No IV access	Less predictable effect	Hypertensive emergency
Nitroglycerin (SL)	Very rapid onset (<15 min)	No IV access Angina	Less predictable effect Can lead to dramatically ↓ BP and CO in dehydrated patients	Dehydrated patients

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Guidelines for selecting the drug treatment of hypertension				
Class of drugs	Compelling indications	Possible indications	Compelling contraindications	Possibly contraindications
Diuretics	Heart failure Old patient Systolic HTN	Diabetics	Gout	Dyslipidemia Sexually active males
Beta blockers	Angina After MI Tachyarrhythmia	Heart Failure Pregnancy Diabetes	Asthma COPD Heart block	Dyslipidemia Athletes PVD
ACE I	Heart failure LV dysfunction Diabetic nephropathy		Pregnancy Hyperkalemia Bilateral Renal artery stenosis	
Calcium antagonist	Angina Old patient Systolic HTN	Peripheral Vascular Disease (PWD)	Heart block CHF	
ARB	ACE I cough			
Alpha blockers	Prostatic hypertrophy	Heart failure Glucose intolerance		Orthostatic hypotension

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Drug Used in Preeclampsia

Methyldopa

Hydralazine

Nefedipine

Labetalol

Magnesium sulphate