Antihypertensive Agents

BLOOD PRESURE

- The **outward pressure of blood against blood vessel wall**
- Product of **blood flow from the heart** and **inward resistance of blood vessel walls**
- **Directly proportional** to cardiac output (CO) and peripheral vascular resistance (PVR)

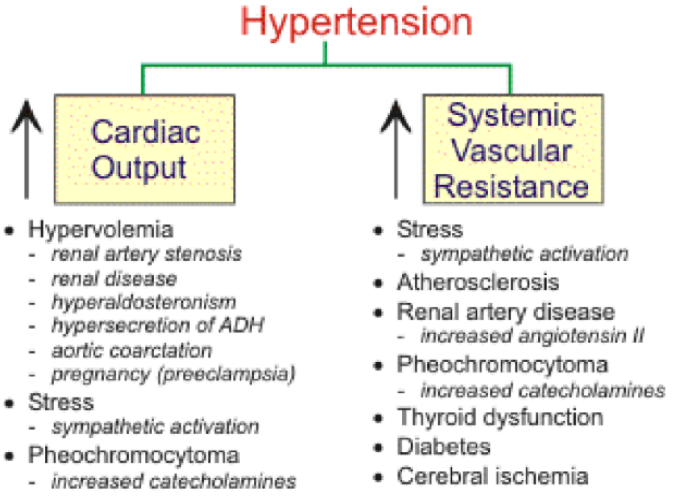
HYPERTENSION

- A sustained **systolic BP** of greater than **140 mm Hg** or a sustained **diastolic BP** of greater than **90 mm Hg**
  - **American Heart Association (AHA)**: >140/90 mm Hg
  - **World Health Organization (WHO)**: >160/95 mm Hg
- **ESSENTIAL/PRIMARY HTN** - **no specific cause**; heritability is 30%
- **SECONDARY HTN** - with a **specific etiology** *(renal artery constriction, coarctation of the aorta, pheochromocytoma, Cushing's disease, and primary aldosteronism)*; **multifactorial**

CLASSIFICATION OF HYPERTENSION			
JOINT NATIONAL COMMITTEE		**ACC/AHA GUIDELINES**	
< 120/80	Normal	< 120/80	Normal
120-135/80-89	Pre-HTN	120-129/< 80	Pre-HTN
≥ 140/90	HTN	130-139/80-89	Stage 1
140-159/90-99	Stage 1 HTN	≥140/90	Stage 2
≥ 160/100	Stage 2 HTN	≥ 180/120	Hypertensive Crisis

COMPLICATIONS OF HYPERTENSIONS

- **HEART:** Coronary Heart Disease (CHD), Heart Failure (HF), Left Ventricular Hypertrophy (LVH), Cardiomyopathy
- **KIDNEY:** Renal Disease/Failure
- **ARTERY:** Coronary Artery Disease (CAD), Atherosclerosis, Aneurysm, Peripheral Vascular Disease (PVD)
- **BRAIN:** Ischemic Stroke, Stroke
- **EYES:** Retinal Disease



BLOOD PRESSURE REGULATION

1. **RESISTANCE ARTERIOLES** - responsible for controlling blood flow
   - Constriction: ↓ space to pass → resistance → ↑ BP
   - Dilation: ↑ space to pass → ↓ BP

2. **CAPACITANCE VENULES** - responsible for storing blood
    - Constriction: more blood to pump → ↑ BP
    - Dilation: blood stays in the heart → ↓ pump → ↓ BP
3. **PUMP HEART OUTPUT** - faster → ↑ BP
4. **VOLUME KIDNEYS** - ↑ water → ↑ blood volume → ↑ CO → ↑ BP

All actions in the anatomic sites are **directly proportional to blood pressure**.

MECHANISMS OF BLOOD PRESSURE REGULATION

- **BARORECEPTOR REFLEX ARCH** - responsible for **rapid, moment-to-moment adjustments in BP**, such as in transition from a reclining to an upright posture
- **RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM** - **common** esp. in secondary HTN; by controlling blood volume, the **kidney is primarily responsible for long-term BP control**

BARORECEPTOR REFLEX ARCH

1. Change in BP is detected by baroreceptors
2. Baroreceptors sends out signals to the brain
3. Brain changes sympathetic and parasympathetic activity
4. Heart and blood vessels responds, causing BP to return normal

Increasing Pressure

↓ of BP → less stretch of aortic arch and carotid sinus (baroreceptors) → less signals goes to IX (afferent; glossopharyngeal nerve) and X (efferent; vagus nerve; from aortic arch) → ↓ vasomotor center activity → ↑ sympathetic activity, ↓ parasympathetic activity → ↑ heart rate and vasoconstriction → ↑ CO and PVR → ↑ BP

Decreasing Pressure

↑ BP → more stretch of aortic arch and carotid sinus (baroreceptors) → more signals goes to IX (afferent) and X (efferent) → ↑ vasomotor center activity → ↓ sympathetic activity, ↑ parasympathetic activity → ↓ heart rate and vasodilation → ↓ CO and PVR decreases = ↓ BP

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

1. Kidneys release **renin** in response to low BP
2. Renin acts on **angiotensinogen** from the liver and converts it into **Angiotensin I (Ang I)**
3. **Angiotensin-Converting Enzyme (ACE)** converts Ang I to **Angiotensin II (Ang II)**
4. Angiotensin produces the following effects:
    a. ↑ sympathetic activity
    b. ↑ tubular NaCl reabsorption, K^+ secretion, Water retention
    c. ↑ arteriolar vasoconstriction = ↑ BP
    d. ↑ ADH secretion
    e. ↑ Aldosterone secretion

TREATMENT OF HYPERTENSION

THERAPEUTIC GOALS

- Reduction of the sign itself by drugs whose mechanisms of action at the system level are altered:
    - blood volume
    - cardiac output
    - peripheral vascular resistance
- Limit development of subsequent organ pathology

MAJOR CLASSES OF ANTI-HTN AGENTS

1. **Diuretics**
2. **Sympathogenic Agents**
3. **Direct Vasodilators**
   - Older Oral Vasodilators *(Hydralazine)*
   - Calcium Blockers *(Nifedipine)*
   - Parenteral Vasodilators *(Nitroprusside)*
4. **Angiotensin Antagonist/Modifiers**
5. **Renin Inhibitor**
   - Aliskiren

DRUGS ACTING ON THE VASCULAR SMOOTH MUSCLE:
Hydralazine, Minoxidil, Nitroprusside, Diazoxide, Fenoldopram, Verapamil and other calcium channel blockers

ANTI-HTN DRUGS

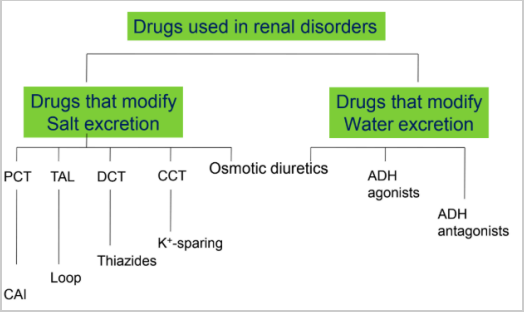
CHOICE OF ANTI-HTN DRUGS

Drugs	Physiologic Play-back Mechanisms	Appropriate Drug combinations
Furosemide Chlorothiazide	Increase renin-angiotensin-aldosterone axis	β-blocker ACE inhibitors
Clonidine Methyldopa	Increase fluid retention	Diuretics
Reserpine Guanethidine	Increase fluid retention	Diuretics
Beta-blockers	Increase plasma volume	Diuretics
Vasodilator	Increase reflex sympathetic stimulation Renin-angiotensin-aldosterone axis	β-blocker Diuretics
ACE inhibitors	No physiologic play-back mechanisms	

PATIENTS	CHOICE OF TREATMENT	AVOID
CKD + Diabetes	Angiotensin Antagonist (to delay diabetic nephropathy	
CAD	Beta-blocker, Calcium Antagonist	Hydralazine (may cause heart attack and angina)
CHF	ACEIs and/or Diuretics	Beta-blocker, Calcium Antagonist
Athletes		Beta-blockers and Diuretics
Broncho-pulmonary DX	Calcium Antagonist	Beta-blocker
Dyslipidemia		Beta-blocker and Thiazide Diuretics
PV DX	Calcium Antagonist (Nifedipine), Vasodilators or ACEIs	Beta-blocker
End-stage Renal DX	Calcium Antagonist, Diuretics and Centrally-acting Agents	Caution on ACEIs
Stroke	ACEIs and/or Diuretics	
Elderly PX	Diuretics (lower dose)	Be wary on pseudohypertension wherein elevated BP is due to brachial artery atherosclerosis and not HTN per se

DIURETICS

Lower blood pressure by **depleting the body of sodium and reducing blood volume** and perhaps by other mechanisms.



Drug Group	NaCl	$NaHCO_3$	K^+	Ca^{2+}	Body pH
CAI	↑	↑↑↑	↑	–	Acidosis
Loop	↑↑↑↑	-	↑	↑↑	Alkalosis
Thiazides	↑↑	↑	↑	↓↓	Alkalosis
K^+-Sparing	↑	(+)	↓	–	Acidosis

TYPE	SITE OF ACTION	NORMAL PHYSIOLOGY	MECHANISM OF ACTION	CLINICAL USES	EXAMPLES
Carbonic Anhydrase Inhibitors	Proximal Convoluted Tubule (PCT)	**Reabsorption of HCO_3^- occur in PCT** 1. Na^+ enters PCT through Na^+/H^+ exchanger, where: a. Na^+ (Lumen) → Cell b. H^+ (Cell) → Lumen 2. H^+ combines with HCO_3^- in the lumen to form **Carbonic Acid (H_2CO_3)** 3. **Carbonic anhydrase (CA)** in the lumen breaks carbonic acid down into **CO_2 + H_2O** 4. CO_2 enters PCT, and is converted back into H_2CO_3 by the intracellular CA 5. HCO_3^- dissociates into H^+ and HCO_3, where: a. H^+ can be used again b. HCO_3^- is transported into the blood	**Inhibition of Carbonic anhydrase (CA)** CA Inhibition → ↓ **HCO_3^- reabsorption** (Na^+ reabsorption will also decrease) → HCO_3^- and Na^+ will remain in the urine → Water follows Na^+ and HCO_3^- → ↑ urine output	• **Glaucoma** ○ CAIs **reduce aqueous humor formation** = decrease IOP • **Urinary alkalinization** • **Metabolic alkalosis** • **Acute mountain sickness** ○ CAIs decrease CSF formation and the pH of CSF and brain = increase ventilation and diminish symptoms of mountain sickness • **Adjuvants** in the treatment of **epilepsy** • Increase **urinary phosphate excretion** during **severe hyperphosphatemia**	**Acetazolamide** Brinzolamide Dorzolamide

Loop Diuretics	Thick Ascending Limb (TAL)	**Reabsorption of Na^+, K^+, and $2Cl^-$ occur in TAL** 1. TAL reabsorbs Na^+, K^+, and $2Cl^-$ through the **NKCC2 cotransporter** from the lumen into the epithelial cell 2. Na^+ is pumped out of the cell into the blood by the **Na^+/K^+ ATPase** 3. Some K^+ goes back into the lumen, creating a **positive electrical charge** 4. Cations such as **Ca^{2+} and Mg^{2+}** can be reabsorbed	**Inhibition of Na^+, K^+, and $2Cl^-$ cotransporter (NKCC2)** NKCC2 Inhibition → ↓ **Na^+, K^+, $2Cl^-$, Ca^{2+} and Mg^2 reabsorption** → Na^+ will remain in the urine → Water follows Na^+ and → ↑ urine output	• For **severe** hypertension • **Acute Pulmonary edema** and other **edematous** condition • Acute **hypercalcemia** • **Hyperkalemia** • **Acute Renal Failure** • **Anion overdose**	Ethacrynic Acid Bumetanide **Furosemide** Torsemide Muzolamide
Thiazide Diuretics	Distal Convoluted Tubule (DCT)	**Reabsorption of Na^+ and Cl^- occur in DCT** 1. DCT reabsorbs Na^+ and Cl^- through the **NCC** 2. Na^+ is pumped out of the cell into the blood by the **Na^+/K^+ ATPase** 3. Na^+ + Cl^- are reabsorbed, causing water retention	**Inhibition of Na^+-Cl^- cotransporter (NCC)** NCC Inhibition → ↓ **Na^+ and Cl^- reabsorption** → Na^+ will remain in the urine → Water follows Na^+ → ↑ urine output **NOTE: Thiazides ↑ Ca^{2+} reabsorption**	• For **mild to moderate** hypertension • Mild heart failure • **Chronic calcium stone formation** • **Nephrogenic diabetes insipidus**	Hydroclorothiazide **Chlorthiazide** Chlorthalidone Metolazone Indapamide
Potassium -Sparing Diuretics	Collecting Tubule	1. **Aldosterone** acts on **principal cells** and increases the following activities: a. **ENaC** → allows Na^+ to	**Aldosterone Antagonists** Blocks aldosterone receptor	• Useful both to **avoid excessive potassium depletion** and enhance the natriuretic effects of other diuretics • Hyperaldosteronism ○ Primary – Conn's syndrome,	**Aldosterone Antagonist: Spironolactone** Eplerenone

		enter the cell from urine b. **Na^+/K^+ ATPase** → moves Na^+ into blood c. **K^+ secretion** into urine **NOTE: Potassium-sparring Diuretics decreases K^+ secretion which can cause hyperkalemia**	↓ ENaC, Na^+/K^+ ATPase Activity → ↓ **Na^+ influx and reabsorption** → Na^+ will remain in the urine → Water follows Na^+ → ↑ urine output **ENaC Blockers** ENaC Inhibition → ↓ **Na^+ reabsorption** → Na^+ will remain in the urine → Water follows Na^+ → ↑ urine output	ectopic ACTH production ○ Secondary – evoked by heart failure, hepatic cirrhosis, nephrotic syndrome • Alternative to loop and thiazide diuretics, if K+ wasting is to be avoided • Eplerenone – reduce myocardial perfusion defects • Amiloride – Liddle's syndrome • Finerenone – Cardioprotectant	**ENaC Blockers:** Triamterene **Amiloride**
Osmotic Diuretics	Descending Loop of Henle	**Reabsorption of water occurs along the nephron, especially in the PCT and descending limb** 1. Water is normally reabsorbed from the tubular fluid into the blood due to osmotic gradients.	Osmotics remains in the tubular lumen → ↑ osmolarity → ↑ solute in the tubular fluid → ↑ water retention → ↑ urine output	• Increase urine volume • Reduction of ICP and IOP	Mannitol Urea Isosorbide
ADH Antagonists	Collecting Duct	**Reabsorption of water occurs in the collecting duct through ADH** 1. **ADH (vasopressin)** binds to the **V_2 receptor** on the collecting duct epithelial cell. 2. V_2 receptor activation increases **cAMP**, which signals the cell to insert **Aquaporin-2 (AQP2) channels** into the membrane. 3. **Aquaporin-2 allows water to move** from the lumen into the epithelial cell.	**Inhibition of ADH action at the V_2 receptor** V_2 receptor inhibition → ↓ cAMP → ↓ Aquaporin-2 channels → ↓ water reabsorption → Water remains in the urine → ↑ water excretion/urine output	• To manage SIADH (Syndrome of Inappropriate ADH) • Used in other conditions where there is elevated ADH (CHF) • Autosomal Dominant Polycystic Kidney Disease	Demeclocycline Lithium Conivaptan Tolvaptan Lixivaptan Satavapytan

		4. Water then moves into the **blood**, resulting in **water reabsorption** and concentrated urine.			

OTHER INFORMATION

OTHER DIURETICS:

- **XANTHINE DIURETICS** *(Caffeine, Theobromine, Theophylline)*
  - Caffeine - weak diuretic; nonspecifically and weakly blocks adenosine receptors that participate in the control of proximal tubule Na+ reabsorption
- **UREARETICS**
  - **UT-A** - located in the **inner medullary collecting duct** and **thin descending limb**
  - **UT-B** - located in the **descending vasa recta**
  - Aquaretics that **increase urea and water excretion** but not sodium excretion; these agents may prove to be useful in **edematous states** and even in SIADH
- **SODIUM GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS** - weak diuretic; third-line therapy for diabetes mellitus
- **MERCURICAL DIURETICS** *(Mercaptomerin)*
- **ACIDIFYING SALTS** *(Ammonium Chloride)*
- **ADH AGONIST** (*Vasopressin and Desmopressin)*

DIURETIC COMBINATIONS:

- Loop diuretics and Thiazides
  - Can mobilize a large amount of fluid
  - K^+-wasting
- Loop agents or thiazides and Potassium sparing

ADVERSE EFFECTS:

Furosemide	**Metabolic alkalosis, hypokalemia, hypocalcemia, hypovolemia, hypotension, hypomagnesemia,** hyperuricemia, ototoxicity
Chlorthiazide	**Metabolic alkalosis, hypokalemia, hypocalcemia, hypovolemia, hypotension, hypocalcemia, hypomagnesemia,** hyperuricemia, hyperglycemia, hyperlipidemia
Spironolactone	**Metabolic acidosis, hyperkalemia**, menstrual disorders, impotence, gynecomastia, loss of libido, hirsutism, acute renal failure (triamterene + indomethacin), kidney stones (with triamterene)
OD	Extracellular volume expansion, dehydration, hyperkalemia, hypernatremia hyponatremia (when used with patient with diminished renal function), acu renal failure
ADHs	Nephrogenic diabetes insipidus, renal failure, dry mouth and thirst

CLINICAL USES

EDEMATOUS STATE

- Edema associated with Heart failure
- Kidney disease and renal failure
- Hepatic cirrhosis
- Idiopathic edema

NON-EDEMATOUS STATE

- High salt intake resulting to Hypertension
- Nephrolithiasis
- Hypercalcemia
- Diabetes Insipidus
- Renal & cardiac protection

SYMPATHOPLEGICS

Lower blood pressure by **reducing peripheral vascular resistance, inhibiting cardiac function, and increasing venous pooling in capacitance vessels.**

NORMAL PHYSIOLOGY	1. Sympathetic nerves releases **Norepinephrine** 2. NE binds to receptors that produces the following effects: a. ↑ HR b. ↑ CO c. ↑ PVR d. ↑ Contractility e. Vasoconstriction	
TYPE	**MECHANISM OF ACTION**	**EXAMPLES**
Centrally Acting Sympathoplegic Drugs	**α_2 receptor activation** → ↓ sympathetic activity → ↓ NE release → ↓ HR, contractility, CO, vasodilation, PVR	**Methyldopa** • Converted to α-methyldopamine and α-methylnorepinephrine • Potential advantage is that it causes reduction in renal vascular resistance • TX HTN during pregnancy (Category B) **Clonidine** • Initial effect: Brief hypertension • Prolonged effect: Hypotension • Taken sublingually; used for sudden rise of BP **Guanabenz** **Guanfacine**
Adrenergic Neuron-Blocking Agents	**NE release inhibition → ↓ postganglionic sympathetic activity →** ↓ HR, contractility, vasodilation	**Guanethidine** • Rarely used because of its toxicity (pharmacologic sympathectomy) ○ Marked postural hypotension, diarrhea, and impaired ejaculation **Guanadrel** (Guanethidine-like drug) **Reserpine** • Alkaloid from *Rauwolfia serpentina* • First drug used in large scale for treatment of hypertension (rarely used today) • Low doses: little postural hypotension • High doses: sedation, lassitude, nightmares and severe mental depression • Extrapyramidal effects (less frequent): Parkinsonism (Common)

	Pharmacologic actions	Toxicity/Undesirable effects
METHYLDOPA	• decrease PVR • variable reduction in HR and CO • reduce renal vasculature resistance (adv.)	• sedation • nightmares, vertigo, and extrapyramidal signs* • lactation* • Positive Coomb's test
CLONIDINE	• ↓ BP due to ↓ CO and decr. PVR • decr. renal vasculature resistance • reduce BP in supine position, rarely cause postural hypotension (same as methyldopa)	• dry mouth and sedation are common • Should not be given to patients who are at risk for mental depression

<table>
<tr><td></td><td></td><td colspan="3">• Contraindicated to patient with gastric ulcer
• Produces GI cramps, increases gastric acid secretion, and mild diarrhea</td></tr>
<tr><td>Ganglion-Blocking Agents</td><td>Blocked nicotinic receptors → ↓ autonomic nerve function → ↓ sympathetic activity → ↓ HR, contractility, CO, vasodilation, PVR</td><td>Mecamylamine
Trimethaphan
Hexamethonium</td><td colspan="2"><u>ADVERSE EFFECTS OF GANGLIONIC BLOCKERS</u>

Tissues predominantly under parasympathetic (cholinergic) tone

• Myocardium (atrium; S-A node) – Tachycardia
• Eye (Iris; Ciliary muscle) – Mydriasis
• GI tract – decrease in tone and motility; constipation
• Urinary bladder – urinary retention
• Salivary gland – dry mouth

Tissues predominantly under sympathetic (adrenergic) tone

• Myocardium (ventricles) – decrease in contractile force
• Arterioles – increase in peripheral blood flow; hypotension
• Veins – pooling of blood; decrease in venous return; decrease in cardiac output
• Sweat glands – decrease in secretion</td></tr>
<tr><td>Adrenoreceptor Antagonists</td><td>Blocked adrenergic receptors = NE cannot bind → ↓ sympathetic activity → ↓ HR, contractility, CO, vasodilation, PVR</td><td colspan="3">β1-selective blockers — Bisoprolol, Betaxolol, Esmolol (9-10 minute HL - IV Infusion; used for intraoperative and postoperative HTN), *Acebutolol, *Metoprolol (*Cardioselective)
Atenolol, Nebivolol
Non-selective β-adrenergic antagonists — Nadolol, Sotalol, Timolol, Propanolol
β-blockers with ISA — Acebutolol, Pindolol
β-blockers with α-blocking capacity — Labetalol, Carvedilol (Mixed Antagonists)
Long half-lives — Nadolol, Carteolol, Bisoprolol, Betaxolol
Partial agonists with ISA — Pindolol, Acebutolol, Penbutolol
β-blocking and vasodilating effects — Labetalol, Carvedilol, Nebivolol (not mediated by alpha blockade)
α blockers — Prazosin, Phentolamine, Phenoxybenzamine (activate RAAS, causing fluid retention; cause first-dose phenomenon)</td></tr>
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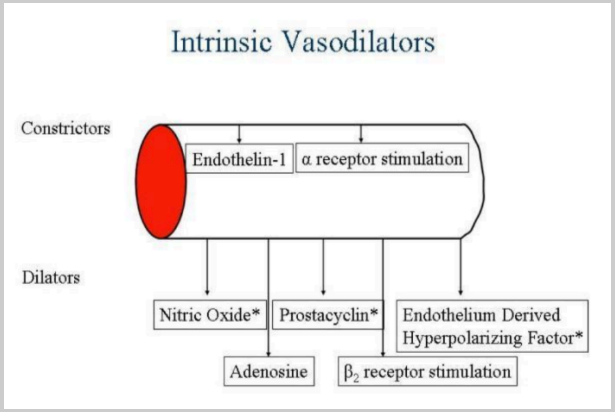
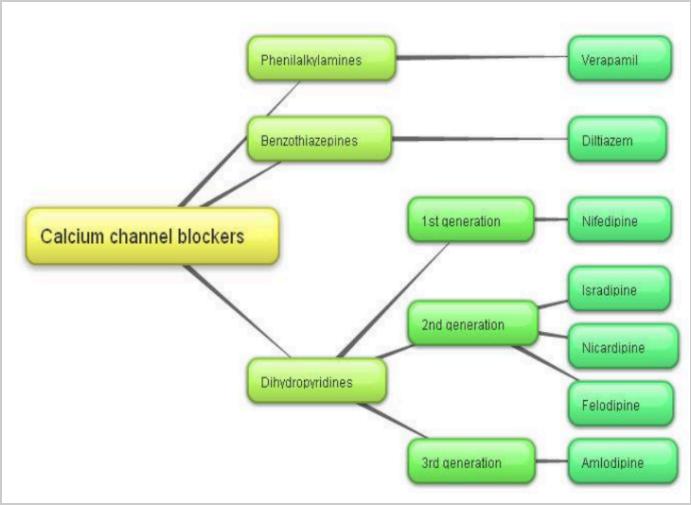
VASODILATORS

Reduce pressure by **relaxing vascular smooth muscle,** thus dilating resistance vessels and—to varying degrees—**increasing capacitance** as well.



Mechanism of Vasodilation	Drug
Release of nitric oxide (from drug or endothelium)	Hydralazine, Nitroprusside, Nitrates, Histamine, Acetylcholine
Opening of potassium channels and hyperpolarization	Minoxidil, Diazoxide
Block L-type calcium channels	Calcium channel blockers (Nifedipine, Diltiazem, Verapamil)
Activation of dopamine receptors	Fenoldopam



TYPE	NORMAL PHYSIOLOGY	MECHANISM OF ACTION	CLINICAL USES	EXAMPLES
Calcium Channel Blockers	**Ca^{2+} enters vascular smooth muscle cells through L-type Ca^{2+} channels** 1. Ca^{2+} enters the vascular smooth muscle cell through L-type Ca^{2+} channels. 2. Ca^{2+} binds to calmodulin, activating myosin light-chain kinase (MLCK). 3. MLCK promotes interaction between actin and myosin, causing smooth muscle contraction. 4. Contraction of vascular smooth muscle causes vasoconstriction → ↑ PVR → ↑ BP.	**Inhibition of L-type Ca^{2+} channels** L-type Ca^{2+} channel inhibition → ↓ Ca^{2+} entry → ↓ smooth muscle contraction → vasodilation → ↓ PVR → ↓ BP	● Hypertension ● Angina ○ Prophylactic therapy in both effort and vasospastic angina ○ Abort acute anginal attacks ○ Atherosclerotic angina – in combination with nitrates ● Supraventricular tachycardia ○ Verapamil, diltiazem (not FDA approved) ● Migraine ● Preterm labor ● Stroke ● Hemorrhagic stroke associated with subarachnoid hemorrhage – ● Raynaud's syndrome	1st Generation: (Non-dihydropyridines except Nifedipine – cardioselective; intermediate effects) Diltiazem *(intermediate action)* Verapamil (*greatest depressant effect on the heart)* Bepridil Nifedipine *(dihydropyridine; ultra short acting used in emergency management of severe hypertension)* 2nd Generation: (Dihydropyridines – vasoselective) Amlodipine Felodipine Isradipine Nicardipine Nisoldipine Nimodipine Clevidipine

Arteriolar (Direct) Vasodilators	1. Contraction of arteriolar smooth muscle causes vasoconstriction 2. Vasoconstriction increases the resistance against blood flow, causing ↑ PVR → ↑ BP.	**Direct relaxation of arteriolar smooth muscle** Direct arteriolar vasodilation → ↓ PVR → ↓ BP		**Hydralazine** ● Dilates arterioles but not veins ● Effective in severe hypertension ● When combined with nitrates, it is effective in heart failure ● **Minoxidil** ● Orally active vasodilator ● Dilates arterioles but not veins ● Used topically as a stimulant to hair growth for correction of baldness **Diazoxide** ● Effective and relatively long-acting parenterally administered arteriolar dilator ● Occasionally used to treat hypertensive emergencies ● Also used to treat hypoglycemia secondary to insulinoma

Arterial And Venous (Nonselective) Vasodilators	1. Contraction of arterial and venous smooth muscle increases BP	**Direct relaxation of arterial and venous smooth muscle** Arterial + venous vasodilation → ↓ PVR → ↓ BP		Sodium Nitroprusside ● Parenterally administered vasodilator ● Dilates both arterial and venous vessels ● Reduced peripheral vascular resistance and venous return Organic nitrates α–adrenoceptor blockers

OTHER INFORMATION

VASODILATION BY NO

NO causes vascular smooth muscle relaxation

1. **Nitric oxide (NO)** enters the vascular smooth muscle cell.
2. NO activates **guanylyl cyclase (GC).**
3. Guanylyl cyclase converts **GTP → cGMP.**
4. ↑ cGMP causes vascular smooth muscle relaxation.
5. Smooth muscle relaxation causes vasodilation → ↓ PVR → ↓ BP.

Activation of NO–cGMP pathway

NO → ↑ guanylyl cyclase → GTP → ↑ cGMP → smooth muscle relaxation → vasodilation → ↓ PVR → ↓ BP

FENOLDOPAM: D1 RECEPTOR AGONIST

- Dilation of peripheral arteries*
- **D1 receptor activation** in the renal vasculature may also induce natriuresis
- Used for **hypertensive emergencies and postoperative hypertension**
- Half-life is 10 minutes (Administered by continuous **IV infusion**)
- Toxicities
  - Reflex tachycardia
  - Headache and flushing
  - Increases IOP

ADVERSE EFFECTS

Calcium Channel	Constipation, Pretibial edema, Dizziness, nausea and vomiting, Flushing, fatigue, confusion, Allergic reactions With verapamil - bradycardia, CHF, AV block, sinus node depression

Blockers	With Bepridil - torsade de pointes (an uncommon and distinctive form of polymorphic ventricular tachycardia (VT) characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line)
Minoxidil	Edema due to sodium and water retention, Reflex tachycardia, flushing, Headache, Hirsutism/Hypertrichosis
Hydralazine	Lupus-like syndrome, Cardiovascular effects (Hypotension, Reflex tachycardia, Palpitation, Angina), CNS effects (headache, nausea, anorexia)
Sodium Nitroprusside	Hypotension, Metabolic acidosis, Arrhythmias, Methemoglobinemia may also develop during infusion, Accumulation of Cyanide* Cyanide Toxicity TX: ● Sodium thiosulfate - A sulfur donor that facilitates the metabolism of cyanide (by rhodanase enzyme) into less toxic thiocyanate ○ May accumulate (thiocyanate) over prolonged administration characterized by weakness, ● Hydroxocobalamin combines with cyanide*
Diazoxide	Excessive hypotension, Reflex tachycardia. Hyperglycemia (inhibit insulin release)

ANGIOTENSIN ANTAGONISTS

Reduce peripheral vascular resistance and (potentially) blood volume.

TYPE	NORMAL PHYSIOLOGY	MECHANISM OF ACTION	CLINICAL USES	EXAMPLES
Angiotensin-Converting Enzyme Inhibitors (ACEIs)	**ACE converts Angiotensin I → Angiotensin II** 1. Renin converts angiotensinogen → Angiotensin I (Ang I). 2. ACE converts Ang I → Ang II 3. Ang II binds to AT_1 receptors → vasoconstriction → ↑ PVR → ↑ BP 4. Ang II also stimulates aldosterone secretion.	**Inhibition of Angiotensin-Converting Enzyme (ACE)** ACE inhibition → ↓ Ang II formation + ↑ bradykinin → ↓ vasoconstriction + ↓ aldosterone → ↓ PVR + ↓ Na^+/water retention → ↓ blood volume → ↓ BP	● Mild to moderate hypertension ● Can be used safely in ischemic heart disease patients ● Most effective in conditions associated with high renin activity	Captopril Enalapril *(A prodrug converted to enalaprilat)* Lisinopril Alacepril Cilazapril Zopenopril Benazepril Fosinopril Moexipril Perindopril

	5. Aldosterone causes ↑ Na^+ reabsorption, and water follows → ↑ blood volume → ↑ BP 6. ACE also normally breaks down bradykinin. 7. Therefore, ACE inhibition causes ↑ bradykinin, which promotes vasodilation.		• Useful in treating patients with chronic kidney disease • CHF • Diabetes mellitus	Quinapril Ramipril Randolapril
Angiotensin II-Receptor Blockers	**Angiotensin II binds to AT_1 receptors → vasoconstriction and aldosterone secretion** 1. Angiotensin II (Ang II) normally binds to AT_1 receptors on vascular smooth muscle. 2. AT_1 receptor stimulation causes vasoconstriction. 3. Vasoconstriction causes ↑ peripheral vascular resistance (PVR) → ↑ BP. 4. Ang II also stimulates aldosterone secretion from the adrenal cortex. 5. Aldosterone causes ↑ Na^+ reabsorption in the kidney → water follows Na^+ → ↑ blood volume → ↑ BP.	**Inhibition of Angiotensin II binding to AT_1 receptors** AT_1 receptor blockade → ↓ vasoconstriction + ↓ aldosterone secretion → ↓ PVR + ↓ Na^+/water retention → ↓ blood volume → ↓ BP	• In patients with heart failure and chronic kidney disease	Saralasin Losartan Valsartan Telmisartan Olmesartan Irbesartan Candesartan Eprosartan Azilsartan
Renin Inhibitor	**Renin converts angiotensinogen → Angiotensin I** 1. When BP or renal perfusion decreases, the kidney releases renin.	**Inhibition of Renin** Renin inhibition → ↓ Angiotensin I formation → ↓ Angiotensin II → ↓ vasoconstriction + ↓	**<u>Cardiorenal Effects of Renin Inhibitors</u>** • Vasodilation (arterial & venous)	**Aliksikren** • Approved for TX HTN by the US FDA in 2007

	2. Renin acts on angiotensinogen. 3. Angiotensinogen is converted into Angiotensin I. 4. Ang I is then converted into Ang II by ACE. 5. Ang II causes: a. Vasoconstriction → ↑ PVR → ↑ BP b. Aldosterone secretion → ↑ Na^+/water retention → ↑ blood volume → ↑ BP	aldosterone → ↓ PVR + ↓ Na^+/water retention → ↓ blood volume → ↓ BP	○ reduce arterial & venous pressures ○ reduce ventricular afterload and preload ● Decrease blood volume ○ Natriuretic ○ Diuretic ● Depress sympathetic activity ● Inhibit cardiac and vascular hypertrophy	● Orally active, half-life of about 24 hours (once daily dosing) ● Side effects ○ GI disturbances ○ Cough and angioedema (lesser incidence than ACEIs and ARBs) ○ Hyperkalemia

OTHER INFORMATION

ADVERSE EFFECTS

ARBs Hemophilia, Headache, Fever, Hyperkalemia, Allergy, Orthostatic hypotension, Cough and Angioedema* (Bradykinin and Substance P seems to be responsible), Renal damage in nondiabetic renal vascular disease, Teratogenic* = Fetal hypotension, anuria, and renal failure, Hypotension, Hyperkalemia*, Altered taste, allergic skin rashes, and drug fever in 10% of patients

ACEIs DRUG INTERACTION: Potassium-sparing Diuretics – hyperkalemia
DRUG INTERACTION: NSAIDs – May impair the hypotensive effects of ACE inhibitors by blocking the bradykinin-mediated vasodilation (partly prostaglandin mediated)