Drugs Acting on Cardiovascular System

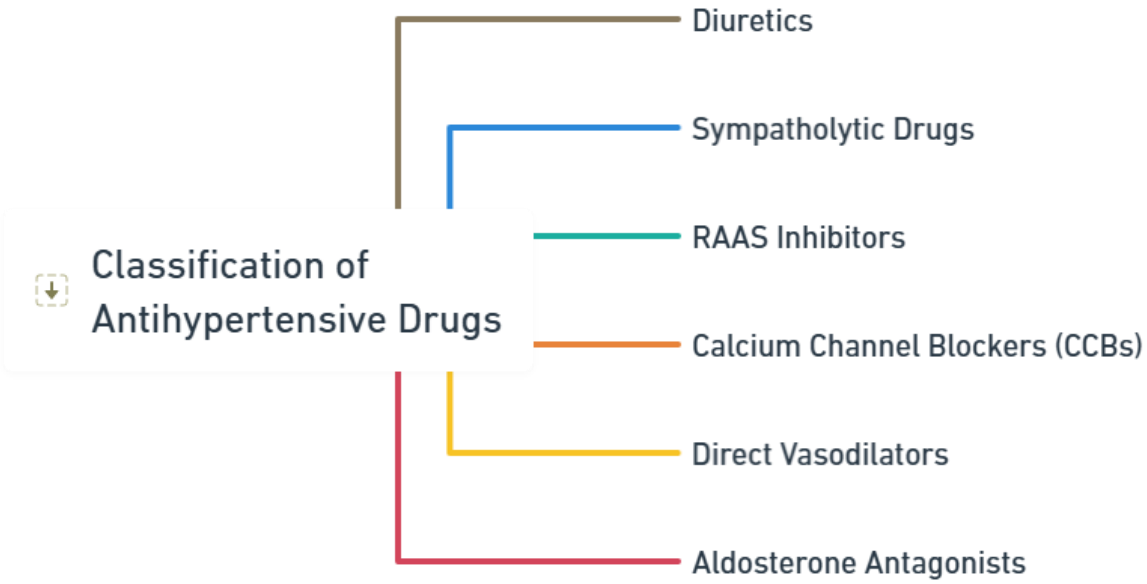
Anti-Hypertensive Drugs

Introduction

- **Hypertension** is defined as a sustained increase in arterial blood pressure. Persistent hypertension can lead to serious complications such as stroke, myocardial infarction, renal failure, and heart failure.
- Antihypertensive therapy aims to reduce morbidity and mortality by lowering blood pressure and preventing target organ damage.
- Blood pressure is determined by:
    - **Cardiac output (CO)**
    - **Peripheral vascular resistance (PVR)**
- Thus, drugs that reduce CO and/or PVR can lower blood pressure. Antihypertensives work by:
    - Decreasing blood volume
    - Suppressing sympathetic nervous system activity
    - Causing vasodilation
    - Inhibiting the renin-angiotensin-aldosterone system (RAAS)

Classification

Antihypertensives are classified based on their mechanism of action:



A. Diuretics

- **Thiazide diuretics**: Hydrochlorothiazide, Chlorthalidone
- **Loop diuretics**: Furosemide, Bumetanide
- **Potassium-sparing diuretics**: Spironolactone, Amiloride, Eplerenone

B. Sympatholytic Drugs

- **Centrally acting alpha-2 agonists**: Clonidine, Methyldopa
- **Beta-blockers**: Atenolol, Metoprolol, Propranolol
- **Alpha-1 blockers**: Prazosin, Terazosin
- **Combined alpha and beta-blockers**: Labetalol, Carvedilol

C. RAAS Inhibitors

- **ACE inhibitors**: Enalapril, Lisinopril, Ramipril
- **Angiotensin II receptor blockers (ARBs)**: Losartan, Valsartan
- **Direct renin inhibitors**: Aliskiren

D. Calcium Channel Blockers (CCBs)

- **Dihydropyridines**: Amlodipine, Nifedipine
- **Non-dihydropyridines**: Verapamil, Diltiazem

E. Direct Vasodilators

- Hydralazine
- Minoxidil
- Sodium nitroprusside (for emergencies)
- Diazoxide

F. Aldosterone Antagonists

- Spironolactone
- Eplerenone

Mechanism of Action

Each class acts at a different site:

1. Diuretics

- Promote sodium and water excretion → decrease blood volume → decrease CO → reduce BP.
- Long-term: reduce PVR.

2. Beta-blockers

- Block β1 receptors in the heart → decrease heart rate and contractility → ↓ CO.
- Inhibit renin release from juxtaglomerular cells → ↓ RAAS activation.

3. Alpha-blockers

- Block α1 receptors in vascular smooth muscle → vasodilation → ↓ PVR.

4. **Centrally acting drugs**
   - ➢ Stimulate central α2 receptors → decrease sympathetic outflow → reduced HR and vasodilation.
5. **ACE inhibitors**
   - ➢ Inhibit conversion of Angiotensin I to II → vasodilation + ↓ aldosterone → ↓ PVR and blood volume.
6. **ARBs**
   - ➢ Block angiotensin II receptors → prevent vasoconstriction and aldosterone secretion.
7. **Direct Renin Inhibitors**
   - ➢ Inhibit renin → ↓ Ang I and Ang II → vasodilation + reduced aldosterone effect.
8. **Calcium Channel Blockers**
   - ➢ Block L-type calcium channels in heart and smooth muscle:
     - Dihydropyridines: mainly vasodilation
     - Non-dihydropyridines: reduce HR and contractility (verapamil, diltiazem)
9. **Vasodilators**
   - ➢ Direct relaxation of arteriolar smooth muscle → reduce PVR.
   - ➢ Sodium nitroprusside releases nitric oxide → vasodilation (used in emergencies).

Pharmacokinetics

- Varies by class and drug; examples:
  - **Thiazides**: Oral, onset in hours, duration 12–24 hours, renal excretion.
  - **Beta-blockers**: Oral, hepatic metabolism (e.g., propranolol), renal (atenolol).
  - **ACE inhibitors**: Oral, converted to active forms (except lisinopril), excreted by kidneys.
  - **CCBs**: High oral bioavailability, hepatic metabolism, long half-life (e.g., amlodipine).

Pharmacodynamics

- Reduction in systolic and diastolic BP
- **Onset**: Immediate (IV drugs), days to weeks (oral)
- **Effect plateau**: Often seen after 4–6 weeks of therapy
- **Tolerability**: Most classes are well tolerated; side effects vary.

Adverse Effects

Class	Common Adverse Effects
Diuretics	Hypokalemia, hyperuricemia, hyponatremia

β-blockers	Bradycardia, fatigue, erectile dysfunction, bronchospasm
ACE inhibitors	Dry cough, hyperkalemia, angioedema
ARBs	Hyperkalemia, less cough
CCBs	Peripheral edema, headache, flushing, bradycardia (verapamil)
Vasodilators	Reflex tachycardia, lupus-like syndrome (hydralazine), hypertrichosis (minoxidil)
Central agents	Sedation, dry mouth, rebound hypertension (clonidine)

Contraindications

- **Beta-blockers**: Asthma, bradycardia, AV block
- **ACE inhibitors & ARBs**: Pregnancy, bilateral renal artery stenosis, hyperkalemia
- **Thiazides**: Gout, severe renal failure
- **Non-dihydropyridine CCBs**: Heart block, bradycardia
- **Alpha-blockers**: Elderly (risk of falls)
- **Centrally acting agents**: Depression, mental status changes

Therapeutic Uses

- Primary hypertension
- Hypertensive emergencies (e.g., nitroprusside, labetalol)
- Heart failure (ACEIs, ARBs, beta-blockers, diuretics)
- Post-myocardial infarction (beta-blockers, ACEIs)
- Chronic kidney disease (ACEIs, ARBs)
- Diabetes with proteinuria (ACEIs, ARBs)
- Benign prostatic hyperplasia (alpha-blockers)

Drug Interactions

- **ACEIs/ARBs + potassium-sparing diuretics** → Hyperkalemia
- **NSAIDs + ACEIs/ARBs/Diuretics** → Reduced antihypertensive effect, risk of renal dysfunction
- **Beta-blockers + non-dihydropyridine CCBs** → Bradycardia, AV block
- **Diuretics + digoxin** → Risk of digoxin toxicity due to hypokalemia
- **Alpha-blockers + other vasodilators** → Severe hypotension

Dose and Route of Administration

Doses vary by drug and patient characteristics. Some examples:

A. Hydrochlorothiazide

- Dose: 12.5–25 mg/day orally
- Route: Oral

B. Amlodipine

- Dose: 5–10 mg/day orally
- Route: Oral

C. Lisinopril

- Dose: 10–40 mg/day orally
- Route: Oral

D. Losartan

- Dose: 50–100 mg/day orally
- Route: Oral

E. Metoprolol

- Dose: 50–200 mg/day (divided)
- Route: Oral

F. Sodium Nitroprusside

- Dose: IV infusion, 0.3–10 mcg/kg/min
- Route: Intravenous (used in hypertensive emergencies)

- Dosing must be individualized based on blood pressure response, renal function, and comorbidities.

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