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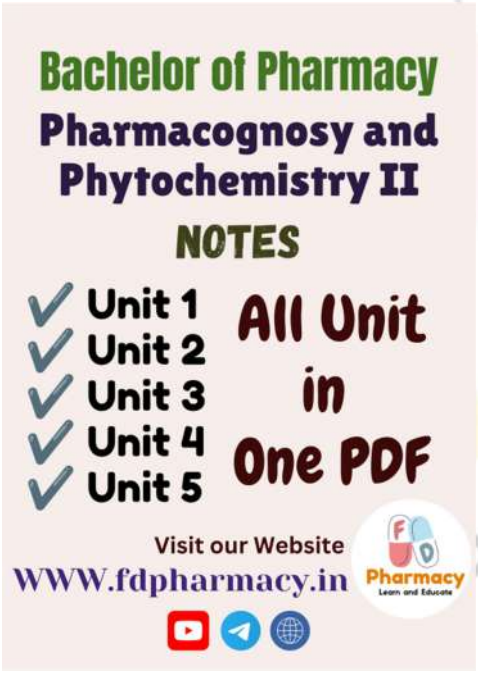
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PHARMACOLOGY - II

UNIT 1

TOPIC :

- **Pharmacology of drugs acting on cardio vascular system**
  a. Introduction to hemodynamic and electrophysiology of heart.
  b. Drugs used in congestive heart failure
  c. Anti-hypertensive drugs.
  d. Anti-anginal drugs.
  e. Anti-arrhythmic drugs.
  f. Anti-hyperlipidemic drugs.

Introduction to Hemodynamics and Electrophysiology of the Heart

The human heart is a muscular pumping organ that circulates blood throughout the body to supply oxygen and nutrients to tissues and remove waste products.

Its proper function depends on two important physiological mechanisms:

1. Hemodynamics – which deals with the movement of blood and the forces involved in circulation.
2. Electrophysiology – which deals with the generation and conduction of electrical impulses that initiate and coordinate cardiac contraction.

Together, these mechanisms ensure that blood flows efficiently and rhythmically through the cardiovascular system.

Hemodynamics

- Hemodynamics is the branch of physiology that studies the flow of blood and the forces involved in its circulation through the heart and blood vessels.

It helps to understand:

- How blood pressure is generated and regulated
- How blood flows through different parts of the circulatory system
- How the heart's pumping efficiency is maintained

Basic Principles of Hemodynamics

1. Blood Flow (Q):
    - It is the volume of blood passing through a vessel or organ per unit time.
    - Formula:

$$Q - \frac{\Delta P}{R}$$

Where:

Q = Blood flow

ΔP = Pressure difference

R = Resistance to flow

Blood Pressure

- It is the force exerted by blood on the walls of blood vessels.
- Normal value: 120/80 mmHg
- Determined by cardiac output and peripheral resistance.

Cardiac Output (CO)

- The volume of blood pumped by each ventricle per minute.
- Formula:

$$CO = HR \times SV$$

Where:

HR = Heart Rate (beats per minute)

SV = Stroke Volume (amount of blood pumped per beat)

Normal value ≈ 5 L/min

Stroke Volume (SV)

- The amount of blood pumped by one ventricle in a single heartbeat.
- Influenced by:
  - Preload (venous return or end-diastolic volume)
  - Afterload (resistance against which heart pumps)
  - Contractility (strength of ventricular contraction)

Resistance (R)

- Opposition to blood flow, mainly determined by diameter of arterioles.
- Formula (Poiseuille's Law):

$$R \propto \frac{1}{r^4}$$

→ Small changes in vessel radius cause large changes in resistance.

1. Venous Return:
   - The amount of blood returning to the heart per minute.
   - Must equal cardiac output for stable circulation.

Factors Affecting Hemodynamics

- Viscosity of blood: Increases with hematocrit; increases resistance.
- Vessel diameter: Major determinant of resistance.
- Vessel length: Longer vessels increase resistance.
- Elasticity of vessels: Maintains diastolic pressure and smooth flow.
- Heart rate and stroke volume: Affect cardiac output and blood pressure.

Regulation of Blood Flow and Pressure

1. **Autonomic Nervous System (ANS):**
    - Sympathetic stimulation → ↑ heart rate, ↑ contractility, vasoconstriction → ↑ BP
    - Parasympathetic stimulation → ↓ heart rate, vasodilation → ↓ BP
2. **Hormonal Control:**
    - Adrenaline/Noradrenaline: Increase heart rate and cardiac output.
    - Renin-Angiotensin-Aldosterone System (RAAS): Increases blood volume and pressure.
    - Atrial Natriuretic Peptide (ANP): Decreases blood pressure by promoting salt and water loss.
3. **Local (Autoregulation):**
    - Tissues regulate their own blood flow based on oxygen and nutrient needs.

ELECTROPHYSIOLOGY OF THE HEART

- Cardiac electrophysiology is the study of the generation and propagation of electrical impulses in the heart that trigger its rhythmic contractions.
- The heart has an intrinsic conduction system that allows it to contract without external nerve stimulation — known as automaticity.

Electrical Activity of the Heart

→ The contraction of the heart is triggered by action potentials (APs) that spread through the cardiac muscle fibers.
→ These APs are generated by specialized pacemaker cells.

Cardiac Conduction System

The pathway of electrical conduction is as follows:

1. **Sinoatrial (SA) Node:**
   - Located in the right atrium.
   - Natural pacemaker of the heart.
   - Generates impulses at 60–100 beats/min.
   - Initiates atrial contraction.
2. **Atrioventricular (AV) Node:**
   - Located between atria and ventricles.
   - Delays impulse (~0.1 sec) to allow complete atrial emptying before ventricular contraction.
3. **Bundle of His (AV Bundle):**
   - Conducts impulses from AV node to ventricles.
4. **Right and Left Bundle Branches:**
   - Conduct impulses to respective ventricles.
5. **Purkinje Fibers:**
   - Spread impulses rapidly through ventricular myocardium → cause ventricular contraction.

Cardiac Action Potential (Phases)

In ventricular muscle fibers, the action potential has 5 phases:

Phase	Event	Description
0	Depolarization	Na^+ influx through fast channels
1	Initial repolarization	Transient K^+ efflux
2	Plateau phase	Ca^{2+} influx balances K^+ efflux
3	Repolarization	K^+ efflux restores resting potential
4	Resting phase	Stable membrane potential (–90 mV)

Pacemaker Potential (SA Node)

- SA node cells show spontaneous depolarization during phase 4 due to:
  - Slow Na^+ influx (funny current)
  - Ca^{2+} influx
  - Reduced K^+ efflux
- This automaticity ensures continuous rhythmic heartbeat.

Electrocardiogram (ECG)

The ECG is a recording of the electrical activity of the heart.

Wave	Represents
P wave	Atrial depolarization
QRS complex	Ventricular depolarization
T wave	Ventricular repolarization

Abnormal ECG patterns indicate arrhythmias, ischemia, or conduction blocks.

Relationship Between Electrical and Mechanical Events

- Electrical excitation → contraction (systole)
- Repolarization → relaxation (diastole)
- This sequence ensures effective pumping of blood.

Disorders Related to Electrophysiology

- Arrhythmias: Abnormal rhythm due to conduction defects.
- Heart block: Delay or failure in impulse conduction.
- Fibrillation: Uncoordinated, rapid contractions.
- Ectopic pacemakers: Abnormal sites generating impulses.

Congestive Heart Failure (CHF)

- Congestive Heart Failure (CHF) is a pathophysiological condition in which the heart is unable to pump sufficient blood to meet the metabolic demands of body tissues or can do so only with elevated filling pressures.
- It represents the final common pathway of various cardiovascular diseases such as hypertension, myocardial infarction, valvular heart diseases, or cardiomyopathy.
- Heart failure is defined as a condition in which the heart's pumping efficiency decreases, leading to inadequate tissue perfusion and accumulation of fluid (congestion) in lungs, liver, and peripheral tissues.
- Hence the term "Congestive Heart Failure".

Normal Cardiac Function

The heart functions as a pump that maintains adequate blood circulation by:

- Receiving blood from veins (venous return)
- Pumping it into arteries through rhythmic contractions

Cardiac output (CO) = Heart Rate (HR) × Stroke Volume (SV)
In CHF, both stroke volume and cardiac output decrease.

Types of Heart Failure

Type	Description
Left-sided heart failure	Failure of left ventricle → blood backs up in lungs → pulmonary congestion, dyspnea (breathlessness)
Right-sided heart failure	Failure of right ventricle → systemic venous congestion → edema of feet, ascites, hepatomegaly
Systolic failure	Reduced contractility of heart → decreased ejection fraction
Diastolic failure	Impaired filling of ventricles due to stiffness → normal ejection fraction but reduced filling
Acute heart failure	Sudden onset, often due to myocardial infarction
Chronic heart failure	Progressive and long-term, often due to hypertension or valvular disease

Causes (Etiology) of Heart Failure

A. Myocardial Causes

- Coronary artery disease (most common)
- Myocardial infarction
- Cardiomyopathy

B. Pressure Overload

- Hypertension
- Aortic stenosis

C. Volume Overload

- Valvular regurgitation
- Renal failure causing fluid retention

D. Arrhythmias

- Tachycardia or bradycardia affecting cardiac output

E. Others

- Anemia, thyrotoxicosis, infection, or pregnancy can aggravate heart failure.

Pathophysiology of CHF

- When cardiac output decreases, the body activates compensatory mechanisms to maintain circulation.
  However, these mechanisms may worsen the condition over time.

(i) Decreased Cardiac Output

↓ CO → ↓ tissue perfusion → activation of reflex mechanisms

(ii) Compensatory Mechanisms

1. Frank–Starling Mechanism:
   - Increased venous return stretches cardiac muscle → increases stroke volume (up to a limit).
2. Sympathetic Nervous System Activation:
   - ↓ CO → ↓ BP → activation of baroreceptors → ↑ sympathetic discharge
     → ↑ HR, ↑ contractility, vasoconstriction.
3. Renin–Angiotensin–Aldosterone System (RAAS):
   - Reduced renal perfusion → renin release → angiotensin II → vasoconstriction & aldosterone secretion → Na^+ and water retention → ↑ blood volume.
4. Ventricular Hypertrophy:
   - Heart enlarges to cope with increased workload → later leads to stiffness and reduced efficiency.

(iii) Result

Initially compensatory mechanisms maintain BP and CO, but prolonged activation leads to:

- Ventricular remodeling
- Congestion
- Edema
- Further decline in cardiac function

Clinical Manifestations (Symptoms)

A. Left-Sided Heart Failure

- Dyspnea (difficulty breathing)
- Orthopnea (breathlessness when lying flat)
- Pulmonary congestion (crackles on auscultation)
- Fatigue and weakness
- Cough with frothy sputum

B. Right-Sided Heart Failure

- Peripheral edema (swelling of feet and ankles)
- Ascites (fluid accumulation in abdomen)
- Hepatomegaly (enlarged liver)
- Jugular venous distension
- Weight gain due to fluid retention

Goals of Therapy

- To improve symptoms and quality of life
- To increase cardiac output
- To reduce fluid overload and congestion
- To slow disease progression
- To reduce mortality

Drugs Used in Congestive Heart Failure

1. Positive Inotropic Drugs

Increase force of myocardial contraction → improve cardiac output.

a. Cardiac Glycosides

- Example: Digoxin, Digitoxin
- Mechanism:
  - Inhibit Na^+/K^+-ATPase → increase intracellular Na^+
  - Leads to ↑ intracellular Ca^{2+} → stronger contraction
- Effects:
  - Positive inotropic (↑ contractility)
  - Negative chronotropic (↓ HR)
  - Negative dromotropic (↓ AV conduction)
- Uses: Chronic heart failure, atrial fibrillation
- Toxicity: Nausea, vomiting, arrhythmia, visual disturbances

2. Diuretics

Reduce blood volume and edema, thus decreasing cardiac workload.

- Loop diuretics: Furosemide, Bumetanide
  (Rapid relief from pulmonary congestion)
- Thiazides: Hydrochlorothiazide
  (Used in mild cases)
- Potassium-sparing diuretics: Spironolactone
  (Also reduces aldosterone effects)

3. Vasodilators

Reduce preload and afterload to improve cardiac output.

- Venodilators (reduce preload): Nitroglycerin
- Arteriolar dilators (reduce afterload): Hydralazine
- Mixed dilators: Sodium nitroprusside

4. ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors)

- Examples: Captopril, Enalapril, Lisinopril
- Mechanism:
  - Block conversion of Angiotensin I → II

    - Reduce vasoconstriction and aldosterone secretion
- Effects: ↓ Afterload, ↓ Preload, prevent remodeling
- Benefits: Prolong survival in CHF patients

5. Angiotensin II Receptor Blockers (ARBs)

- Examples: Losartan, Valsartan
- Used as alternative to ACE inhibitors (when cough occurs)
- Similar benefits on cardiac remodeling and BP reduction.

6. Beta-Blockers

- Examples: Carvedilol, Metoprolol, Bisoprolol
- Mechanism:
    - Block β_1 receptors → reduce HR, myocardial oxygen demand
    - Prevent harmful effects of chronic sympathetic activation.
- Use: Chronic stable CHF (low doses)
- Caution: Avoid in acute heart failure

7. Aldosterone Antagonists

- Example: Spironolactone, Eplerenone
- Prevent Na^+ and water retention and reduce cardiac fibrosis.
- Shown to reduce mortality in CHF.

8. Vasodilator + Nitrate Combinations

- Example: Hydralazine + Isosorbide dinitrate
- Used in patients who cannot tolerate ACE inhibitors.

9. Newer Drugs

- Ivabradine: Slows HR by inhibiting If current in SA node.
- Sacubitril + Valsartan: ARNI (Angiotensin receptor–neprilysin inhibitor) combination — enhances natriuretic peptide action and reduces cardiac remodeling.

10. Non-Pharmacological Management

- Salt and fluid restriction
- Regular physical activity (mild)
- Weight monitoring
- Avoid alcohol and smoking
- Treat underlying causes (hypertension, anemia, infection)

Anti-hypertensive drugs

- Hypertension is a chronic disorder characterized by a persistent elevation of arterial blood pressure above normal physiological levels (≥140/90 mmHg).
  If left untreated, it can lead to stroke, heart failure, kidney damage, and atherosclerosis.
- To control hypertension and prevent complications, anti-hypertensive drugs are used.
- Anti-hypertensive drugs are agents that lower elevated blood pressure to normal levels, thereby reducing the risk of cardiovascular morbidity and mortality.
- Their actions are achieved by:
  - Reducing cardiac output (CO)
  - Decreasing peripheral vascular resistance (PVR)
  - Reducing blood volume

Classification of Anti-Hypertensive Drugs

Anti-hypertensive drugs can be classified based on site and mechanism of action:

A. Drugs Acting on Central Nervous System

1. Central α_2-agonists
   - Examples: Methyldopa, Clonidine
   - Mechanism: Stimulate α_2-receptors in the medulla → ↓ sympathetic outflow → ↓ heart rate, cardiac output, and peripheral resistance.
   - Adverse Effects: Sedation, dry mouth, rebound hypertension (on withdrawal)
   - Special Note: Methyldopa is safe in pregnancy.

B. Drugs Acting on Sympathetic Nervous System

1. Ganglion Blockers (rarely used)

- Examples: Trimethaphan, Mecamylamine
- Mechanism: Block nicotinic receptors in autonomic ganglia → inhibit sympathetic tone → vasodilation.
- Use: Only in hypertensive emergencies.

2. Adrenergic Neuron Blockers

- Examples: Guanethidine, Reserpine
- Mechanism: Deplete norepinephrine from nerve terminals → ↓ sympathetic activity.
- Adverse Effects: Depression, nasal congestion, postural hypotension.

C. Drugs Acting on Adrenergic Receptors

1. α-Adrenergic Blockers

- Examples: Prazosin, Terazosin, Doxazosin
- Mechanism: Block α_1-receptors in arterioles and veins → cause vasodilation → ↓ peripheral resistance and BP.
- Adverse Effects: Postural hypotension, dizziness, headache, tachycardia.
- Uses: Mild to moderate hypertension, benign prostatic hyperplasia.

2. β-Adrenergic Blockers

- Examples: Propranolol (non-selective), Atenolol, Metoprolol (β_1-selective)
- Mechanism:
  - Block β_1-receptors in heart → ↓ heart rate, ↓ contractility, ↓ cardiac output
  - Also inhibit renin release from kidneys.
- Uses: Hypertension with angina, arrhythmias, or post-MI.

- Adverse Effects: Bradycardia, fatigue, bronchoconstriction (avoid in asthma), hypoglycemia.

3. α + β Blockers (Mixed Blockers)

- Examples: Labetalol, Carvedilol
- Mechanism: Block both α_1 and β receptors → cause vasodilation and ↓ HR.
- Use: Hypertensive emergencies, chronic hypertension.

D. Drugs Acting on Blood Vessels (Vasodilators)

These drugs directly relax vascular smooth muscle → reduce peripheral resistance.

1. Arteriolar Dilators

- Examples: Hydralazine, Minoxidil
- Mechanism: Direct relaxation of arteriolar smooth muscle → ↓ afterload.
- Adverse Effects: Reflex tachycardia, edema, headache.
- Note: Minoxidil causes hypertrichosis (excess hair growth) – used topically for alopecia.

2. Arteriolar and Venous Dilators (Mixed)

- Example: Sodium Nitroprusside
- Mechanism: Releases nitric oxide (NO) → potent vasodilation of both arteries and veins.
- Use: Hypertensive emergencies (IV only).
- Adverse Effects: Hypotension, cyanide toxicity (on prolonged use).

E. Drugs Acting on Renin–Angiotensin System (RAS)

The Renin–Angiotensin–Aldosterone System (RAAS) plays a major role in BP regulation by controlling blood volume and vascular tone.

1. ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors)

- Examples: Captopril, Enalapril, Lisinopril, Ramipril
- Mechanism:
  - Inhibit conversion of Angiotensin I → Angiotensin II (a potent vasoconstrictor)
  - ↓ Aldosterone secretion → ↓ Na^+ and water retention
  - Cause vasodilation and ↓ blood volume.
- Advantages: Do not cause reflex tachycardia; prevent cardiac remodeling.
- Adverse Effects: Cough (due to bradykinin), hyperkalemia, hypotension, angioedema.
- Contraindicated: Pregnancy and renal artery stenosis.

2. Angiotensin II Receptor Blockers (ARBs)

- Examples: Losartan, Valsartan, Irbesartan
- Mechanism: Block AT_1 receptors → inhibit effects of Angiotensin II → vasodilation and ↓ aldosterone secretion.
- Advantages: No cough (unlike ACEIs).
- Uses: Hypertension, heart failure.

3. Direct Renin Inhibitors

- Example: Aliskiren
- Mechanism: Directly inhibits renin enzyme → prevents Angiotensin I formation.
- Uses: Essential hypertension (alternative to ACEIs/ARBs).

F. Calcium Channel Blockers (CCBs)

- Examples: Verapamil, Diltiazem, Nifedipine, Amlodipine
- Mechanism:
  - Block L-type calcium channels in smooth muscle and heart.
  - Cause vasodilation, ↓ heart rate, and ↓ cardiac contractility.
- Types:
    - Dihydropyridines (Amlodipine, Nifedipine) – mainly vasodilators
    - Non-dihydropyridines (Verapamil, Diltiazem) – affect heart rate and conduction
- Uses: Hypertension, angina, arrhythmias.
- Adverse Effects: Headache, ankle edema, constipation, bradycardia (verapamil).

G. Diuretics

- Examples: Thiazides (Hydrochlorothiazide), Loop (Furosemide), Potassium-sparing (Spironolactone)
- Mechanism:
  - Promote excretion of Na^+ and water → reduce plasma volume → ↓ cardiac output.
  - Long-term: ↓ peripheral resistance.
- Uses: Mild to moderate hypertension; useful in elderly and black patients.
- Adverse Effects: Hypokalemia, dehydration, hyperglycemia (thiazides).
- Note: Spironolactone also blocks aldosterone – beneficial in heart failure.

Anti-Anginal Drugs

- Angina pectoris is a clinical syndrome of chest pain or discomfort that occurs when there is insufficient blood flow (oxygen supply) to the heart muscle (myocardium) relative to its demand.
  This imbalance between oxygen supply and oxygen demand leads to
- Anti-anginal drugs are agents used to prevent or relieve angina pectoris by improving oxygen supply to the heart or reducing myocardial oxygen demand.

Types of Angina

Type	Cause/Features	Treatment Focus
1. Stable (Exertional) Angina	Due to fixed atherosclerotic narrowing of coronary arteries; pain occurs on exertion or stress	↓ Oxygen demand (β-blockers, nitrates, CCBs)
2. Unstable Angina	Due to rupture of atherosclerotic plaque and platelet aggregation; occurs at rest	Emergency treatment (nitrates, antiplatelet drugs)
3. Variant (Prinzmetal's) Angina	Due to coronary artery spasm	↑ Oxygen supply (Calcium channel blockers, nitrates)

Pathophysiology

- Myocardial oxygen demand depends on:
  - Heart rate
  - Myocardial contractility
  - Myocardial wall tension (preload & afterload)
- Myocardial oxygen supply depends on:
  - Coronary blood flow
  - Duration of diastole
  - Oxygen-carrying capacity of blood

Anti-anginal drugs act by:

- ↓ Oxygen demand, or
- ↑ Oxygen supply, or both.

Classification of Anti-Anginal Drugs

A. Drugs Decreasing Myocardial Oxygen Demand

1. Organic Nitrates
2. β-Adrenergic Blockers
3. Calcium Channel Blockers (some types)

B. Drugs Increasing Myocardial Oxygen Supply

1. Calcium Channel Blockers (vasodilator types)
2. Vasodilators acting on coronary arteries

C. Miscellaneous / Newer Antianginal Agents

1. Potassium Channel Activators – Nicorandil
2. If Channel Inhibitors – Ivabradine
3. Metabolic Modulators – Trimetazidine, Ranolazine

Mechanism of Action and Details of Drug Classes

A. Organic Nitrates

Examples:

- Short-acting: Nitroglycerin (Glyceryl trinitrate)
- Long-acting: Isosorbide dinitrate, Isosorbide mononitrate, Erythrityl tetranitrate

Mechanism of Action:

1. Nitrates are prodrugs → release Nitric Oxide (NO) in vascular smooth muscle.
2. NO activates guanylate cyclase → ↑ cyclic GMP → relaxation of smooth muscle.
3. Venodilation → ↓ venous return (↓ preload)
   Arteriolar dilation → ↓ afterload
   → both lead to ↓ myocardial oxygen demand.

4. They also dilate coronary arteries → ↑ oxygen supply.

Pharmacological Effects:

- ↓ Myocardial oxygen consumption
- ↑ Coronary blood flow
- ↓ Left ventricular end-diastolic pressure (LVEDP)

Pharmacokinetics:

- Nitroglycerin: high first-pass metabolism → given sublingually for rapid relief.
- Isosorbide mononitrate: oral route for prophylaxis.

Adverse Effects:

- Headache (due to vasodilation)
- Flushing
- Postural hypotension
- Reflex tachycardia
- Tolerance (reduced effect with continuous use)

Prevention of Tolerance:

- Maintain a nitrate-free interval of 8–12 hours/day.

Contraindications:

- Hypotension, head injury, or use of phosphodiesterase-5 inhibitors (e.g., sildenafil) — causes severe hypotension.

Uses:

- Acute attack of angina (sublingual nitroglycerin)
- Prophylaxis of stable and variant angina
- Heart failure

B. β-Adrenergic Blockers

Examples:

- Non-selective: Propranolol
- Cardioselective: Atenolol, Metoprolol, Bisoprolol

Mechanism of Action:

- Block β_1-receptors in the heart → ↓ heart rate, ↓ contractility, ↓ blood pressure → ↓ oxygen demand.

Advantages:

- Prevent reflex tachycardia caused by nitrates.
- Increase exercise tolerance.

Adverse Effects:

- Bradycardia, fatigue, depression, Bronchospasm (avoid in asthma)

Uses:

- Prophylaxis of stable angina (not effective in variant angina)
- Used in combination with nitrates and calcium channel blockers.

C. Calcium Channel Blockers (CCBs)

Examples:

- Phenylalkylamine: Verapamil
- Benzothiazepine: Diltiazem
- Dihydropyridines: Nifedipine, Amlodipine, Felodipine

Mechanism of Action:

- Block L-type calcium channels in smooth muscle and myocardium. → ↓ calcium influx → relaxation of vascular smooth muscle → vasodilation.

Effects:

- Decrease myocardial oxygen demand (by reducing HR and contractility)
- Increase oxygen supply (by dilating coronary arteries)

Uses:

- Stable angina (↓ demand), Variant (Prinzmetal's) angina (↑ supply)

Adverse Effects:

- Hypotension, ankle edema, flushing, constipation (verapamil)
- Bradycardia (verapamil, diltiazem)

D. Potassium Channel Activators

Example: *Nicorandil*

Mechanism:

- Opens ATP-sensitive K^+ channels → hyperpolarization and relaxation of vascular smooth muscle.
- Also donates NO → dual vasodilator action.

Effects:

- Arteriolar and venous dilation → ↓ preload and afterload.
- ↑ Coronary blood flow.

Uses:

- Chronic stable angina, variant angina

Adverse Effects:

- Headache, flushing, ulceration (rare)

E. Metabolic Modulators

Example: *Trimetazidine, Ranolazine*

Mechanism:

- Shift cardiac metabolism from fatty acid oxidation → glucose oxidation, which requires less oxygen.
- Improves efficiency of oxygen utilization by myocardium.

Uses:

- Chronic stable angina (adjunct therapy)
- Useful in patients intolerant to hemodynamic drugs.

Adverse Effects:

- Mild dizziness, nausea

F. If Channel Inhibitor

Example: *Ivabradine*

Mechanism:

- Selectively inhibits If (funny current) in SA node → reduces heart rate without affecting contractility or blood pressure.

Uses:

- Stable angina (alternative to β-blockers)
- Chronic heart failure

Adverse Effects:

- Bradycardia, visual disturbances (phosphenes)

Anti-Arrhythmic Drugs

→ The heart normally beats in a regular rhythmic manner due to the orderly generation and conduction of electrical impulses through specialized cardiac tissues (SA node → AV node → Bundle of His → Purkinje fibers).

→ When this normal rhythm is disturbed, it leads to arrhythmias — which may cause palpitations, dizziness, syncope, or even sudden cardiac death.

→ Cardiac Arrhythmia:
An arrhythmia is an abnormality in the rate, rhythm, or sequence of cardiac electrical impulses, leading to inefficient cardiac function.

→ Anti-arrhythmic drugs:
These are agents that prevent or correct abnormal heart rhythms by modifying the generation or conduction of cardiac impulses.

Normal Electrical Activity of Heart

- SA node = natural pacemaker (generates impulses at 60–100 bpm)
- AV node = delays impulse for ventricular filling
- Purkinje system = spreads impulse rapidly to ventricular muscles

Normal ECG components:

- P wave: atrial depolarization
- QRS complex: ventricular depolarization
- T wave: ventricular repolarization

Arrhythmias occur due to:

- Abnormal impulse formation (increased automaticity, ectopic foci)
- Abnormal impulse conduction (reentry, block)

Classification of Anti-Arrhythmic Drugs (Vaughan Williams Classification)

Antiarrhythmic agents are classified according to their main electrophysiological action on cardiac tissue:

Class	Site/Action	Examples	Main Effect
Class I	Sodium (Na^+) channel blockers	Quinidine, Lidocaine, Flecainide	↓ Phase 0 depolarization (↓ conduction)
Class II	β-Adrenergic blockers	Propranolol, Atenolol, Metoprolol	↓ Sympathetic activity (↓ HR, ↓ conduction)
Class III	Potassium (K^+) channel blockers	Amiodarone, Sotalol, Dofetilide	↑ Repolarization (↑ refractory period)
Class IV	Calcium (Ca^{2+}) channel blockers	Verapamil, Diltiazem	↓ SA/AV node conduction
Others	Miscellaneous	Adenosine, Digoxin, Magnesium sulfate	Various mechanisms

CLASS I – Sodium Channel Blockers

- These drugs block fast Na^+ channels responsible for phase 0 depolarization of cardiac action potential.
- They reduce automaticity, excitability, and conduction velocity in cardiac muscle.

Subclasses:

Subclass	Examples	Action on Action Potential	Main Uses
Class IA	Quinidine, Procainamide, Disopyramide	Moderate Na^+ block, ↑ AP duration	Atrial & ventricular arrhythmias
Class IB	Lidocaine, Mexiletine	Weak Na^+ block, ↓ AP duration	Ventricular arrhythmias (esp. post-MI)
Class IC	Flecainide, Propafenone	Strong Na^+ block, no change in AP duration	Severe refractory arrhythmias

A. Class IA: Quinidine, Procainamide

- Mechanism: Moderate Na^+ channel blockade → slows conduction and prolongs repolarization.
- Effects: Prolongs QRS and QT interval.
- Uses: Atrial fibrillation, supraventricular and ventricular tachycardia.
- Adverse Effects: QT prolongation → torsades de pointes (arrhythmia), hypotension, diarrhea, cinchonism (quinidine).

B. Class IB: Lidocaine

- Mechanism: Weak Na^+ channel blockade; shortens repolarization.
- Use: Effective in ventricular arrhythmias (especially after myocardial infarction).
- Route: IV only (due to high first-pass metabolism).
- Adverse Effects: CNS effects (drowsiness, confusion, tremors).

C. Class IC: Flecainide, Propafenone

- Mechanism: Strong Na^+ channel blockade; slows conduction markedly.
- Use: Life-threatening ventricular arrhythmias; resistant supraventricular arrhythmias.
- Adverse Effects: Proarrhythmic effects; negative inotropy.

CLASS II – β-Adrenergic Blockers

Examples:

Propranolol, Atenolol, Metoprolol, Esmolol

Mechanism of Action:

- Block β_1 receptors → inhibit sympathetic stimulation of heart.
- ↓ SA node automaticity, ↓ AV node conduction, ↓ HR and contractility.

Effects:

- Prolong AV nodal conduction time.
- Prevent arrhythmias caused by excess catecholamines.

Uses:

- Supraventricular tachycardia (SVT)
- Atrial flutter and fibrillation (rate control)
- Ventricular arrhythmias (especially post-MI)
- Prevention of sudden cardiac death

Adverse Effects:

- Bradycardia, hypotension
- Bronchospasm (non-selective agents)
- Fatigue, depression

CLASS III – Potassium Channel Blockers

Examples:

Amiodarone, Dronedarone, Sotalol, Dofetilide, Ibutilide

Mechanism of Action:

- Block K^+ efflux during repolarization (Phase 3)
- Prolong action potential duration (APD) and refractory period
- ↓ Re-entry phenomena → prevent recurrent arrhythmias

Effects:

- ↑ QT interval
- ↓ Conduction velocity in AV node

Amiodarone (Main Drug)

- Mechanism: Blocks K^+, Na^+, and Ca^{2+} channels; also has β-blocking activity.
- Uses: Broad-spectrum – effective in atrial and ventricular arrhythmias.
- Adverse Effects:
  - Pulmonary fibrosis
  - Thyroid dysfunction (hypo/hyperthyroidism)
  - Corneal deposits
  - Blue-gray skin discoloration
  - Hepatotoxicity
  - QT prolongation

Sotalol:

- Has both β-blocking and K^+ channel blocking properties.
- Used for ventricular and supraventricular arrhythmias.
- Adverse effect: Torsades de pointes.

CLASS IV – Calcium Channel Blockers

Examples:

Verapamil, Diltiazem

Mechanism of Action:

- Block L-type Ca^{2+} channels in SA and AV nodes.
- ↓ Slow inward Ca^{2+} current → ↓ automaticity and conduction velocity.
- Prolong refractory period in AV node.

Uses:

- Supraventricular tachycardia (SVT)
- Atrial flutter/fibrillation (rate control)
- Angina and hypertension

Adverse Effects:

- Bradycardia, hypotension
- Constipation (verapamil)
- Worsening of heart failure

Other Anti-Arrhythmic Drugs

1. Adenosine

- Mechanism: Activates adenosine receptors → opens K^+ channels → hyperpolarization of AV node → blocks conduction.
- Use: Drug of choice for terminating acute paroxysmal supraventricular tachycardia (PSVT).
- Route: IV (very short half-life, ~10 sec).
- Adverse Effects: Flushing, dyspnea, chest discomfort (short-lived).

2. Digoxin

- Mechanism:
  - Increases vagal tone → slows AV nodal conduction.
  - Also increases contractility (positive inotrope).
- Use: Atrial fibrillation and atrial flutter (for rate control).
- Adverse Effects: Arrhythmias, nausea, visual disturbances (yellow vision).

3. Magnesium Sulfate

- Mechanism: Stabilizes cardiac membrane; affects Na^+/K^+ ATPase and Ca^{2+} channels.
- Use: Torsades de pointes, digitalis-induced arrhythmias.
- Adverse Effects: Hypotension (rapid IV administration).

Anti-Hyperlipidemic Drugs

- Hyperlipidemia (or hyperlipoproteinemia) is a condition characterized by elevated levels of lipids (cholesterol and triglycerides) and/or lipoproteins in the blood.
  It is one of the major risk factors for atherosclerosis, coronary artery disease (CAD), stroke, and myocardial infarction.
- Drugs that lower lipid levels in blood are called anti-hyperlipidemic or hypolipidemic drugs.

Normal Lipid Transport

- Lipids are transported in the blood as lipoprotein complexes:
  1. Chylomicrons – carry dietary triglycerides
  2. VLDL (Very Low-Density Lipoproteins) – transport endogenous triglycerides
  3. LDL (Low-Density Lipoproteins) – transport cholesterol to tissues ("bad cholesterol")
  4. HDL (High-Density Lipoproteins) – remove cholesterol from tissues ("good cholesterol")

An increase in LDL or VLDL and a decrease in HDL leads to atherosclerosis.

Goals of Anti-Hyperlipidemic Therapy

- Reduce total cholesterol, LDL, and triglycerides.
- Increase HDL levels.
- Prevent development of atherosclerosis and cardiovascular complications.

Classification of Anti-Hyperlipidemic Drugs

Class	Examples	Main Action
1. HMG-CoA reductase inhibitors (Statins)	Lovastatin, Simvastatin, Atorvastatin, Rosuvastatin	↓ Cholesterol synthesis in liver
2. Fibrates	Gemfibrozil, Fenofibrate, Bezafibrate	↓ Triglycerides, ↑ HDL
3. Bile acid sequestrants (Resins)	Cholestyramine, Colestipol	↓ LDL by increasing bile acid excretion
4. Nicotinic acid (Niacin, Vitamin B3)	Nicotinic acid, Niacinamide	↓ LDL & TG, ↑ HDL
5. Cholesterol absorption inhibitors	Ezetimibe	↓ Cholesterol absorption from intestine
6. PCSK9 inhibitors	Evolocumab, Alirocumab	↓ LDL by increasing receptor recycling
7. Omega-3 fatty acids	Fish oil (EPA, DHA)	↓ Triglycerides

Mechanism of Action and Details of Each Class

A. HMG-CoA Reductase Inhibitors (Statins)

Examples: Lovastatin, Simvastatin, Atorvastatin, Rosuvastatin, Pravastatin

Mechanism of Action:

- Competitively inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis.
- ↓ Hepatic cholesterol → ↑ LDL receptor expression → ↑ LDL uptake → ↓ plasma LDL.

Pharmacological Effects:

- ↓ LDL (25–60%)
- ↓ Triglycerides (10–30%)
- ↑ HDL (5–10%)

Uses:

- First-line therapy for hypercholesterolemia
- Prevention of coronary artery disease, stroke, and myocardial infarction

Adverse Effects:

- Myopathy (muscle pain or weakness)
- Hepatotoxicity (↑ liver enzymes)
- Gastrointestinal disturbances

Note: Contraindicated in pregnancy and liver disease.

B. Fibrates

Examples: Gemfibrozil, Fenofibrate, Bezafibrate
Mechanism of Action:

- Activate PPAR-α (Peroxisome proliferator-activated receptor alpha) → ↑ lipoprotein lipase activity → ↑ breakdown of triglyceride-rich VLDL.
- ↑ HDL synthesis.

Effects:

- ↓ Triglycerides (30–50%)
- ↓ LDL (10–20%)
- ↑ HDL (10–20%)

Uses:

- Hypertriglyceridemia
- Mixed hyperlipidemia

Adverse Effects:

- Dyspepsia, nausea
- Myopathy (especially with statins)
- Gallstone formation (cholesterol gallstones)
- Mild liver dysfunction

C. Bile Acid Sequestrants (Resins)

Examples: Cholestyramine, Colestipol, Colesevelam

Mechanism of Action:

- Bind bile acids in intestine → prevent their reabsorption → increased conversion of cholesterol to bile acids → ↓ hepatic cholesterol → ↑ LDL receptor expression.

Effects:

- ↓ LDL (10–20%)
- Slight ↑ HDL
- May ↑ triglycerides (unfavorable)

Uses:

- Primary hypercholesterolemia
- Useful in combination with statins.

Adverse Effects:

- Constipation, bloating, nausea
- May interfere with absorption of fat-soluble vitamins (A, D, E, K).

D. Nicotinic Acid (Niacin, Vitamin B3)

Mechanism of Action:

- Inhibits lipolysis in adipose tissue → ↓ free fatty acid supply to liver → ↓ VLDL and LDL synthesis.
- Also increases HDL by decreasing its catabolism.

Effects:

- ↓ LDL (15–25%)
- ↓ Triglycerides (20–50%)
- ↑ HDL (15–35%)

Uses:

- Mixed hyperlipidemia
- In combination with statins or fibrates.

Adverse Effects:

- Flushing (due to prostaglandin release; minimized by aspirin)
- Pruritus
- Hyperuricemia (can precipitate gout)
- Hyperglycemia
- Hepatotoxicity (with prolonged use)

E. Cholesterol Absorption Inhibitor

Example: Ezetimibe

Mechanism of Action:

- Inhibits NPC1L1 transporter in the intestinal brush border → ↓ absorption of dietary and biliary cholesterol.

Effects:

- ↓ LDL (18–20%)
- ↓ Total cholesterol
- Minimal effect on HDL or TG.

Uses:

- Used alone or in combination with statins in hypercholesterolemia.

Adverse Effects:

- Diarrhea, abdominal pain
- Headache
- Rare: liver enzyme elevation when combined with statins

F. PCSK9 Inhibitors

Examples: Evolocumab, Alirocumab

Mechanism of Action:

- Monoclonal antibodies inhibit PCSK9 enzyme, which normally degrades LDL receptors → increased receptor recycling → enhanced LDL clearance from blood.

Effects:

- ↓ LDL up to 60%
- ↓ Total cholesterol
- Minimal effect on TG or HDL.

Uses:

- Familial hypercholesterolemia
- Statin-intolerant patients

Adverse Effects:

- Injection-site reactions
- Flu-like symptoms

G. Omega-3 Fatty Acids

Source: Fish oil containing EPA (Eicosapentaenoic acid) and DHA (Docosahexaenoic acid)

Mechanism:

- Inhibit hepatic synthesis of triglycerides and increase fatty acid oxidation.

Effect:

- ↓ Triglycerides (20–50%)

Uses:

- Hypertriglyceridemia
- Prevention of cardiovascular events

Adverse Effects:

- Fishy aftertaste, nausea, diarrhea