


BACHELOR OF PHARMACY · SEMESTER IV

# BP402T Medicinal Chemistry

## Unit III — Drugs Acting on the Cardiovascular System

**Final Unit Notes**

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Four chapters · Anti-anginals · Anti-hypertensives
Congestive heart failure · Anti-arrhythmic drugs

**Pills & Python**
Pharmacy • Data • AI • Healthcare

# Chapter 1 — Anti-anginals

## 1. Learning Objectives

After studying this chapter, you will be able to:

- Define angina pectoris and explain, in simple words, why it causes chest pain.
- Classify anti-anginal drugs chemically into nitrates/organic nitrites, calcium channel blockers (three sub-classes) and miscellaneous agents.
- Describe the chemical structure (scaffold + key substituents) of all 13 anti-anginal drugs in the syllabus.
- Explain the mechanism of anti-anginal action of nitrates (NO → cGMP pathway) and of calcium channel blockers at the drug–chemistry level.
- Write the complete synthesis of Isosorbide dinitrate, naming every reagent and intermediate.
- List the SAR highlights of 1,4-dihydropyridines.
- State the therapeutic uses of each drug.
- Draw the classification flowchart, the nitrate action flowchart, and the 1,4-dihydropyridine scaffold with numbered positions.

## 2. Definitions

**Angina pectoris.** Angina pectoris is a pressing, squeezing chest pain that appears when the heart muscle does not get enough oxygen-rich blood. "Angina" comes from a Latin word meaning "to choke or squeeze"; "pectoris" means "of the chest." It is not a heart attack, but a warning that the heart's blood supply (through the coronary arteries) cannot meet the heart's oxygen demand — usually during exercise, stress or excitement, and it goes away with rest.

**Anti-anginal drug.** An anti-anginal drug is a medicine that prevents or relieves angina chest pain. It does this in one of two chemical ways: (a) by **dilating (widening) blood vessels**, so more blood reaches the heart, or (b) by **reducing the heart's work and oxygen demand**, so the limited blood supply becomes enough. Many drugs do both.

**Myocardial oxygen demand.** "Myocardial" means "of the heart muscle." Myocardial oxygen demand is how much oxygen the heart muscle needs. It rises when the heart beats faster, contracts harder, or pumps against high blood pressure. Angina happens when demand exceeds supply.

**Vasodilator.** A vasodilator is a drug that widens (dilates) blood vessels. "Vaso" = vessel, "dilator" = widener. Wider vessels carry more blood with less resistance.

**Organic nitrate / organic nitrite.** An organic nitrate is a carbon-containing molecule in which an $–O–NO_2$ group (nitrate ester) is attached to carbon, e.g., nitroglycerin. An organic nitrite has an –O–N=O group (nitrite ester) attached to carbon, e.g., amyl nitrite. Both act as **prodrugs of nitric oxide (NO)** — inside the body they release NO gas, which is the real vasodilator.

**Calcium channel blocker (CCB).** A calcium channel blocker is a drug that blocks L-type calcium channels in muscle cells, reducing the entry of $Ca^{2+}$ ions. Less calcium inside the cell means weaker contraction of vascular smooth muscle (so vessels relax and widen) and, for some CCBs, a slower, gentler heartbeat.

**Nitrate tolerance.** Nitrate tolerance is the loss of effect when nitrates are used continuously without a break — the body stops responding and the same dose no longer relieves angina. It is overcome by keeping a daily **nitrate-free interval** (usually 8–12 hours, often overnight).

## 3. Terminology (word-by-word from zero)

| Term | What it means in plain words |
|---|---|
| Scaffold | The central ring or carbon framework of a drug molecule — the "skeleton" to which substituents are attached. Example: the 1,4-dihydropyridine ring is the scaffold of nifedipine. |
| Substituent | A group of atoms attached to the scaffold, e.g., $–NO_2$, $–CH_3$, $–OCH_3$. Substituents decide the drug's exact properties. |
| Ester | A group formed from an acid and an alcohol joined together (–COO– or $–O–NO_2$). Many nitrates and DHP drugs contain ester groups. |
| Aryl | A ring group derived from benzene, e.g., phenyl ($C_6H_5–$). |
| Prodrug | An inactive (or less active) compound that the body converts into the active drug. Example: enalapril → enalaprilat. Organic nitrates are prodrugs of nitric oxide. |
| Vasospasm | A sudden, abnormal tightening (spasm) of a blood vessel, which can itself cause angina (variant/Prinzmetal angina). |
| Preload | The amount of blood returning to the heart (the "load before pumping"). Nitrates mainly reduce preload by dilating veins. |
| Afterload | The resistance the heart must pump against (the "load after pumping"). Arterial dilators mainly reduce afterload. |
| cGMP | Cyclic guanosine monophosphate — a messenger molecule inside cells. Nitric oxide raises cGMP, and cGMP relaxes smooth muscle. |
| Guanylate cyclase | The enzyme that makes cGMP. Nitric oxide switches this enzyme ON. |
| Phenylalkylamine | A chemical family: a phenyl (benzene) ring attached through an alkyl (carbon) chain to an amine (nitrogen) group — the scaffold of verapamil. |
| Benzothiazepine | A fused two-ring system containing benzene + nitrogen + sulphur in a seven-membered ring — the scaffold of diltiazem. |
| 1,4-Dihydropyridine (DHP) | A six-membered ring with one nitrogen, partially saturated (two double bonds) — the scaffold of nifedipine, amlodipine, felodipine, nicardipine and nimodipine. |

## 4. Explanation: what anti-anginals do and why they work

**Technical concept.** Angina is an imbalance: myocardial oxygen demand exceeds coronary oxygen supply. Anti-anginals restore the balance either by increasing supply (coronary vasodilation) or by decreasing demand (reduced heart rate, contractility, preload and afterload).

**Simple explanation.** Think of the heart as a hardworking labourer and oxygen as his food. Angina means the labourer is working very hard but his food supply is short — he gets a painful cramp. An anti-anginal drug helps in two ways: it **widens the food pipe** (dilates blood vessels, so more oxygen reaches the heart), or it **tells the labourer to work more gently** (slows and softens the heartbeat, so he needs less food). Nitrates mainly widen the pipes; calcium channel blockers do both.

**Example.** A patient gets chest pain while climbing stairs. A nitroglycerin tablet under the tongue releases nitric oxide within 1–2 minutes, veins dilate, less blood returns to the heart (preload falls), the heart's work falls, and the pain fades — the labourer gets relief because his workload dropped.

**Key takeaway.** Every anti-anginal either improves the heart's oxygen **supply** or reduces its oxygen **demand**; most do both, through either the nitric-oxide pathway (nitrates) or calcium-channel blockade (CCBs).

# 5. Classification of anti-anginals

**Technical concept.** Anti-anginals are classified by their chemical structure and mechanism into three groups.

**Simple explanation.** Just as students are grouped into sections, these 13 drugs fall into three classrooms: the **nitrate family** (NO donors), the **calcium channel blocker family** (with three sub-sections), and a small **miscellaneous** group.

**The classification:**

**A. Nitrates and organic nitrites (nitric oxide donors)**

1. Amyl nitrite — alkyl nitrite
2. Nitroglycerin (glyceryl trinitrate) — organic nitrate
3. Pentaerythritol tetranitrate — organic nitrate
4. Isosorbide dinitrate* — organic nitrate

**B. Calcium channel blockers (L-type $Ca^{2+}$ channel blockers)**

- *Phenylalkylamines:* 5. Verapamil
- *Benzothiazepines:* 6. Diltiazem
- *1,4-Dihydropyridines:* 7. Nifedipine, 8. Amlodipine, 9. Felodipine, 10. Nicardipine, 11. Nimodipine
- *(Non-DHP, miscellaneous CCB):* 12. Bepridil hydrochloride

**C. Miscellaneous**

1. Dipyridamole — pyrimidopyrimidine coronary vasodilator

**Key takeaway.** Four nitrates, seven calcium channel blockers (1 phenylalkylamine + 1 benzothiazepine + 5 dihydropyridines + bepridil), and one miscellaneous drug (dipyridamole) = 13 drugs.

# 6. Mechanisms of anti-anginal action (drug–chemistry level)

## 6a. Nitrates — the nitric oxide (NO) → cGMP pathway

**Technical concept.** Organic nitrates and nitrites are prodrugs. Inside vascular smooth-muscle cells they are biotransformed (with the help of thiol groups, –SH) to release **nitric oxide (NO)**. NO activates the enzyme **soluble guanylate cyclase**, which converts GTP into **cyclic GMP (cGMP)**. Rising cGMP relaxes vascular smooth muscle → vasodilation.

**Simple explanation.** The nitrate tablet is like a sealed parcel. Inside the blood-vessel wall, the body's chemistry opens the parcel and out comes a tiny gas, nitric oxide. This gas rings a bell (the enzyme guanylate cyclase), the bell makes a messenger (cGMP), and the messenger orders the vessel wall muscles to relax and widen. Wider vessels = less work for the heart = no pain.

**Example.** Nitroglycerin (with three –O–$NO_2$ groups) releases NO; the veins dilate most, so less blood returns to the heart (preload drops), and the heart's oxygen demand drops within minutes.

**Key takeaway.** Nitrates = NO donors → NO activates guanylate cyclase → more cGMP → smooth-muscle relaxation → vasodilation → less cardiac work.

## 6b. Calcium channel blockers — blocking $Ca^{2+}$ entry

**Technical concept.** Contraction of vascular smooth muscle and heart muscle needs $Ca^{2+}$ ions to enter the cell through L-type calcium channels. CCBs bind to these channels and block $Ca^{2+}$ entry. With less intracellular $Ca^{2+}$, vascular smooth muscle relaxes (arterial dilation → afterload falls → coronary flow improves) and cardiac contraction softens. Verapamil and diltiazem also slow the heart rate (less demand); dihydropyridines act mainly on vessels (supply side).

**Simple explanation.** Muscle contraction needs calcium the way a lock needs a key. CCBs jam the keyhole (the calcium channel), so calcium cannot enter, the vessel-wall muscles cannot tighten, and the pipes stay wide and relaxed. Verapamil and diltiazem additionally tell the heart to beat slower and softer.

**Example.** Amlodipine blocks calcium channels mainly in artery walls → arteries relax → blood pressure and afterload fall → the heart works less → angina attacks become rarer.

**Key takeaway.** CCBs block L-type $Ca^{2+}$ channels → less $Ca^{2+}$ inside muscle cells → relaxed vessels + gentler heartbeat → oxygen demand falls and supply rises.

## 7. Diagrams (describe textually so they can be drawn)

**Diagram 1 — Nitrate action pathway (draw as a vertical flow of 5 boxes with arrows).** Box 1: "Organic nitrate (e.g., nitroglycerin, R–O–$NO_2$) enters vascular smooth-muscle cell." Arrow down to Box 2: "Biotransformation with thiol (–SH) groups → releases nitric oxide (NO)." Arrow down to Box 3: "NO activates soluble guanylate cyclase (enzyme switched ON)." Arrow down to Box 4: "GTP → cGMP (messenger level rises)." Arrow down to Box 5: "Smooth-muscle relaxation → vasodilation (veins > arteries) → preload and cardiac work fall → angina relieved." Label the whole diagram: "Nitrates are prodrugs of nitric oxide."

**Diagram 2 — The 1,4-dihydropyridine scaffold with numbered positions (draw a hexagon).** Draw a six-membered ring: position 1 at the bottom is NH; going clockwise, positions 2 and 6 (lower-left and lower-right) each carry a –$CH_3$; positions 3 and 5 (upper-left and upper-right) each carry a –COOR ester group; position 4 at the top carries the aryl ring (drawn as a smaller hexagon with, e.g., –$NO_2$ at ortho position for nifedipine). Mark double bonds between C2=C3 and C5=C6 (the "dihydro" part: N1 and C4 are saturated). Write beneath: "N1–H essential; C4 aryl essential; C3/C5 esters essential."

**Diagram 3 — Calcium channel blockade (draw a cell membrane cross-section).** Draw a horizontal double line (cell membrane) with a barrel-shaped channel protein crossing it, labelled "L-type $Ca^{2+}$ channel." Draw $Ca^{2+}$ ions (small circles with "$Ca^{2+}$") outside the cell with an arrow trying to pass through the channel; draw a CCB molecule (labelled e.g., "verapamil / nifedipine") sitting in the channel like a cork, with a red cross on the arrow. Inside the cell write: "Less $Ca^{2+}$ entry → muscle relaxes → vessel widens." Add a side note: "Verapamil/diltiazem also slow the heart; DHPs act mainly on vessels."

## 8. Flowcharts

**Flowchart 1 — Classification of anti-anginals (draw as a tree).** "ANTI-ANGINALS (13 drugs)" branches into three boxes: "A. Nitrates / organic nitrites (NO donors): amyl nitrite, nitroglycerin, pentaerythritol tetranitrate, isosorbide dinitrate*" → "B. Calcium channel blockers" which sub-branches into "Phenylalkylamine: verapamil," "Benzothiazepine: diltiazem," "Dihydropyridines: nifedipine, amlodipine, felodipine, nicardipine, nimodipine," "Misc. CCB: bepridil HCl" → "C. Miscellaneous: dipyridamole (pyrimidopyrimidine)."

**Flowchart 2 — How a nitrate relieves angina (draw left to right).** "Nitrate dose" → "NO released in vessel wall" → "Guanylate cyclase ON" → "cGMP rises" → "Veins dilate (mainly) + coronary arteries dilate" → "Preload ↓, cardiac work ↓, $O_2$ supply ↑" → "Chest pain relieved." Add a dashed side box: "Continuous use without break → tolerance (keep a daily nitrate-free interval)."

**Flowchart 3 — Synthesis of Isosorbide dinitrate (see full details in Section 12).** "D-Sorbitol" —(conc.

## 9. Infographic concept box

💊 **ANTI-ANGINALS AT A GLANCE The problem:** Heart needs more oxygen than coronaries can supply → chest pain. **Two chemical fixes:** ① **Give NO** — nitrates/nitrites release nitric oxide → cGMP → vessels widen (nitroglycerin works in 1–2 min under the tongue). ② **Block $Ca^{2+}$** — CCBs jam calcium channels → vessels relax + heart calms (verapamil slows the heart; "dipines" widen vessels). **Name tricks:** "-dipine" = dihydropyridine CCB (nifedipine, amlodipine, felodipine, nicardipine, nimodipine). Nitrates carry –O–$NO_2$ groups (count them: nitroglycerin has 3, ISDN has 2, PETN has 4). **Safety stars:** Nitrates need a daily drug-free interval (tolerance); never combine nitrates with sildenafil-type drugs (dangerous BP fall); sublingual nitroglycerin must be stored in amber glass, away from air. **Star synthesis:** Isosorbide dinitrate = sorbitol $\rightarrow(-2\ H_2O)\rightarrow$ isosorbide $\rightarrow$(nitration)$\rightarrow$ ISDN.

## 10. Master table — Chapter 1 drugs

| Drug | Chemical class | Key structure (scaffold + substituents) | Main uses |
|---|---|---|---|
| Amyl nitrite | Alkyl nitrite (organic nitrite) | Isoamyl chain (3-methylbutyl) + –O–N=O nitrite ester | Acute angina attack (inhalation, rapid); rarely used today |
| Nitroglycerin | Organic nitrate | Glycerol scaffold + 3 nitrate ester (–O–$NO_2$) groups | Acute angina (sublingual), chronic angina prophylaxis (patch/ointment), heart failure, hypertensive emergency (IV) |
| Pentaerythritol tetranitrate | Organic nitrate | Pentaerythritol (quaternary carbon + 4 –$CH_2$–) + 4 –O–$NO_2$ groups | Chronic angina prophylaxis (long-acting oral) |
| Isosorbide dinitrate* | Organic nitrate | Bicyclic isosorbide (two fused tetrahydrofuran rings) + 2 –O–$NO_2$ at C2/C5 | Chronic angina prophylaxis; heart failure (with hydralazine) |
| Dipyridamole | Pyrimidopyrimidine (miscellaneous) | Pyrimido[5,4-d]pyrimidine core + 2 piperidino + 2 bis(2-hydroxyethyl)amino groups | Coronary vasodilation/chronic angina (older use); antiplatelet with warfarin in prosthetic valves; pharmacologic cardiac stress testing |
| Verapamil | Phenylalkylamine CCB | Two 3,4-dimethoxyphenyl rings + tertiary methylamino N + nitrile (–CN) + isopropyl branch on alkyl chain | Chronic stable & vasospastic angina; hypertension; supraventricular arrhythmias |
| Bepridil HCl | Diarylalkylamine CCB (miscellaneous/non-DHP) | N-benzyl-N-phenyl (anilino) N + 3-isobutoxy-2-(benzylthio)propyl chain | Chronic stable angina (refractory cases); arrhythmias |
| Diltiazem | Benzothiazepine CCB | 1,5-benzothiazepine ring + 4-methoxyphenyl at C2 + acetoxy at C3 + dimethylaminoethyl at N5 | Chronic stable & vasospastic angina; hypertension; supraventricular arrhythmias |
| Nifedipine | 1,4-Dihydropyridine CCB | DHP ring + 2-nitrophenyl at C4 + methyls at C2/C6 + methyl esters at C3/C5 | Chronic stable & vasospastic angina; hypertension; Raynaud phenomenon |
| Amlodipine | 1,4-Dihydropyridine CCB | DHP ring + 2-chlorophenyl at C4 + (2-aminoethoxy)methyl at C2 + ethyl/methyl esters at C3/C5 | Hypertension; chronic stable & vasospastic angina (long half-life, once daily) |
| Felodipine | 1,4-Dihydropyridine CCB | DHP ring + 2,3-dichlorophenyl at C4 + methyls at C2/C6 + ethyl/methyl esters at C3/C5 | Hypertension; chronic stable angina |
| Nicardipine | 1,4-Dihydropyridine CCB | DHP ring + 3-nitrophenyl at C4 + N-benzyl-N-methylaminoethyl ester side chain at C5 | Hypertension (oral; IV in hypertensive emergency); chronic stable angina |
| Nimodipine | 1,4-Dihydropyridine CCB | DHP ring + 3-nitrophenyl at C4 + 2-methoxyethyl / isopropyl esters at C3/C5 | Subarachnoid haemorrhage — prevents cerebral vasospasm (crosses blood–brain barrier) |

# 11. Drug-by-drug profiles — structure and uses

## A. NITRATES AND ORGANIC NITRITES

### 1. Amyl nitrite

- **Chemical classification:** Alkyl nitrite (organic nitrite ester).
- **Structure:** The scaffold is a simple branched alkyl chain — the **isoamyl (3-methylbutyl) group**, $(CH_3)_2CHCH_2CH_2$–, attached through oxygen to a nitroso group: R–**O–N=O** (a nitrite ester, not a nitrate). Key point: one –O–N=O group; the molecule is small and volatile (a liquid that evaporates easily).
- **Uses:** Inhaled for the **rapid relief of an acute angina attack** (effect in seconds); also a historical antidote in cyanide poisoning. Rarely used today because sublingual nitroglycerin is more convenient.

### 2. Nitroglycerin (glyceryl trinitrate, GTN)

- **Chemical classification:** Organic nitrate (nitrate ester); the most famous anti-anginal.
- **Structure:** Scaffold = **glycerol** (propane-1,2,3-triol, a 3-carbon chain). All three –OH groups are esterified with nitric acid, giving **three –O–$NO_2$ (nitrate ester) groups** — propane-1,2,3-triyl trinitrate. Key substituents: 3 × –O–$NO_2$. (Note: despite the name, it is not the explosive used as such in medicine — medicinal doses are in micrograms to milligrams.)
- **Uses: Acute angina** — sublingual tablet/spray (acts in 1–2 minutes, the drug of choice for an attack); **chronic angina prophylaxis** — transdermal patch and ointment; acute heart failure and hypertensive emergency (IV infusion).

### 3. Pentaerythritol (pentaerythritol tetranitrate, PETN)

- **Chemical classification:** Organic nitrate (long-acting).
- **Structure:** Scaffold = **pentaerythritol**, $C(CH_2OH)_4$ — a central quaternary carbon carrying four –$CH_2OH$ arms. All four hydroxyls are converted to nitrate esters, giving **four –O–$NO_2$ groups**: $C(CH_2ONO_2)_4$. More nitrate groups and a bulkier molecule → slower, longer action than nitroglycerin.
- **Uses: Prophylaxis (prevention) of chronic stable angina** — taken orally on a regular schedule; not for an acute attack (too slow).

**4. Isosorbide dinitrate* (ISDN)**

- **Chemical classification:** Organic nitrate (medium/long-acting).
- **Structure:** Scaffold = **isosorbide** (1,4:3,6-dianhydro-D-sorbitol) — a rigid **bicyclic system of two fused tetrahydrofuran rings** shaped like a folded "V". Two secondary hydroxyl groups (at positions 2 and 5) are converted to **two –O–$NO_2$ nitrate ester groups**. In the body one nitrate is removed to give isosorbide mononitrate, which is itself active and long-acting.
- **Uses: Prophylaxis of chronic angina** (oral, sustained); **heart failure** — combined with hydralazine; also used sublingually for acute attacks in some settings.
- **Synthesis:** see Section 12 (starred — full steps, reagents and intermediates).

## B. CALCIUM CHANNEL BLOCKERS

### 5. Verapamil

- **Chemical classification:** Phenylalkylamine calcium channel blocker (non-dihydropyridine).
- **Structure:** Scaffold = a **phenylalkylamine** framework: two aromatic rings joined by a branched alkyl chain carrying a **tertiary amine nitrogen** (methylamino, –N($CH_3$)–). Key substituents: **two 3,4-dimethoxyphenyl rings** (benzene rings with two –$OCH_3$ groups each), an **isopropyl branch**, and a **nitrile (–C≡N) group** on the chain next to one ring. Full name: 2-(3,4-dimethoxyphenyl)-5-{[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino}-2-isopropylpentanenitrile.
- **Uses: Chronic stable angina and vasospastic (Prinzmetal) angina**; hypertension; **supraventricular arrhythmias** (SVT, atrial fibrillation rate control — because it slows AV-node conduction); migraine prophylaxis.

### 6. Diltiazem

- **Chemical classification:** Benzothiazepine calcium channel blocker (non-dihydropyridine).
- **Structure:** Scaffold = **1,5-benzothiazepine** — a benzene ring fused to a seven-membered ring containing one nitrogen and one sulphur. Key substituents: a **4-methoxyphenyl ring at C2**, an **acetoxy (–$OCOCH_3$) group at C3**, and a **2-(dimethylamino)ethyl chain at N5**. The molecule has defined stereochemistry (2S,3S).
- **Uses: Chronic stable and vasospastic angina**; hypertension; **supraventricular arrhythmias** (like verapamil, it slows the heart).

### 7. Nifedipine

- **Chemical classification:** 1,4-Dihydropyridine (DHP) calcium channel blocker — the prototype DHP.
- **Structure:** Scaffold = **1,4-dihydropyridine ring** (six-membered, one NH). Key substituents: **2-nitrophenyl ring at C4** (ortho-nitro aryl), **methyl groups at C2 and C6**, and **methyl ester (–$COOCH_3$) groups at C3 and C5**. Short-acting; mainly a vascular (artery) dilator.
- **Uses: Chronic stable and vasospastic angina**; hypertension; Raynaud phenomenon (painful finger/toe vasospasm).

### 8. Amlodipine

- **Chemical classification:** 1,4-Dihydropyridine calcium channel blocker (long-acting).
- **Structure:** DHP scaffold with **2-chlorophenyl at C4** (ortho-chloro aryl), **methyl at C6**, **ethyl and methyl esters at C3/C5**, and the signature substituent: a **(2-aminoethoxy)methyl side chain (–$CH_2OCH_2CH_2NH_2$) at C2**. This basic amino side chain is protonated at body pH, giving very slow receptor binding/unbinding → **half-life 30–50 hours**, once-daily dosing.
- **Uses: Hypertension** (one of the most prescribed drugs in India); **chronic stable and vasospastic angina**.

### 9. Felodipine

- **Chemical classification:** 1,4-Dihydropyridine calcium channel blocker.
- **Structure:** DHP scaffold with **2,3-dichlorophenyl at C4** (two chlorines on the aryl ring), **methyls at C2/C6**, and **ethyl + methyl esters at C3/C5** (unsymmetrical esters). Highly vascular-selective.
- **Uses: Hypertension**; chronic stable angina. (Counselling point: avoid grapefruit juice — it raises felodipine blood levels.)

### 10. Nicardipine

- **Chemical classification:** 1,4-Dihydropyridine calcium channel blocker.
- **Structure:** DHP scaffold with **3-nitrophenyl at C4** (meta-nitro aryl), **methyls at C2/C6**, a **methyl ester at C3**, and a distinctive **aminoalkyl ester at C5**: –$COOCH_2CH_2N(CH_3)CH_2Ph$ (an N-benzyl-N-methylaminoethyl ester). This basic side chain improves water solubility for IV use.
- **Uses: Hypertension** — oral for chronic use and **IV for hypertensive emergency**; chronic stable angina.

### 11. Nimodipine

- **Chemical classification:** 1,4-Dihydropyridine calcium channel blocker (cerebro-selective).
- **Structure:** DHP scaffold with **3-nitrophenyl at C4**, **methyls at C2/C6**, and **2-methoxyethyl and isopropyl esters at C3/C5**. Highly **lipophilic** (fat-soluble) → crosses the blood–brain barrier easily.
- **Uses: Subarachnoid haemorrhage** — prevents/dilates cerebral vasospasm after brain bleeding. Its main value is in the brain's vessels, not the heart.

### 12. Bepridil hydrochloride

- **Chemical classification:** Diarylalkylamine calcium channel blocker — grouped as a **non-dihydropyridine / miscellaneous CCB** (also has class-III antiarrhythmic character).
- **Structure:** Scaffold = a central **tertiary amine nitrogen** carrying three carbon groups: an **N-benzyl** group, an **N-phenyl (anilino)** group, and a **3-isobutoxy-2-(benzylthio)propyl chain** — i.e., N-benzyl-N-[3-isobutoxy-2-(benzylthio)propyl]aniline. Key substituents: two benzyl-type aromatic rings, an **isobutoxy (–$OCH_2CH(CH_3)_2$) ether**, and a **benzylthio (–$SCH_2Ph$) thioether**. Used as the hydrochloride salt.
- **Uses: Chronic stable angina** (reserved for refractory cases); cardiac arrhythmias.

### C. MISCELLANEOUS

**13. Dipyridamole**

- **Chemical classification:** Pyrimidopyrimidine derivative — miscellaneous coronary vasodilator/antiplatelet.
- **Structure:** Scaffold = **pyrimido[5,4-d]pyrimidine** — two fused six-membered rings, each containing two nitrogens (a "double pyrimidine"). Key substituents: **two piperidino rings** at positions 4 and 8, and **two bis(2-hydroxyethyl)amino groups** [–$N(CH_2CH_2OH)_2$] at positions 2 and 6. It inhibits phosphodiesterase and blocks adenosine uptake.
- **Uses:** Older use in **chronic angina** (coronary vasodilator); **antiplatelet** — combined with warfarin to prevent clots in prosthetic heart valves; **pharmacologic cardiac stress testing** (dipyridamole–thallium stress test dilates coronaries to reveal blockages).

## 12. Synthesis of Isosorbide dinitrate* (starred)

> **Technical concept.** Isosorbide dinitrate is made in two chemical operations from the sugar alcohol D-sorbitol: (1) **double dehydration** (removing two water molecules with strong acid) to build the bicyclic isosorbide scaffold, then (2) **nitration** (esterification with nitric acid) of its two hydroxyl groups.

**Step 1 — Dehydration of D-sorbitol to isosorbide.**

- **Starting material:** D-Sorbitol — $HOCH_2–(CHOH)_4–CH_2OH$, a six-carbon sugar alcohol (glucitol).
- **Reagent and conditions:** Concentrated sulphuric acid (conc. $H_2SO_4$), with heating.
- **Reaction:** Two molecules of water are removed intramolecularly (–2 $H_2O$); the chain folds and closes into two ether linkages, forming the bicyclic dianhydro structure.
- **Intermediate/product of step 1: Isosorbide** (1,4:3,6-dianhydro-D-sorbitol) — two fused tetrahydrofuran rings with two free secondary –OH groups (at C2 and C5).

**Step 2 — Nitration of isosorbide to isosorbide dinitrate.**

- **Starting material:** Isosorbide (from Step 1).
- **Reagents and conditions: Mixed acid** — concentrated nitric acid (conc. $HNO_3$) + concentrated sulphuric acid (conc. $H_2SO_4$), at low temperature (0–5 °C). (The sulphuric acid generates the nitronium ion $NO_2^+$, the active nitrating species.)
- **Reaction:** Esterification (O-nitration) of both secondary hydroxyl groups: 2 × (–OH → $–O–NO_2$).
- **Final product: Isosorbide 2,5-dinitrate (isosorbide dinitrate, ISDN).**

> **Simple explanation.** Start with sorbitol, a sweet sugar-like alcohol. Boil it with strong sulphuric acid and it loses two waters and folds into a rigid double-ring (isosorbide) — like folding a strip of paper into a heart shape. Then treat it with a cold mixture of nitric and sulphuric acids, which sticks a nitrate group ($–O–NO_2$) onto each of its two –OH handles. The result is isosorbide dinitrate.

> **Example of the balanced change:** Sorbitol ($C_6H_{14}O_6$) – $2H_2O$ → Isosorbide ($C_6H_{10}O_4$); Isosorbide + 2 $HNO_3$ → Isosorbide dinitrate ($C_6H_8N_2O_8$) + 2 $H_2O$.

**Key takeaway.** Sorbitol —(conc. $H_2SO_4$, heat; $–2H_2O$)→ isosorbide —($HNO_3/H_2SO_4$ mixed acid, 0–5 °C)→ isosorbide dinitrate. Two steps, two reagents systems, one bicyclic intermediate.

## 13. SAR highlights of 1,4-dihydropyridines

**Technical concept.** SAR (structure–activity relationship) = how each part of the molecule contributes to calcium-channel-blocking activity. The 1,4-DHP pharmacophore is strict: small changes switch activity ON or OFF.

**The SAR rules (learn these six):**

1. **The 1,4-dihydropyridine ring is essential.** Oxidation (aromatization) of the DHP ring to a fully aromatic **pyridine** ring destroys activity — the partially saturated "dihydro" state is required for the correct 3D shape.
2. **N1 must carry a hydrogen (N–H).** The N–H acts as a hydrogen-bond donor to the receptor. **N-substitution** (replacing the H with any carbon group) **abolishes activity**.
3. **A C4 aryl (or heteroaryl) substituent is essential.** The phenyl ring at C4 sits **perpendicular** to the DHP ring (bisecting it) — this twisted shape is the key to receptor fit. **Ortho- or meta-substituted phenyls** (2-nitro, 2-chloro, 2,3-dichloro, 3-nitro) are best; para-substitution alone is weaker. Removing the C4 aryl kills activity.
4. **C3 and C5 need ester (or electron-withdrawing) groups.** Two –COOR ester groups are optimal; they act as hydrogen-bond acceptors. **Unsymmetrical esters** (different R groups at C3 vs C5, e.g., felodipine's ethyl/methyl, amlodipine's ethyl/methyl) fine-tune vascular selectivity and duration.
5. **C2 and C6 carry small alkyl groups (methyl is best).** Larger groups at C2/C6 reduce activity; the methyls lock the ring's shape.
6. **Stereochemistry matters — C4 is a chiral centre.** The two mirror images (enantiomers) differ in potency; e.g., **(S)-amlodipine is the active enantiomer** (sold separately as S-amlodipine/levamlodipine in India), while the (R)-form is nearly inactive as a CCB.

**Simple explanation.** Think of the DHP molecule as a key: the DHP ring is the key's blade, the N–H is a tooth that grips the lock, the twisted aryl ring at C4 is the precisely cut pattern, and the two ester groups are the handle's grip points. File down any tooth (oxidize the ring, substitute the N–H, remove the aryl) and the key no longer opens the calcium-channel lock.

**Example.** Nifedipine (2-nitrophenyl at C4, methyl esters) is the prototype; amlodipine keeps the same key pattern but adds the aminoethoxymethyl "handle" at C2, which makes it bind longer → 30–50-hour half-life → once-daily tablet.

**Key takeaway.** DHP activity needs: intact 1,4-DHP ring + free N1–H + perpendicular ortho/meta-substituted C4 aryl + C3/C5 esters + C2/C6 methyls + correct (S) stereochemistry at C4.

## 14. Worked examples

**Example 1 — Counting nitrate groups.** Nitroglycerin has 3 –O–$NO_2$ groups, isosorbide dinitrate has 2, pentaerythritol tetranitrate has 4 ("tetra" = 4). Exam questions often ask "how many nitrate ester groups" — read the prefix: di- = 2, tri- = 3, tetra- = 4.

**Example 2 — Spot the DHP.** Which of these is a dihydropyridine: verapamil, diltiazem, amlodipine? Amlodipine — the name ends in "-dipine," and its structure has the 1,4-DHP ring with a C4 aryl group. Verapamil is a phenylalkylamine (no ring at the centre, just a chain with a nitrogen); diltiazem is a benzothiazepine (fused benzene + N/S seven-membered ring).

**Example 3 — Prodrug logic.** Isosorbide dinitrate loses one –$NO_2$ group in the liver to become isosorbide mononitrate, which is still active. So ISDN is effectively a prodrug of its own longer-acting metabolite — which is why ISDN acts longer than nitroglycerin.

## 15. Analogies

1. **Nitrates as "parcel + gas."** The nitrate tablet is a sealed parcel; the vessel wall opens it and releases NO gas, like opening a soda bottle releases fizz that relaxes everything around it.
2. **CCBs as "cork in the keyhole."** The calcium channel is a keyhole, calcium is the key that tightens muscles; the CCB is a cork jammed in the keyhole — no key, no tightening, the vessel stays relaxed.
3. **Preload vs afterload as "inbox vs outbox."** Preload is the inbox (blood arriving at the heart); afterload is the outbox resistance (pressure the heart pushes against). Nitrates mainly empty the inbox (dilate veins); DHPs mainly clear the outbox (dilate arteries).
4. **DHP SAR as "a key's teeth."** Each substituent (N–H, C4 aryl, C3/C5 esters) is a tooth on a key; grinding off any tooth means the key fails to open the calcium-channel lock.

## 16. Pharmacy relevance

- **Counselling on sublingual nitroglycerin:** keep tablets in the original **amber glass bottle**, tightly closed (they lose potency in air/light/plastic); sit down before taking (dizziness from sudden BP fall); if pain persists after 3 doses 5 minutes apart, seek emergency care (possible heart attack).
- **Nitrate-free interval:** advise patients on patches/ointment to remove the patch at bedtime (8–12 hours off) to prevent tolerance.
- **Never combine nitrates with sildenafil/tadalafil** (erectile-dysfunction drugs) — the combination can cause a fatal fall in blood pressure. A pharmacist must screen for this.
- **Verapamil + beta-blocker caution:** both slow the heart — the combination can cause dangerous bradycardia/heart block; flag it.
- **Grapefruit juice** markedly raises blood levels of felodipine (and some other DHPs) — counsel avoidance.
- **Amlodipine ankle swelling** is the commonest reason patients stop it — reassure that it is expected (vasodilation), not kidney failure, and refer if severe.

## 17. India context

- **Amlodipine** is among the most prescribed antihypertensive/anti-anginal tablets in India, available as low-cost generics (often combined with atenolol or telmisartan).
- **Sublingual nitroglycerin (e.g., "sorbitrate" is ISDN; nitroglycerin as "nitrocontin"/sublingual)** — isosorbide dinitrate sublingual tablets are widely stocked in Indian pharmacies for angina; pharmacists must counsel on storage and the headache side effect (common, usually fades).
- **S-Amlodipine (levamlodipine)** is marketed in India as the single active enantiomer — a direct application of DHP stereochemistry SAR.
- Rheumatic and coronary heart disease burden in India makes anti-anginal counselling (chest-pain action plans) a core community-pharmacy role.

## 18. Key points

1. Angina = oxygen demand exceeds supply; anti-anginals restore the balance.
2. Two main chemistries: **NO donors** (nitrates/nitrites → NO → guanylate cyclase → cGMP → vasodilation) and **$Ca^{2+}$ channel blockers** (block L-type channels → relaxed vessels ± slower heart).
3. Nitrates: amyl nitrite (nitrite, inhaled, acute), nitroglycerin (3 –O–$NO_2$, sublingual, acute), pentaerythritol tetranitrate (4 –O–$NO_2$, chronic prophylaxis), isosorbide dinitrate* (2 –O–$NO_2$, chronic prophylaxis; synthesis: sorbitol → isosorbide → nitration).
4. CCBs: verapamil (phenylalkylamine), diltiazem (benzothiazepine), five DHPs (–dipines), bepridil (miscellaneous CCB).
5. DHP SAR: intact 1,4-DHP ring, free N1–H, perpendicular ortho/meta C4 aryl, C3/C5 esters, C2/C6 methyls, (S) stereochemistry at C4.
6. Dipyridamole = pyrimidopyrimidine, miscellaneous — coronary vasodilator + antiplatelet + stress-test agent.

## 19. Common confusions

- **Nitrite vs nitrate:** Amyl **nitrite** = R–O–N=O (one N, one double-bonded O); **nitrates** = R–O–$NO_2$. One letter changes the functional group — write it carefully.
- **Isosorbide dinitrate vs isosorbide mononitrate:** the dinitrate has 2 –O–$NO_2$ groups and is partly converted in the body to the mononitrate (1 group, longer-acting). They are different medicines.
- **Nifedipine vs nicardipine vs nimodipine:** all DHPs ("-dipine"), but nifedipine = prototype angina/HTN, nicardipine = IV option in hypertensive emergency, nimodipine = brain vasospasm after subarachnoid haemorrhage.
- **Verapamil vs diltiazem vs DHPs:** verapamil/diltiazem slow the heart (used in arrhythmias); DHPs mainly dilate vessels (little heart-rate effect).

## 20. Common mistakes

- Drawing the DHP ring as fully aromatic pyridine and still calling it active — aromatization **destroys** activity.
- Writing "N-substituted DHP is more active" — N-substitution **abolishes** activity; the N–H must stay free.
- Calling amyl nitrite a "nitrate" — it is a **nitrite**.
- Forgetting that nitrates need a **daily drug-free interval** to avoid tolerance.
- Mixing up preload (veins, nitrates) with afterload (arteries, DHPs).

## 21. Mnemonics

- **"DiPINEs dilate arteries":** all five DHPs end in **-dipine** — niFeDipine, amloDipine, feloDipine, nicarDipine, nimoDipine.
- **"Nitro counts": Tri**nitrate = 3 (nitroglycerin), **Di**nitrate = 2 (ISDN), **Tetra**nitrate = 4 (pentaerythritol) — the prefix counts the –O–$NO_2$ groups.
- **"Very Dashing Doctors":** CCB sub-classes in order — **V**erapamil (phenylalkylamine), **D**iltiazem (benzothiazepine), **D**HPs (the -dipines).
- **DHP SAR — "NEACMS": N**1–H free, **E**sters at C3/C5, **A**ryl at C4 (perpendicular), **C**orrect (S) stereochemistry, **M**ethyls at C2/C6, **S**aturated dihydro ring (not pyridine).

## 22. Exam summary

Anti-anginals relieve chest pain by improving myocardial oxygen supply or reducing demand. **Nitrates** (amyl nitrite, nitroglycerin, pentaerythritol tetranitrate, isosorbide dinitrate*) are NO-donor prodrugs: NO activates guanylate cyclase → ↑cGMP → vasodilation (veins > arteries) → ↓preload and cardiac work. **Calcium channel blockers** block L-type $Ca^{2+}$ entry: verapamil (phenylalkylamine) and diltiazem (benzothiazepine) also slow the heart; the five **1,4-dihydropyridines** (nifedipine, amlodipine, felodipine, nicardipine, nimodipine) are vascular-selective. **Bepridil** is a miscellaneous CCB; **dipyridamole** (pyrimidopyrimidine) is miscellaneous. ISDN synthesis: D-sorbitol —(conc. $H_2SO_4$, heat)→ isosorbide —($HNO_3$/$H_2SO_4$, 0–5 °C)→ isosorbide dinitrate. DHP SAR: intact DHP ring, free N1–H, perpendicular C4 aryl (ortho/meta), C3/C5 esters, C2/C6 methyls, (S) configuration.

## 23. One-minute revision

- Angina: demand > supply. Fix = widen vessels or calm the heart.
- Nitrates → NO → cGMP → dilation. GTN = acute (sublingual); ISDN/PETN = chronic.
- ISDN synthesis: sorbitol → isosorbide → dinitrate (mixed acid, cold).
- CCBs block $Ca^{2+}$ entry. Verapamil (phenylalkylamine) + diltiazem (benzothiazepine) slow the heart; "-dipines" (DHPs) dilate arteries.
- DHP SAR: N–H free, C4 aryl twisted, C3/C5 esters, C2/C6 methyls, S-form active.
- Dipyridamole: pyrimidopyrimidine, antiplatelet + stress test.

## 24. Exam questions

### Short-answer questions

1. Define angina pectoris. How do anti-anginal drugs relieve it? (2 mechanisms)
2. Classify anti-anginal drugs with two examples in each class.
3. Explain the NO → cGMP pathway of nitrate action with a labelled flow diagram.
4. Why do nitrates require a daily drug-free interval?
5. Write the structure (scaffold + substituents) of nifedipine and of diltiazem.
6. Give the uses of nimodipine and dipyridamole.
7. State any four SAR highlights of 1,4-dihydropyridines.

### Long-answer questions

1. Classify anti-anginal drugs chemically. Describe the mechanism of action of organic nitrates and calcium channel blockers at the molecular level, with diagrams.
2. Write the complete synthesis of isosorbide dinitrate starting from D-sorbitol, naming all reagents, intermediates and reaction conditions. Give its structure and uses.
3. Discuss the structure–activity relationship of 1,4-dihydropyridine calcium channel blockers. Illustrate with the structures of nifedipine and amlodipine.

### MCQs (answers at the end)

1. Which drug is an alkyl nitrite?
   a) Nitroglycerin b) Amyl nitrite c) Isosorbide dinitrate d) Pentaerythritol tetranitrate
2. Nitrates relieve angina mainly by releasing:
   a) Calcium b) Nitric oxide c) Potassium d) Prostaglandin
3. The enzyme activated by nitric oxide is:
   a) Adenylate cyclase b) Guanylate cyclase c) Phosphodiesterase d) ACE
4. Which CCB belongs to the benzothiazepine class?
   a) Verapamil b) Diltiazem c) Amlodipine d) Bepridil
5. In the synthesis of isosorbide dinitrate, sorbitol is first treated with:
   a) Dilute HCl b) Conc. $H_2SO_4$ with heat c) NaOH d) $H_2$/Pd
6. Which substituent pattern is essential for DHP activity at N1?
   a) N–$CH_3$ b) Free N–H c) N–$COCH_3$ d) N–Ph
7. (S)-amlodipine is the active enantiomer because:
   a) It is cheaper b) C4 stereochemistry fits the receptor c) It is more soluble d) It has no chiral centre
8. Nimodipine is preferred in subarachnoid haemorrhage because it:
   a) Lowers cholesterol b) Crosses the blood–brain barrier c) Is given IV only d) Blocks beta receptors

*Answers: 1-b, 2-b, 3-b, 4-b, 5-b, 6-b, 7-b, 8-b*

### Viva questions

1. What is the difference between a nitrate and a nitrite ester?
2. Why is nitroglycerin given sublingually and not swallowed for an acute attack?
3. Name the intermediate in ISDN synthesis.
4. Which DHP has the longest half-life, and which structural feature causes it?
5. Why should nitrates not be combined with sildenafil?

### Application-based questions

1. A patient on a nitroglycerin patch 24 hours a day reports returning chest pain. Explain the chemistry-based reason and the pharmacist's advice.
2. A prescription contains verapamil + atenolol. Identify the interaction risk and explain it using the drugs' mechanisms.
3. Design a counselling checklist for a patient starting sublingual nitroglycerin (storage, use, when to seek help).

## 25. References


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# Chapter 2 — Anti-hypertensives

## 1. Learning Objectives

After studying this chapter, you will be able to:

- Define hypertension and blood pressure in simple words.
- Classify anti-hypertensive drugs chemically into beta-blockers, ACE inhibitors (three zinc-binding types), centrally acting agents, peripheral sympatholytics, direct vasodilators and the Rauwolfia alkaloid.
- Describe the chemical structure (scaffold + key substituents) of all 15 anti-hypertensive drugs in the syllabus.
- Explain the SAR of ACE inhibitors, naming the three key binding groups that grip the enzyme.
- Write the complete synthesis of Methyldopate, naming every reagent and intermediate.
- State the therapeutic uses of each drug.
- Draw the classification flowchart, the ACE-inhibitor binding model, and the methyldopate synthesis flowchart.

## 2. Definitions

**Blood pressure (BP).** Blood pressure is the force that flowing blood exerts on the walls of the arteries. It is written as two numbers, e.g., 120/80 mmHg: the higher (systolic) is the pressure when the heart contracts and pushes blood out; the lower (diastolic) is the pressure when the heart relaxes between beats.

**Hypertension.** Hypertension is persistently high blood pressure (commonly ≥140/90 mmHg on repeated measurement). It usually has no symptoms but silently damages the heart, brain, kidneys and eyes — which is why it is called the "silent killer."

**Anti-hypertensive drug.** An anti-hypertensive drug is a medicine that lowers high blood pressure. Different chemical families do this at different control points: slowing the heart (beta-blockers), blocking the angiotensin system (ACE inhibitors), calming the brain's signals (centrally acting agents), blocking nerve signals to vessels (peripheral sympatholytics), or directly relaxing vessel walls (direct vasodilators).

**ACE (angiotensin-converting enzyme).** ACE is a zinc-containing enzyme that converts angiotensin I (inactive) into angiotensin II — a very powerful vessel-constrictor that also triggers aldosterone release (salt and water retention). Blocking ACE therefore dilates vessels and removes salt/water → blood pressure falls.

**Zinc-binding group.** ACE carries a $Zn^{2+}$ ion at its active site, which is essential for its cutting action. ACE inhibitors work by offering a chemical group (–SH, $–COO^-$ or $–PO_2^-$) that **grips this zinc ion** like a magnet, switching the enzyme off.

**Prodrug.** An inactive compound converted by the body into the active drug. Several ACE inhibitors (enalapril, benazepril, quinapril) are ester prodrugs of their active di-acid forms; methyldopate is the ethyl ester prodrug of methyldopa.

**Sympatholytic.** A drug that reduces the activity of the sympathetic ("fight-or-flight") nervous system — the system that normally tightens vessels and quickens the heart. Less sympathetic drive → relaxed vessels, slower heart → lower BP.

**Vasodilator.** A drug that directly relaxes vascular smooth muscle, widening the vessels (see Chapter 1 terminology).

## 3. Terminology (word-by-word from zero)

| Term | What it means in plain words |
|---|---|
| Beta-blocker | A drug that blocks beta-adrenergic receptors (β1 in heart, β2 in lungs/vessels) — the "receivers" for adrenaline. Blocked receivers → slower, gentler heartbeat → lower BP. Timolol is the syllabus example. |
| Aryloxypropanolamine | The chemical scaffold of most beta-blockers: an aromatic ring–O–$CH_2$–CH(OH)–$CH_2$–NH– chain. Timolol carries this side chain. |
| Sulfhydryl (–SH) | A sulphur–hydrogen group ("thiol"). Captopril's –SH grips the zinc of ACE. |
| Dicarboxylate | A molecule carrying two carboxylic-acid/carboxylate (–COOH/–$COO^-$) groups. Enalaprilat, lisinopril, benazeprilat and quinaprilat are dicarboxylate-type ACE inhibitors. |
| Phosphinate (–$PO_2^-$) | A phosphorus-based zinc-binding group used by the third ACE-inhibitor type (e.g., fosinopril — named for classification only). |
| Imidazoline | A five-membered ring with two nitrogens, partially saturated — the scaffold of clonidine. |
| Guanidine | A strongly basic group, –NH–C(=NH)–$NH_2$, that is positively charged at body pH — the key group of guanethidine and guanabenz. |
| Benzothiadiazine | A benzene fused to a six-membered ring containing two nitrogens and one sulphur (as –$SO_2$–) — the scaffold of diazoxide. |
| Phthalazine | A benzene fused to a six-membered ring with two adjacent nitrogens (a diazanaphthalene) — the scaffold of hydralazine. |
| Indole alkaloid | A natural product built on the indole ring (benzene fused to a nitrogen five-ring) — reserpine is a complex indole alkaloid from *Rauwolfia*. |
| Rebound hypertension | A dangerous BP spike when a drug (especially clonidine) is stopped suddenly — the body overreacts after being suppressed. |
| Dry cough (ACE-inhibitor cough) | A persistent tickly cough caused by ACE inhibitors (bradykinin build-up); a class side effect pharmacists must recognise. |

## 4. Explanation: how anti-hypertensives lower blood pressure

**Technical concept.** Blood pressure = cardiac output × peripheral resistance. Drugs lower it by reducing cardiac output (beta-blockers), reducing peripheral resistance (vasodilators, CCBs, ACE inhibitors), reducing blood volume (less salt/water via ACE blockade), or reducing sympathetic drive (central and peripheral sympatholytics).

**Simple explanation.** Blood pressure is like water pressure in a garden pipe system. You can lower it four ways: (1) **turn down the pump** — slow the heart (beta-blockers like timolol); (2) **widen the pipes** — relax vessel walls (direct vasodilators, ACE inhibitors); (3) **drain some water** — lose salt and water (ACE inhibitors do this via aldosterone); (4) **calm the controller** — reduce the brain's "tighten up!" signals (clonidine, guanabenz centrally; guanethidine, reserpine peripherally).

**Example.** Captopril blocks ACE → less angiotensin II → vessels relax AND less aldosterone → less salt/water retained → BP falls by two routes at once. That is why ACE inhibitors are first-line drugs.

**Key takeaway.** Every anti-hypertensive lowers BP by acting on one (or more) of four handles: heart rate/force, vessel width, blood volume, or nerve signals.

# 5. Classification of anti-hypertensives

**Technical concept.** The 15 drugs fall into six chemical/mechanistic families.

**Simple explanation.** Fifteen drugs, six classrooms — grouped by where and how their chemistry acts.

**The classification:**

**A. Beta-adrenergic blocker**

1. Timolol — aryloxypropanolamine, non-selective β1/β2 blocker

**B. ACE inhibitors** (by zinc-binding group)

- *Sulfhydryl type:* 2. Captopril
- *Dicarboxylate type:* 3. Lisinopril (active), 4. Enalapril (prodrug → enalaprilat), 5. Benazepril (prodrug → benazeprilat), 6. Quinapril (prodrug → quinaprilat)
- *Phosphinate type:* (fosinopril — named for classification completeness; not in syllabus drug list)

**C. Centrally acting sympatholytics**

1. Methyldopate* (prodrug of methyldopa) — α-methyl amino acid derivative
2. Clonidine — imidazoline α2-agonist
3. Guanabenz — aminoguanidine α2-agonist

**D. Peripheral sympatholytic (adrenergic neuron blocker)**

1. Guanethidine — guanidine derivative

**E. Direct vasodilators**

1. Sodium nitroprusside — iron–nitrosyl complex (NO donor)
2. Diazoxide — benzothiadiazine ($K^+$-channel opener)
3. Minoxidil — pyrimidine N-oxide ($K^+$-channel opener)
4. Hydralazine — phthalazine (hydrazinophthalazine)

**F. Rauwolfia alkaloid**

1. Reserpine — indole (yohimbane) alkaloid; catecholamine depletor

**Key takeaway.** 1 beta-blocker + 5 ACE inhibitors + 3 centrally acting + 1 peripheral sympatholytic + 4 direct vasodilators + 1 Rauwolfia alkaloid = 15 drugs.

# 6. Mechanisms (drug–chemistry level)

## 6a. ACE inhibitors — gripping the zinc

**Technical concept.** ACE is a zinc metallopeptidase: its $Zn^{2+}$ ion polarises the carbonyl of angiotensin I so the enzyme can cut it. ACE inhibitors insert a **zinc-binding group** (–SH in captopril, $–COO^-$ in the dicarboxylates) that coordinates the $Zn^{2+}$, while the inhibitor's **C-terminal carboxylate** binds a positively charged pocket and its **amide carbonyl** hydrogen-bonds — a three-point grip that freezes the enzyme. No ACE activity → no angiotensin II → vasodilation + less aldosterone → BP falls.

**Simple explanation.** ACE is a pair of scissors, and the zinc ion is the screw holding the blades. An ACE inhibitor jams the screw (zinc-binding group), grabs the handle (carboxylate) and blocks the blades

**Example.** Captopril's –SH group latches onto $Zn^{2+}$; its proline carboxylate sits in the enzyme's positive pocket — two anchors, one molecule, enzyme off.

**Key takeaway.** ACE inhibitors = zinc grip + carboxylate anchor + carbonyl H-bond → no angiotensin II → vessels relax, salt/water lost, BP falls.

### 6b. Centrally acting agents — calming the brain's signals

**Technical concept.** Clonidine and guanabenz stimulate **α2-receptors in the brainstem**; methyldopa (from methyldopate) is converted in the brain to α-methylnorepinephrine, which also stimulates α2-receptors. α2 stimulation switches OFF sympathetic outflow — fewer "tighten vessels / speed heart" signals leave the brain → vasodilation + slower heart → BP falls.

**Simple explanation.** The brain is the control room sending "tighten the pipes!" orders down the nerves. These drugs press the control room's own OFF switch (the α2 receptor) — the orders stop, the pipes relax, the heart slows.

**Key takeaway.** Central agents activate brain α2-receptors → sympathetic outflow switched off → vessels dilate, heart slows.

### 6c. Direct vasodilators — relaxing the vessel wall itself

**Technical concept.** Sodium nitroprusside releases **NO** (like the nitrates of Chapter 1) → cGMP → relaxation. Diazoxide and minoxidil **open ATP-sensitive $K^+$ channels** → $K^+$ leaves the cell → membrane hyperpolarises → $Ca^{2+}$ channels close → relaxation. Hydralazine relaxes arterial smooth muscle by an incompletely defined direct action (interferes with $Ca^{2+}$ movements).

**Simple explanation.** These drugs skip the brain and nerves and talk directly to the vessel wall: "Relax!" — via NO gas, via potassium doors, or (hydralazine) by interfering with the muscle's calcium machinery.

**Key takeaway.** Direct vasodilators act on the vessel muscle itself — NO donation (nitroprusside), $K^+$-channel opening (diazoxide, minoxidil), or direct arterial relaxation (hydralazine).

## 7. Diagrams (describe textually so they can be drawn)

**Diagram 1 — ACE-inhibitor three-point binding model (draw the enzyme pocket as a U-shaped cleft).** Draw a U-shaped pocket labelled "ACE active site." At the bottom of the U draw a circle labelled "$Zn^{2+}$." Draw the inhibitor as three connected blocks sitting in the U: block 1 (left) labelled "Zinc-binding group: –SH (captopril) or $–COO^-$ (dicarboxylates)" with an arrow gripping the $Zn^{2+}$ circle; block 2 (middle) labelled "Amide C=O — H-bonds to enzyme"; block 3 (right) labelled "Terminal $–COO^-$ — binds positive (Arg) pocket"; attached to block 3 draw a small hexagon labelled "Hydrophobic side chain (e.g., phenethyl) fits S1 pocket" and a pentagon labelled "Proline ring — optimal fit." Caption: "Three-point grip + hydrophobic pocket = ACE switched off."

**Diagram 2 — Captopril vs enalaprilat skeletons (draw side by side).** Left: draw captopril — a five-membered proline ring (N at top) with –COOH at the bottom carbon and, on the N, a $–CO–CH(CH_3)–CH_2–SH$ side chain; circle the –SH and label "zinc-binding group." Right: draw enalaprilat — the same proline ring with –COOH, but on the N a longer chain: $–CO–CH(CH_3)–NH–CH(COOH)–CH_2CH_2–Ph$; circle the side-chain –COOH and label "zinc-binding group (carboxylate)"; circle the phenethyl ($–CH_2CH_2Ph$) and label "hydrophobic pocket fit." Beneath write: "Same proline anchor, different zinc grip: –SH vs $–COO^-$."

**Diagram 3 — Central vs peripheral vs direct action sites (draw a simple body outline).** Draw a head with a brain (label "Brainstem α2-receptors — clonidine, guanabenz, methyldopa (from methyldopate) switch OFF sympathetic outflow"), a spinal cord with nerves running to a blood vessel (label "Nerve endings —

## 8. Flowcharts

**Flowchart 1 — Classification of anti-hypertensives (draw as a tree).** "ANTI-HYPERTENSIVES (15 drugs)" → "A. Beta-blocker: timolol" → "B. ACE inhibitors: sulfhydryl (captopril) | dicarboxylate (lisinopril, enalapril, *benazepril*, quinapril) | *phosphinate (fosinopril — classification only)*" → "*C. Centrally acting: methyldopate*, clonidine, guanabenz" → "D. Peripheral sympatholytic: guanethidine" → "E. Direct vasodilators: sodium nitroprusside, diazoxide, minoxidil, hydralazine" → "F. Rauwolfia alkaloid: reserpine." (* = prodrug.)

**Flowchart 2 — ACE-inhibitor action (draw left to right).** "ACE inhibitor binds $Zn^{2+}$" → "ACE switched OFF" → "Angiotensin I NOT cut → less angiotensin II" → "Vessels relax + less aldosterone → less $Na^{+}$/water retained" → "Blood pressure falls." Side note: "More bradykinin also accumulates → dry cough in some patients."

**Flowchart 3 — Synthesis of methyldopate (see full details in Section 12).** "3,4-Dimethoxyphenylacetone" —($NH_3$ + HCN, Strecker)→ "α-aminonitrile" —(conc. HCl, heat; hydrolysis)→ "α-methyl-3,4-dimethoxyphenylalanine" —(48% HBr, reflux; ether cleavage)→ "Methyldopa" —(EtOH, dry HCl gas; esterification)→ "Methyldopate HCl."

## 9. Infographic concept box

💊 **ANTI-HYPERTENSIVES AT A GLANCE The problem:** Persistently high pressure in the arteries — the "silent killer." **Four handles to lower it:** ① **Slow the pump** — timolol blocks beta receptors. ② **Block angiotensin II** — the "-prils" grip ACE's zinc (captopril: –SH; others: $–COO^{-}$). ③ **Calm the control room** — clonidine/guanabenz/methyldopa switch off brain signals. ④ **Widen the pipes directly** — nitroprusside (NO), diazoxide/minoxidil ($K^{+}$ doors), hydralazine; guanethidine & reserpine cut nerve signals. **Name tricks:** "-pril" = ACE inhibitor (captopril, lisinopril, enalapril, benazepril, quinapril). Enalapril/benazepril/quinapril are ester **prodrugs** (liver activates them); lisinopril and captopril are already active. **Safety stars:** ACE inhibitors → dry cough, never in pregnancy; clonidine → never stop suddenly (rebound HTN); nitroprusside → protect IV bottle from light, watch for cyanide toxicity; reserpine → can cause depression. **Star synthesis:** Methyldopate = dimethoxyphenylacetone →(Strecker)→ aminonitrile →(HCl)→ amino acid →(HBr)→ methyldopa →(EtOH/HCl)→ ethyl ester HCl.

## 10. Master table — Chapter 2 drugs

| Drug | Chemical class | Key structure (scaffold + substituents) | Main uses |
|---|---|---|---|
| Timolol | Beta-blocker (aryloxypropanolamine, non-selective) | 1,2,5-Thiadiazole ring + morpholino substituent + oxypropanolamine side chain with tert-butylamino | Hypertension; angina; post-MI; migraine prophylaxis; glaucoma (eye drops — main use) |
| Captopril | ACE inhibitor — sulfhydryl type | L-Proline ring + (2S)-2-methyl-3-mercaptopropanoyl side chain; free –SH = zinc-binding group | Hypertension; heart failure; post-MI; diabetic nephropathy |
| Lisinopril | ACE inhibitor — dicarboxylate type (active, not a prodrug) | L-Lysyl-L-proline dipeptide + (1-carboxy-3-phenylpropyl) side chain; two –COOH groups | Hypertension; heart failure; post-MI; diabetic nephropathy |
| Enalapril | ACE inhibitor — dicarboxylate type (prodrug → enalaprilat) | Proline + ethyl ester of the phenethyl-carboxy side chain (–COOEt masks one –COOH) | Hypertension; heart failure |
| Benazepril | ACE inhibitor — dicarboxylate type (prodrug → benazeprilat) | Benzazepine (benzene-fused 7-membered lactam) ring instead of proline + ethoxy-oxo-phenylbutyl side chain | Hypertension |
| Quinapril | ACE inhibitor — dicarboxylate type (prodrug → quinaprilat) | Tetrahydroisoquinoline ring instead of proline + ethoxy-oxo-phenylbutyl side chain | Hypertension; heart failure |
| Methyldopate* | Centrally acting (α-methyl amino acid ester prodrug) | Methyldopa ethyl ester HCl: 3,4-dihydroxyphenyl + α-methyl + –COOEt, as HCl salt | Hypertensive emergency (IV, when oral not possible); methyldopa: hypertension in pregnancy (drug of choice) |
| Clonidine | Centrally acting α2-agonist (imidazoline) | 2,6-Dichlorophenyl ring + imidazoline ring joined by –NH– bridge | Hypertension; ADHD; opioid withdrawal; menopausal flushing |
| Guanabenz | Centrally acting α2-agonist (aminoguanidine) | 2,6-Dichlorobenzylidene (=CH–Ar) + aminoguanidine (–NH–N=C($NH_2$)$_2$… hydrazinecarboximidamide) via C=N link | Hypertension |
| Guanethidine | Peripheral sympatholytic (guanidine; adrenergic neuron blocker) | Octahydroazocine (8-membered saturated N-ring) + ethylguanidine side chain (–$CH_2CH_2$–NH–C(=NH)$NH_2$) | Severe hypertension (rare now); historical glaucoma use |
| Sodium nitroprusside | Direct vasodilator (iron–nitrosyl complex; NO donor) | $[Fe(CN)_5(NO)]^{2-}$: Fe(II) + 5 cyano ligands + 1 nitrosyl ligand; 2 $Na^+$ counter-ions | Hypertensive emergency (IV); acute heart failure; controlled hypotension in surgery |
| Diazoxide | Direct vasodilator (benzothiadiazine; $K^+$-channel opener) | 3-Methyl-7-chloro-1,2,4-benzothiadiazine 1,1-dioxide (benzene + –$SO_2$–N–C=N ring) | Hypertensive emergency (IV); insulinoma-related hypoglycaemia (inhibits insulin release) |
| Minoxidil | Direct vasodilator (pyrimidine N-oxide; $K^+$-channel opener) | 2,4-Diamino-6-piperidinopyrimidine 3-oxide: pyrimidine + 2 –$NH_2$ + piperidino + N→O | Severe hypertension (oral); androgenetic alopecia (topical) |
| Reserpine | Rauwolfia indole alkaloid (yohimbane type; catecholamine depletor) | Pentacyclic yohimbine skeleton + 11,17-dimethoxy + 16-carbomethoxy + 18-(3,4,5-trimethoxybenzoyl)oxy ester | Hypertension (low dose); historically antipsychotic |
| Hydralazine | Direct vasodilator (phthalazine; hydrazinophthalazine) | Phthalazine ring + hydrazino (–NH–$NH_2$) at C1 | Hypertension (incl. pregnancy); heart failure (with isosorbide dinitrate) |

# 11. Drug-by-drug profiles — structure and uses

## A. BETA-BLOCKER

### 1. Timolol

- **Chemical classification:** Beta-adrenergic blocker — **aryloxypropanolamine** type; **non-selective** (blocks both β1 cardiac and β2 lung/vessel receptors).
- **Structure:** Scaffold = a **1,2,5-thiadiazole ring** (five-membered ring with two nitrogens and one sulphur) carrying a **morpholino** (morpholine ring) substituent at C4, joined through an oxygen to the classic beta-blocker side chain: **–O–$CH_2$–CH(OH)–$CH_2$–NH–$C(CH_3)_3$** (oxypropanolamine with a **tert-butylamino** end). Key features: the thiadiazole–morpholine "head" + the –$OCH_2$CH(OH)$CH_2$NH–t-Bu "tail" (the –OH and –NH are the receptor-gripping groups of all beta-blockers).
- **Uses: Hypertension**; angina; after heart attack (post-MI protection); migraine prophylaxis; **glaucoma** — timolol eye drops are a mainstay treatment (reduce fluid production in the eye).

## B. ACE INHIBITORS

### 2. Captopril

- **Chemical classification:** ACE inhibitor — **sulfhydryl type** (the first ACE inhibitor; prototype).
- **Structure:** Scaffold = **L-proline** (five-membered nitrogen ring with a –COOH). On the proline nitrogen sits the side chain **(2S)-2-methyl-3-mercaptopropanoyl**: –CO–CH($CH_3$)–$CH_2$–**SH**. Key substituents: the **free sulfhydryl (–SH)** — the zinc-binding group; the **proline carboxylate** — the anchor; the **2-methyl branch** — mimics the alanine side chain of the natural substrate. Correct (S,S) stereochemistry is essential.
- **Uses: Hypertension**; **heart failure**; post-myocardial infarction; **diabetic nephropathy** (protects kidneys in diabetes). (Take on an empty stomach; –SH group can cause rash and taste disturbance.)

### 3. Lisinopril

- **Chemical classification:** ACE inhibitor — **dicarboxylate type**; **already active** (not a prodrug).
- **Structure:** Scaffold = an **L-lysyl-L-proline dipeptide** (lysine joined to proline). On the lysine nitrogen sits **(1S)-1-carboxy-3-phenylpropyl**: –CH(COOH)–$CH_2CH_2$–Ph. Key substituents: **two carboxylate groups** (one on proline, one on the side chain — the side-chain –$COO^-$ is the zinc-binding group); a **phenethyl (–$CH_2CH_2$Ph) hydrophobic arm** that fits the enzyme's S1 pocket; a **lysine –$(CH_2)_4NH_2$ side chain** that improves water solubility (so no prodrug ester is needed).
- **Uses: Hypertension**; heart failure; post-MI; diabetic nephropathy. Long-acting, once daily.

### 4. Enalapril

- **Chemical classification:** ACE inhibitor — **dicarboxylate type**; **prodrug** (converted in the liver to **enalaprilat**, the active di-acid).
- **Structure:** Same dicarboxylate skeleton as the active form, but one carboxyl is masked as an **ethyl ester (–COOEt)**: (2S)-1-[(2S)-2-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}propanoyl]pyrrolidine-2-carboxylic acid. Key point: the **ethyl ester improves oral absorption**; liver esterases hydrolyse it to enalaprilat (two free –COOH groups). The phenethyl arm and proline ring are retained.
- **Uses: Hypertension**; **heart failure**. (Enalaprilat itself is given IV in hypertensive emergency — it needs no liver activation.)

### 5. Benazepril

- **Chemical classification:** ACE inhibitor — **dicarboxylate type**; **prodrug** (→ **benazeprilat**).
- **Structure:** The proline ring is replaced by a **benzazepine** scaffold — a benzene ring fused to a seven-membered lactam (cyclic amide) ring carrying an $–CH_2COOH$ arm. Attached is the same ethoxy-oxo-phenylbutyl side chain as enalapril: $–NH–CH(COOEt)–CH_2CH_2Ph$. Key point: the **fused bicyclic ring** is a rigidified proline mimic that fits the enzyme pocket even better.
- **Uses: Hypertension**.

**6. Quinapril**

- **Chemical classification:** ACE inhibitor — **dicarboxylate type**; **prodrug** (→ **quinaprilat**).
- **Structure:** The proline ring is replaced by a **1,2,3,4-tetrahydroisoquinoline** scaffold (benzene fused to a partially saturated nitrogen six-ring) carrying the –COOH. Attached: the same $–CO–CH(CH_3)–NH–CH(COOEt)–CH_2CH_2Ph$ side chain pattern. Key point: another rigid **proline bioisostere** — same zinc-binding carboxylate + hydrophobic phenethyl arm, different ring "anchor."
- **Uses: Hypertension**; heart failure.

## C. CENTRALLY ACTING SYMPATHOLYTICS

**7. Methyldopate* (methyldopa ethyl ester hydrochloride)**

- **Chemical classification:** Centrally acting antihypertensive — **α-methyl amino acid ester prodrug** (of methyldopa).
- **Structure:** Scaffold = **methyldopa**: 3-(3,4-dihydroxyphenyl)-2-methylalanine — a **catechol ring** (benzene with two adjacent –OH groups) attached to an **α-methyl-α-amino acid** backbone ($–C(CH_3)(NH_2)–COOH$). In methyldopate the carboxylic acid is esterified: **–COOEt (ethyl ester)**, supplied as the **hydrochloride salt** for IV solubility. Key point: the ethyl ester makes it suitable for **intravenous** use; blood/liver esterases release active methyldopa, which is decarboxylated in the brain to **α-methylnorepinephrine**, the false transmitter that stimulates α2-receptors.
- **Uses: Hypertensive emergency/crisis** (IV, when oral therapy is not possible). Methyldopa itself is the **drug of choice for hypertension in pregnancy**.
- **Synthesis:** see Section 12 (starred — full steps, reagents and intermediates).

**8. Clonidine**

- **Chemical classification:** Centrally acting sympatholytic — **imidazoline α2-agonist**.
- **Structure:** Scaffold = **4,5-dihydro-1H-imidazoline** (five-membered ring with two nitrogens, one double bond). Joined through an **–NH– bridge** at C2 to a **2,6-dichlorophenyl ring** (benzene with **two ortho chlorines**). Key substituents: the two ortho-Cl atoms (essential for α2 activity — they twist the phenyl ring into the active shape); the basic imidazoline–NH–aryl "guanidine-like" unit that grips the receptor.
- **Uses: Hypertension** (especially resistant cases); **ADHD**; opioid/alcohol withdrawal; menopausal flushing; Tourette syndrome. **Never stop abruptly** — rebound hypertension.

**9. Guanabenz**

- **Chemical classification:** Centrally acting sympatholytic — **aminoguanidine α2-agonist**.
- **Structure:** Scaffold = **aminoguanidine** (hydrazinecarboximidamide): $H_2N–C(=NH)–NH–NH_2$. The terminal hydrazine nitrogen is joined via a **C=N (imine) link** to **2,6-dichlorobenzylidene** ($=CH–C_6H_3Cl_2$): 2-(2,6-dichlorobenzylidene)hydrazinecarboximidamide. Key substituents: the **2,6-dichlorophenyl** (same ortho-dichloro pattern as clonidine) and the **basic guanidine** unit.
- **Uses: Hypertension**.

## D. PERIPHERAL SYMPATHOLYTIC

### 10. Guanethidine

- **Chemical classification:** Peripheral sympatholytic — **guanidine-type adrenergic neuron blocker**.
- **Structure:** Scaffold = **octahydroazocine** (a saturated eight-membered ring containing one nitrogen). From the ring nitrogen extends an **ethylguanidine side chain**: $-CH_2CH_2-NH-C(=NH)-NH_2$. Key point: the **strongly basic guanidine group** (positively charged at body pH) concentrates the drug inside sympathetic nerve endings, where it **blocks noradrenaline release**.
- **Uses: Severe/resistant hypertension** (rarely used now because of side effects like severe postural hypotension); historically for glaucoma.

## E. DIRECT VASODILATORS

### 11. Sodium nitroprusside

- **Chemical classification:** Direct vasodilator — **iron–nitrosyl complex**; an **NO donor** (like the nitrates of Chapter 1, but inorganic).
- **Structure:** No carbon scaffold at all: the anion **$[Fe(CN)_5(NO)]^{2-}$** — an iron(II) centre octahedrally surrounded by **five cyano (–C≡N) ligands** and **one nitrosyl (–N=O) ligand**, with **two $Na^+$ counter-ions** (plus water of crystallisation). Key point: inside red blood cells/vessel walls it **releases nitric oxide (NO)** → cGMP → rapid, powerful vasodilation (arteries AND veins).
- **Uses: Hypertensive emergency** (IV infusion, instant on/off control); **acute heart failure**; **controlled hypotension during surgery**. Must be protected from light; prolonged use risks **cyanide toxicity** (from the cyano ligands) — treated with sodium thiosulphate.

### 12. Diazoxide

- **Chemical classification:** Direct vasodilator — **benzothiadiazine**; **ATP-sensitive $K^+$-channel opener** (a non-diuretic thiazide analogue).
- **Structure:** Scaffold = **1,2,4-benzothiadiazine 1,1-dioxide** — benzene fused to a six-membered ring containing $-SO_2-N-C=N-$. Key substituents: a **chloro (–Cl) at C7** and a **methyl ($-CH_3$) at C3**. Unlike thiazide diuretics it has no sulphonamide $-SO_2NH_2$ diuretic group at the right position — hence vasodilator, not diuretic.
- **Uses: Hypertensive emergency** (IV bolus); **insulinoma/hypoglycaemia** — it inhibits insulin release from the pancreas ($K^+$-channel opening in beta cells).

### 13. Minoxidil

- **Chemical classification:** Direct vasodilator — **pyrimidine N-oxide**; **$K^+$-channel opener** (prodrug activated by sulphation in the liver/vessel wall).
- **Structure:** Scaffold = **pyrimidine** (six-membered ring with two nitrogens). Key substituents: **two amino ($-NH_2$) groups at C2 and C4**, a **piperidino ring at C6**, and an **N-oxide (N→O) at N3**: 2,4-diamino-6-piperidinopyrimidine 3-oxide. The active form is minoxidil sulphate.
- **Uses: Severe hypertension** (oral, reserved for resistant cases — causes fluid retention and hair growth); **androgenetic alopecia** (topical solution — the famous "hair-growth" use comes from the hypertrichosis side effect).

### 14. Hydralazine

- **Chemical classification:** Direct vasodilator — **phthalazine** derivative (**hydrazinophthalazine**); predominantly an **arterial** dilator.
- **Structure:** Scaffold = **phthalazine** (benzene fused to a diazine six-ring with two adjacent nitrogens). Key substituent: a **hydrazino group (–NH–$NH_2$) at C1**: 1-hydrazinylphthalazine. Small, simple molecule; relaxes arterial smooth muscle (interferes with vascular $Ca^{2+}$ movements).
- **Uses: Hypertension** — including **hypertension in pregnancy** (safe option); **heart failure** — combined with **isosorbide dinitrate** (the Chapter 1 drug). Can cause drug-induced lupus on long-term use.

### F. RAUWOLFIA ALKALOID

**15. Reserpine**

- **Chemical classification: Rauwolfia indole alkaloid — yohimbane (yohimban) type**; a **catecholamine depletor** (empties noradrenaline/adrenaline/dopamine storage vesicles in nerve endings).
- **Structure:** Scaffold = a complex **pentacyclic yohimbine skeleton** (indole fused to four more rings, labelled A–E). Key substituents: **methoxy (–$OCH_3$) groups at C11 and C17**, a **carbomethoxy (–$COOCH_3$) ester at C16**, and — the signature — a **3,4,5-trimethoxybenzoyl ester at C18** (–OCO–$C_6H_2(OCH_3)_3$). Full description: methyl (3β,16β,17α)-11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy]yohimban-16-carboxylate. The trimethoxybenzoyl ester is essential for the depleting action.
- **Uses: Hypertension** (low doses); historically as an **antipsychotic/tranquilliser**. Depletes brain amines too — can cause **depression**, so it is avoided in depressed patients.

## 12. Synthesis of Methyldopate* (starred)

> **Technical concept.** Methyldopate (methyldopa ethyl ester hydrochloride) is built from 3,4-dimethoxyphenylacetone in four operations: (1) **Strecker reaction** to install the α-amino nitrile, (2) **acid hydrolysis** of the nitrile to the amino acid, (3) **ether cleavage** with HBr to free the catechol, and (4) **Fischer esterification** to the ethyl ester HCl salt.

**Step 1 — Strecker reaction: ketone → α-aminonitrile.**

- **Starting material: 3,4-Dimethoxyphenylacetone** — (3,4-dimethoxyphenyl)–$CH_2$–CO–$CH_3$.
- **Reagents: Ammonia ($NH_3$)** + **hydrogen cyanide (HCN)** (Strecker conditions).
- **Reaction:** The ketone carbonyl is converted to a carbon carrying both –$NH_2$ and –C≡N.
- **Intermediate: 2-Amino-3-(3,4-dimethoxyphenyl)-2-methylpropanenitrile** (the α-aminonitrile): (3,4-dimethoxyphenyl)–$CH_2$–$C(CH_3)(NH_2)$–C≡N.

**Step 2 — Acid hydrolysis: nitrile → amino acid.**

- **Starting material:** The α-aminonitrile from Step 1.
- **Reagent and conditions: Concentrated hydrochloric acid (conc. HCl), with heating.**
- **Reaction:** The –C≡N group is hydrolysed to –COOH.
- **Intermediate: α-Methyl-3,4-dimethoxyphenylalanine** [3-(3,4-dimethoxyphenyl)-2-methylalanine] — the amino acid with its two phenolic –OH groups still protected as methyl ethers.

**Step 3 — Ether cleavage: dimethyl ether → catechol (methyldopa).**

- **Starting material:** α-Methyl-3,4-dimethoxyphenylalanine from Step 2.
- **Reagent and conditions: 48% Hydrobromic acid (HBr), reflux.**
- **Reaction:** Both aryl methyl ethers are cleaved (–$OCH_3$ → –OH).
- **Intermediate/product of step 3: Methyldopa** [3-(3,4-dihydroxyphenyl)-2-methyl-L-alanine] — the free catechol amino acid. (The synthesis gives the racemate; the **L-isomer** is the pharmacologically active form.)

**Step 4 — Fischer esterification: methyldopa → methyldopate HCl.**

- **Starting material:** Methyldopa from Step 3.
- **Reagents: Absolute ethanol saturated with dry hydrogen chloride gas (EtOH / HCl gas).**
- **Reaction:** The carboxylic acid is esterified to the ethyl ester; the amine is protonated, giving the **hydrochloride salt**.
- **Final product: Methyldopate hydrochloride** — methyldopa ethyl ester HCl: (3,4-dihydroxyphenyl)–$CH_2$–$C(CH_3)(NH_2)$–COOEt · HCl, the IV prodrug that the body hydrolyses back to methyldopa.

> **Simple explanation.** Start with a dimethoxy "masked" building block. Step 1 (Strecker: $NH_3$ + HCN) sticks an amino group and a nitrile onto the ketone carbon. Step 2 (boiling HCl) turns the nitrile into a carboxylic acid — now you have an amino acid, still wearing its two methyl "masks." Step 3 (boiling HBr) rips off the masks, revealing the catechol — this is methyldopa. Step 4 (ethanol + HCl gas) converts the acid into an ethyl ester salt — methyldopate HCl — which dissolves for IV injection and turns back into methyldopa in the blood.

**Key takeaway.** Dimethoxyphenylacetone —($NH_3$/HCN)→ aminonitrile —(conc. HCl, heat)→ dimethoxy amino acid —(48% HBr, reflux)→ methyldopa —(EtOH/HCl gas)→ methyldopate HCl. Four steps: Strecker, hydrolysis, ether cleavage, esterification.

## 13. SAR of ACE inhibitors — the key binding groups

> **Technical concept.** All ACE inhibitors share a common pharmacophore that mimics the natural peptide substrate but grips the enzyme tighter at three points, plus a hydrophobic pocket.

**The SAR rules (learn these seven):**

1. **A zinc-binding group is essential.** It coordinates the active-site $Zn^{2+}$. Three types exist: **sulfhydryl (–SH)** — strongest zinc grip (captopril); **carboxylate (–$COO^-$)** — weaker grip but better tolerated (enalaprilat, lisinopril, benazeprilat, quinaprilat); **phosphinate (–$PO_2^-$)** — the third type (fosinopril, for classification). Removing the zinc-binding group destroys activity.
2. **A C-terminal carboxylate anchors the molecule** in a positively charged pocket (arginine) of the enzyme — this mimics the C-terminal carboxylate of the natural substrate angiotensin I.
3. **The amide carbonyl (–C=O) hydrogen-bonds** to the enzyme backbone, orienting the inhibitor correctly.
4. **A hydrophobic side chain** (e.g., the **phenethyl –$CH_2CH_2$Ph** of enalapril/lisinopril/benazepril/quinapril; the **methyl** of captopril) fits into the enzyme's **S1 hydrophobic pocket** — bigger lipophilic groups here increase potency.
5. **A proline (or rigid proline mimic) at the C-terminus** gives the best fit and protects against digestive enzymes: proline (captopril, enalapril, lisinopril), **benzazepine** (benazepril), **tetrahydroisoquinoline** (quinapril).
6. **Stereochemistry is critical.** The **(S,S,S) configuration** (as in captopril's 2S,2′S) is required — the wrong enantiomer/diastereomer can be hundreds to a thousand times less active, because the three binding groups must point in exact directions.

**Simple explanation.** An ACE inhibitor is like a three-pronged plug: prong 1 (zinc-binding group) jams the zinc screw, prong 2 (carboxylate) clicks into the positive socket, prong 3 (carbonyl) steadies the plug — and a greasy side arm (phenethyl) slides into a greasy pocket. Bend any prong the wrong way (wrong stereochemistry) and the plug won't fit.

**Example.** Captopril: –SH jams zinc, proline –$COO^-$ clicks the socket, amide C=O steadies, methyl fills a small pocket. Enalaprilat keeps the same plug but swaps –SH for –$COO^-$ (fewer side effects) and adds the phenethyl arm for a tighter grip — then hides one –$COO^-$ as an ethyl ester (enalapril) so the tablet is absorbed.

**Key takeaway.** ACE-inhibitor SAR = zinc-binding group (–SH > –$COO^-$ > –$PO_2^-$ types) + terminal carboxylate anchor + amide carbonyl H-bond + hydrophobic S1 side chain + proline-like ring + (S) stereochemistry + optional prodrug ester.

## 14. Worked examples

**Example 1 — Spot the prodrug.** Which of these needs liver activation: captopril, lisinopril, enalapril? Enalapril — it carries an ethyl ester (–COOEt) that the liver hydrolyses to enalaprilat. Captopril and lisinopril are already in active form (lisinopril's lysine amino group gives it enough solubility without an ester mask).

**Example 2 — Zinc-binding group identification.** Captopril = –SH (sulfhydryl type); lisinopril = side-chain –$COO^-$ (dicarboxylate type). If an exam asks "classify captopril by zinc-binding group," the answer is the –SH group — that single group defines its class.

**Example 3 — Counting control levels.** Clonidine (brain), guanethidine (nerve endings), hydralazine (vessel wall) — three drugs, three different levels of the same sympathetic control chain. A question asking "give one drug acting at each level" is answered by this trio.

## 15. Analogies

1. **ACE as "scissors with a zinc screw."** The enzyme cuts angiotensin I like scissors; the zinc ion is the screw. ACE inhibitors jam the screw, hold the handle and block the blades.
2. **Central agents as "the control room's OFF switch."** The brainstem is a control room shouting "tighten!" down the nerves; clonidine presses the room's own α2 OFF switch — silence, and the vessels relax.
3. **Guanethidine/reserpine as "emptying the ammunition store."** Nerve endings store noradrenaline like bullets in a magazine; guanethidine jams the trigger (blocks release), reserpine empties the magazine (depletes stores) — either way, no firing, no vessel tightening.
4. **Prodrugs as "a gift in wrapping paper."** Enalapril is enalaprilat wrapped in an ethyl-ester wrapper for the journey through the gut; the liver unwraps it.

## 16. Pharmacy relevance

- **ACE-inhibitor cough:** a persistent dry cough is a class effect (bradykinin accumulation) — recognise it, reassure, and refer to the prescriber for a switch (often to an ARB); do not just sell cough syrup.
- **Never in pregnancy:** ACE inhibitors are teratogenic — always screen women of childbearing age; **methyldopa is the safe choice in pregnancy**.
- **Clonidine withdrawal:** counsel never to stop suddenly — rebound hypertension can be dangerous; taper only on medical advice. Same caution applies to missed doses.
- **Captopril on empty stomach:** food reduces its absorption — advise 1 hour before meals (unlike most other ACE inhibitors).
- **Nitroprusside handling:** IV bottle and tubing must be **protected from light** (wrap in foil); infusions need ICU monitoring; watch for cyanide toxicity signs (confusion, lactic acidosis) on prolonged use.
- **Reserpine and mood:** ask about depression history — reserpine can worsen depression (it depletes brain amines too).
- **Minoxidil counselling:** oral minoxidil causes hair growth and fluid retention — warn patients; topical minoxidil needs 3–6 months of daily use before results.

## 17. India context

- **Reserpine and *Rauwolfia serpentina* (Sarpagandha):** the Indian snakeroot of Ayurveda, used for centuries for "unmada" (mental disturbance) and hypertension; reserpine was isolated from this Indian plant and became the first modern antihypertensive — a landmark of Indian natural-product chemistry every B.Pharm student should know.
- **Methyldopa** remains the **first-line antihypertensive in pregnancy** across Indian hospitals (e.g., in pre-eclampsia protocols).
- **Amlodipine + telmisartan / atenolol combinations** dominate Indian prescriptions, but **enalapril, lisinopril and ramipril** are the workhorse ACE inhibitors in Indian practice, available as low-cost generics.
- **Topical minoxidil** is one of India's highest-selling dermatology OTC-adjacent products for hair loss — pharmacists field daily questions on its correct use and timelines.

## 18. Key points

1. Hypertension = persistent high arterial pressure; drugs act on heart rate/force, vessel width, blood volume, or nerve signals.
2. **Timolol** = aryloxypropanolamine beta-blocker (non-selective); also the glaucoma eye-drop drug.
3. **ACE inhibitors** ("-prils"): captopril (–SH type); lisinopril, enalapril*, benazepril*, quinapril *(dicarboxylate type;* = prodrug). All grip ACE's $Zn^{2+}$.
4. ACE-inhibitor SAR: zinc-binding group + terminal carboxylate + amide carbonyl + hydrophobic S1 arm + proline-like ring + (S) stereochemistry + optional ester prodrug.
5. **Centrally acting:** methyldopate* (→ methyldopa → α-methylnorepinephrine), clonidine (imidazoline), guanabenz (aminoguanidine) — all switch off sympathetic outflow via α2.
6. **Guanethidine** (guanidine) blocks noradrenaline release at nerve endings; **reserpine** (Rauwolfia indole alkaloid) depletes catecholamine stores.
7. **Direct vasodilators:** sodium nitroprusside (NO donor, IV emergency), diazoxide ($K^+$-channel opener, also anti-insulin), minoxidil ($K^+$-channel opener, hair growth), hydralazine (phthalazine, arterial dilator, pregnancy-safe).
8. Methyldopate synthesis: dimethoxyphenylacetone —(Strecker)→ aminonitrile —(HCl)→ amino acid —(HBr)→ methyldopa —(EtOH/HCl)→ ethyl ester HCl.

## 19. Common confusions

- **Methyldopa vs methyldopate:** methyldopa = the active amino acid (oral, pregnancy-safe); methyldopate = its **ethyl ester hydrochloride** (IV prodrug for emergencies).
- **Enalapril vs enalaprilat vs lisinopril:** enalapril = prodrug (ester); enalaprilat = the active di-acid (IV form); lisinopril = active as swallowed (not a prodrug).
- **Clonidine vs clonazepam:** similar names, totally different drugs — clonidine = antihypertensive (imidazoline); clonazepam = anti-epileptic benzodiazepine. A classic dispensing-error pair.
- **Hydralazine vs hydroxyzine:** similar names — hydralazine = vasodilator; hydroxyzine = antihistamine/anxiolytic. Another look-alike pair.
- **Diazoxide vs thiazide diuretics:** same benzothiadiazine family look, opposite job — diazoxide is a vasodilator (no diuresis), thiazides are diuretics.
- **Reserpine vs "reserpine-like" depletion vs receptor blockade:** reserpine does NOT block receptors — it **empties the transmitter stores**.

## 20. Common mistakes

- Saying captopril's –SH is "for antioxidant effect" — its job in this drug is **binding the zinc of ACE**.
- Calling enalapril the active drug — enalapril is the **prodrug**; enalaprilat is active.
- Writing that clonidine "blocks" α2 receptors — it **stimulates** (agonist) them; the stimulation switches sympathetic outflow OFF.
- Forgetting stereochemistry in ACE inhibitors — the (S,S,S) form is the active one; wrong isomers are nearly inactive.
- Listing sodium nitroprusside as an "organic nitrate" — it is an **inorganic iron–nitrosyl complex** (no carbon scaffold).

## 21. Mnemonics

- **"-pril = ACE pill":** captoPril, lisoPril, enalaPril, benazePril, quinaPril — all ACE inhibitors.
- **"Captopril's SH = Sulphur Hooks zinc":** the –SH group hooks the $Zn^{2+}$.
- **"ENDO-BQ prodrugs": En**alapril, **B**enazepril, **Q**uinapril are the ester prodrugs (liver activates them); **L**isinopril and **C**aptopril are active as-is.
- **"Calm Brain, Block Nerve, Widen Pipe":** three levels — **c**lonidine/guanabenz/methyldopa (brain), **g**uanethidine/reserpine (nerve), **n**itroprusside/diazoxide/minoxidil/hydralazine (pipe).
- **"Methyldopate's 4 S's": S**trecker → **S**trong HCl → **S**trong HBr → **S**alt of ethyl ester.

## 22. Exam summary

Anti-hypertensives lower BP via the heart, vessels, blood volume or nerve signals. **Timolol** is an aryloxypropanolamine non-selective beta-blocker (also used in glaucoma). **ACE inhibitors** end in "-pril": **captopril** (sulfhydryl type, –SH grips $Zn^{2+}$), **lisinopril** (active dicarboxylate), **enalapril/benazepril/quinapril** (ethyl-ester prodrugs → enalaprilat/benazeprilat/quinaprilat). SAR: zinc-binding group + C-terminal carboxylate + amide carbonyl + hydrophobic S1 side chain + proline-like ring + (S) stereochemistry. **Centrally acting:** methyldopate* (prodrug of methyldopa), clonidine (imidazoline α2-agonist), guanabenz (aminoguanidine α2-agonist). **Guanethidine** (guanidine) blocks noradrenaline release peripherally. **Direct vasodilators:** sodium nitroprusside ($[Fe(CN)_5NO]^{2-}$, NO donor, IV emergency), diazoxide (benzothiadiazine $K^+$-opener), minoxidil (pyrimidine N-oxide $K^+$-opener), hydralazine (phthalazine). **Reserpine** is the Rauwolfia indole alkaloid that depletes catecholamines. Methyldopate synthesis: 3,4-dimethoxyphenylacetone —($NH_3$/HCN, Strecker)→ α-aminonitrile —(conc. HCl, heat)→ α-methyl-dimethoxyphenylalanine —(48% HBr, reflux)→ methyldopa —(EtOH/dry HCl)→ methyldopate HCl.

## 23. One-minute revision

- BP = pump × pipes. Timolol slows the pump (beta-blocker).
- "-prils" block ACE: captopril = –SH type; rest = dicarboxylate type; enalapril/benazepril/quinapril = prodrugs.
- ACE SAR: zinc grip + carboxylate anchor + carbonyl + greasy arm + proline ring + S-form.
- Central: methyldopate, clonidine, guanabenz (α2 ON → signals OFF).
- Guanethidine blocks release; reserpine empties stores (Rauwolfia, India).
- Direct: nitroprusside (NO, IV), diazoxide & minoxidil ($K^+$ doors), hydralazine (arteries, pregnancy-safe).
- Methyldopate: Strecker → HCl → HBr → EtOH/HCl.

## 24. Exam questions

### Short-answer questions

1. Classify anti-hypertensive drugs chemically with one example each.
2. Name the three zinc-binding groups of ACE inhibitors with one drug example each.
3. Distinguish between prodrug and active ACE inhibitors with examples.
4. Write the structure (scaffold + substituents) of clonidine and of hydralazine.
5. Why is methyldopa preferred in pregnancy hypertension?
6. Give the uses of sodium nitroprusside and of minoxidil (two uses each).
7. What is rebound hypertension, and with which drug is it associated?

### Long-answer questions

1. Classify anti-hypertensives. Discuss the SAR of ACE inhibitors, explaining the role of the zinc-binding group, carboxylate, carbonyl and stereochemistry with structures of captopril and enalapril.
2. Write the complete synthesis of methyldopate starting from 3,4-dimethoxyphenylacetone, naming all reagents, intermediates and conditions. Give its structure and uses.
3. Describe the chemical classification, structures and uses of (a) clonidine, (b) guanethidine, (c) sodium nitroprusside, (d) reserpine.

### MCQs (answers at the end)

1. The zinc-binding group of captopril is:
   a) –COOH b) –SH c) $–PO_2^-$ d) $–NH_2$
2. Which ACE inhibitor is NOT a prodrug?
   a) Enalapril b) Benazepril c) Lisinopril d) Quinapril
3. Clonidine acts by:
   a) Blocking α2 receptors b) Stimulating α2 receptors in the brain c) Blocking calcium channels d) Donating NO
4. The scaffold of diazoxide is:
   a) Phthalazine b) Benzothiadiazine c) Imidazoline d) Pyrimidine N-oxide
5. In methyldopate synthesis, the Strecker reagents are:
   a) $NH_3$ + HCN b) $HNO_3$ + $H_2SO_4$ c) EtOH + NaOH d) HBr + HCl
6. Reserpine is obtained from:
   a) *Digitalis* b) *Rauwolfia serpentina* c) *Atropa* d) *Ephedra*
7. Which drug must be protected from light during IV infusion?
   a) Hydralazine b) Sodium nitroprusside c) Minoxidil d) Guanabenz
8. The active metabolite of enalapril is:
   a) Enalaprilat b) Lisinopril c) Benazeprilat d) Captopril

*Answers: 1-b, 2-c, 3-b, 4-b, 5-a, 6-b, 7-b, 8-a*

**Viva questions**

1. What does the suffix "-pril" tell you about a drug?
2. Why does captopril cause taste disturbances while enalapril usually does not? (Hint: the –SH group.)
3. Name the intermediate formed after HBr treatment in methyldopate synthesis.
4. How does reserpine lower blood pressure — receptor blockade or transmitter depletion?
5. Why is clonidine never stopped abruptly?

**Application-based questions**

1. A pregnant patient with hypertension is prescribed an ACE inhibitor. As the pharmacist, identify the problem and suggest the appropriate alternative with reason.
2. A patient on clonidine misses doses for two days and presents with severe headache and BP 190/120. Explain the mechanism and the pharmacist's immediate advice.
3. You receive a prescription for IV sodium nitroprusside. List the handling, monitoring and toxicity precautions you would verify before dispensing.

## 25. References


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# Chapter 3 — Drugs to Treat Congestive Heart Failure

## 3.1 Learning Objectives

After studying this chapter, you will be able to:

1. Define congestive heart failure (CHF) and explain why the heart's pumping becomes weak.
2. Name the five drugs in this chapter and place each in its chemical class.
3. Describe the general structure of a cardiac glycoside: steroid part + lactone ring + sugar chain.
4. Explain how cardiac glycosides make the heartbeat stronger (Na+/K+-ATPase inhibition).
5. List the key SAR (structure–activity relationship) points of cardiac glycosides.
6. Compare digoxin and digitoxin — source plant, extra –OH group, half-life, and elimination.
7. Describe nesiritide as a recombinant human peptide and state its use.
8. Describe bosentan and tezosentan as endothelin receptor antagonists and state their uses.
9. Answer short, long, MCQ, viva, and application-based exam questions on this chapter.

## 3.2 Definitions

- **Congestive heart failure (CHF):** A condition in which the heart cannot pump enough blood to meet the body's needs. Blood "backs up" (congests) in the lungs and body — hence the name.
- **Cardiac glycoside:** A drug made of a steroid part (aglycone) joined to one or more sugar molecules by a glycosidic bond. Used to strengthen a weak heartbeat.
- **Cardenolide:** A cardiac glycoside whose lactone ring has 5 members (atoms). Digoxin and digitoxin are cardenolides. (A 6-membered lactone would make it a bufadienolide — not in our syllabus.)
- **Inotrope:** A drug that changes the force of heart contraction. A *positive* inotrope makes the beat stronger.
- **Natriuretic peptide:** A small protein made by the heart that helps the body remove sodium and water through urine.
- **Endothelin:** The strongest natural chemical in the body that narrows blood vessels (a vasoconstrictor).
- **Receptor antagonist:** A drug that sits on a receptor and blocks the natural chemical from acting there.

## 3.3 Terminology

- **Aglycone / genin:** The non-sugar (steroid) part of a glycoside. In digoxin the genin is called *digoxigenin*; in digitoxin it is *digitoxigenin*.
- **Glycone:** The sugar part of the glycoside (here, chains of the rare sugar *digitoxose*).
- **Cardenolide:** 5-membered unsaturated lactone at position C-17 of the steroid. Think "cardenolide = cardiac + enolide (lactone)".
- **3β-OH:** The hydroxyl group at carbon 3 of the steroid, pointing "up" (beta). The sugar chain attaches here.
- **Narrow therapeutic index:** The safe dose and the toxic dose are very close. Digoxin has this property — small overdoses are dangerous.
- **Recombinant:** Made by inserting a human gene into bacteria or cells so they manufacture the human protein. Nesiritide is recombinant human BNP.
- **Dual antagonist:** Blocks two receptor types at once. Bosentan and tezosentan block both ETA and ETB endothelin receptors.

## 3.4 Explanations

**What is congestive heart failure?** Technical concept: In CHF, cardiac output falls below the metabolic demand of tissues, and compensatory mechanisms (fluid retention, vasoconstriction) cause congestion. Simple explanation: The heart is a pump. In heart failure the pump has become weak, so blood does not move forward properly and instead collects (congests) in the lungs and legs. Example: A patient feels breathless on climbing stairs and has swollen ankles — the lungs are congested and fluid collects in the legs. Key takeaway: CHF = weak pump + fluid congestion.

**Why do we need different kinds of drugs for CHF?** Technical concept: Therapy targets contractility, preload, afterload, and neurohormonal activation. Simple explanation: A weak pump can be helped in three ways — (1) make each beat stronger, (2) reduce the fluid load the heart must push (less work), (3) widen the blood vessels so blood flows more easily. Example: Cardiac glycosides do job 1; nesiritide and endothelin blockers do jobs 2 and 3. Key takeaway: Digoxin strengthens the beat; the other drugs in this chapter lighten the heart's workload.

**Where do cardiac glycosides come from?** Technical concept: They are plant secondary metabolites from *Digitalis* (foxglove) species. Simple explanation: They are natural medicines from the foxglove plant. Digoxin comes from *Digitalis lanata* and digitoxin from *Digitalis purpurea* (purple foxglove). Example: Long ago, doctors noticed foxglove tea helped "dropsy" (old word for the swelling of heart failure). Key takeaway: Plant origin, but today used as pure, exact-dose tablets and injections.

## 3.5 Classifications

The five drugs of this chapter fall into three chemical classes:

**Class A — Cardiac glycosides (cardenolides)**

- Digoxin
- Digitoxin
- Chemical idea: steroid aglycone + 5-membered unsaturated lactone + sugar chain.

**Class B — Natriuretic peptide (recombinant human protein)**

- Nesiritide (recombinant human B-type natriuretic peptide, rhBNP)
- Chemical idea: a chain of 32 amino acids; not a small molecule at all.

**Class C — Endothelin receptor antagonists (dual ETA/ETB blockers)**

- Bosentan
- Tezosentan
- Chemical idea: sulfonamide-linked pyrimidine scaffolds.

## 3.6 Mechanisms of Action

**Cardiac glycosides — how they strengthen the heartbeat.** Technical concept: They inhibit the membrane enzyme Na+/K+-ATPase (the sodium–potassium pump). Simple explanation: Heart cells have a tiny pump that throws sodium out and brings potassium in. Digoxin partly switches this pump off. Sodium builds up inside the cell. A second exchanger, which normally throws calcium out in exchange for sodium coming in, now works in reverse — so calcium builds up inside instead. More calcium inside = stronger muscle contraction. Example: Like pressing the accelerator harder — the same heart now squeezes with more force each beat. Key takeaway: Block Na+/K+ pump → more Na+ inside → more Ca2+ inside → stronger contraction (positive inotropic effect). Glycosides also stimulate the vagus nerve, which slows the heart rate — useful in atrial fibrillation.

**Nesiritide — how a heart hormone helps heart failure.** Technical concept: Nesiritide binds natriuretic peptide receptor-A (NPR-A), activating guanylate cyclase and raising intracellular cGMP. Simple explanation: The heart itself makes a hormone (BNP) when it is stretched too much, telling the body to relax vessels and pass more urine. Nesiritide is the laboratory-made copy of this hormone. It widens blood vessels and increases urine output, so the failing heart has less fluid to push and less resistance to push against. Example: Like opening extra outlet pipes so a struggling pump has less pressure to fight. Key takeaway: Mimics the heart's own relief hormone → vasodilation + loss of salt and water → lighter workload.

**Bosentan and tezosentan — blocking the vessel-narrowing signal.** Technical concept: Endothelin-1 acting on ETA and ETB receptors causes powerful vasoconstriction and cell growth; dual antagonists occupy both receptors. Simple explanation: Endothelin is the body's strongest vessel-tightening chemical, and there is too much of it in heart and vessel disease. These drugs sit on both types of endothelin receptors (ETA and ETB) like a cap on a lock, so endothelin cannot tighten the vessels. Example: Like putting earplugs in so the vessels cannot "hear" the tighten-up order. Key takeaway: Dual ETA/ETB blockade → vasodilation → easier pumping.

## 3.7 Diagrams (describe so they can be drawn)

**Diagram 1 — General structure of a cardiac glycoside.** Draw four fused rings (three 6-membered + one 5-membered) — this is the steroid nucleus. At the bottom right (carbon 17), draw a 5-membered unsaturated lactone ring (a ring with one C=O and one C=C). At the top (carbon 3), draw a wavy glycosidic bond going up to a chain of three hexagon sugar units labelled "digitoxose–digitoxose–digitoxose". Mark "3β-OH" at the attachment point and "14β-OH" on the steroid. Label: steroid aglycone (left) + lactone (right) + sugars (top).

**Diagram 2 — How digoxin strengthens contraction (ion flow).** Draw a heart muscle cell as a box. On its wall draw a pump labelled "Na+/K+-ATPase" with an arrow pushing Na+ out and K+ in — put a red cross on it labelled "digoxin blocks". Inside the box, draw Na+ ions accumulating. Draw a second exchanger "Na+/Ca2+ exchanger" with arrows showing less Ca2+ leaving and more Ca2+ staying inside. End with a big arrow: "more Ca2+ inside → stronger contraction".

**Diagram 3 — Endothelin blockade.** Draw a blood vessel cross-section. On its wall draw two locks labelled "ETA" and "ETB". Draw endothelin-1 as a key approaching, but show bosentan/tezosentan already sitting in both locks as caps, with the key bouncing off. Arrow: "vessel stays relaxed".

## 3.8 Flowcharts

**Flowchart 1 — Cardiac glycoside action, step by step.** Digoxin/digitoxin given → binds Na+/K+-ATPase on heart cell → pump inhibited → Na+ builds up inside cell → Na+/Ca2+ exchanger slows → Ca2+ builds up inside cell → actin–myosin interaction stronger → force of contraction increases (positive inotropy) → ALSO vagal stimulation → heart rate falls → heart pumps more blood per beat with less oxygen demand per beat.

**Flowchart 2 — Digoxin vs digitoxin at a glance.** Source: *Digitalis lanata* (digoxin) vs *Digitalis purpurea* (digitoxin) → Extra group: digoxin has 12β-OH; digitoxin has none → Result: digoxin less fat-soluble, half-life ~36 hours, removed by kidneys; digitoxin more fat-soluble, half-life ~7 days, removed by liver → Use caution: kidney disease affects digoxin more; liver disease affects digitoxin more.

## 3.9 Infographic Concept Box

**"Anatomy of a Cardiac Glycoside — 4 parts you must remember"**

1. STEROID CORE — four fused rings; flat shape fits the pump's binding site. (5β-H gives the bent "cis" shape.)
2. LACTONE RING — 5-membered, unsaturated, at C-17β. The "business end": saturation kills activity. (Cardenolide = this ring.)
3. 3β-OH — the handle where sugars attach; also needed for binding.
4. SUGAR CHAIN — 1 to 3 digitoxose units; more sugars = stronger binding and better pharmacokinetics. Genin alone (no sugar) is much weaker.

## 3.10 Master Table — Drug → Class → Key Structure → Uses

| Drug | Chemical class | Key structure (scaffold + substituents) | Main uses |
|---|---|---|---|
| Digoxin | Cardiac glycoside (cardenolide) | Steroid aglycone (digoxigenin) with 12β-OH and 14β-OH + unsaturated 5-membered lactone at C-17β + 3 digitoxose sugars at 3β-OH | CHF (systolic heart failure), atrial fibrillation and atrial flutter (to slow ventricular rate) |
| Digitoxin | Cardiac glycoside (cardenolide) | Same cardenolide scaffold (digitoxigenin) but NO 12β-OH + same lactone + 3 digitoxose sugars | Same as digoxin (CHF, atrial fibrillation/flutter); longer-acting alternative |
| Nesiritide | Recombinant human natriuretic peptide (rhBNP) | 32-amino-acid peptide chain (identical to human B-type natriuretic peptide) | Acutely decompensated heart failure (short-term IV treatment to reduce breathlessness and fluid load) |
| Bosentan | Endothelin receptor antagonist (dual ETA/ETB) | Benzenesulfonamide scaffold: 4-tert-butyl-benzenesulfonamide linked to a bipyrimidine bearing 2-hydroxyethoxy and 2-methoxyphenoxy substituents | Pulmonary arterial hypertension (PAH) — lowers lung vessel pressure |
| Tezosentan | Endothelin receptor antagonist (dual ETA/ETB) | Pyrimidine-sulfonamide scaffold: pyridine-2-sulfonamide (with 5-isopropyl group) linked to a pyrimidine bearing hydroxyethoxy, methoxyphenoxy, and a tetrazolyl-pyridine substituent | Investigational/experimental for acute heart failure (vasodilator); trials did not show clear benefit, so it is not an established therapy |

## 3.11 Examples

1. **Digoxin example:** A 65-year-old man with systolic heart failure and fast atrial fibrillation receives a small daily dose of digoxin; his heart squeezes more strongly and the ventricular rate slows because of the vagal effect.
2. **Digitoxin example:** A patient who cannot tolerate digoxin's kidney-dependent elimination is conceptually a candidate for digitoxin, which is cleared by the liver — but its very long half-life means any toxicity lasts many days.
3. **Nesiritide example:** A patient admitted with sudden severe breathlessness from fluid-filled lungs (acute decompensated HF) receives an IV infusion of nesiritide to quickly reduce vessel resistance and increase urine output.
4. **Bosentan example:** A young woman with pulmonary arterial hypertension (very high pressure in lung vessels) takes bosentan tablets to block endothelin and keep lung vessels open.
5. **Tezosentan example:** In clinical trials, tezosentan was given intravenously to acute heart failure patients as a vasodilator, but it did not improve breathlessness or reduce deaths — a reminder that blocking one pathway is not always enough.

## 3.12 Analogies

- **Weak heart + digoxin:** A tired person pushing a cart. Digoxin is like giving the person stronger arms — each push moves the cart further (positive inotropy).
- **Na+/K+ pump blockade:** A bucket brigade where someone blocks the exit — water (sodium) piles up inside, and that pile-up is traded for stones (calcium) that make the muscle grip harder.
- **Nesiritide:** The heart sending an SOS letter to the kidneys saying "throw out extra water" — nesiritide is a photocopy of that letter.
- **Endothelin antagonists:** Endothelin is a bully squeezing a garden hose; bosentan/tezosentan are hands that hold the bully back so water flows freely.
- **Sugar chain on glycosides:** The steroid is the arrow, the sugars are the feathers — without feathers the arrow flies poorly (weak activity).

## 3.13 Pharmacy Relevance

- **Narrow therapeutic index:** Digoxin's safe blood level is roughly 0.5–2 ng/mL; above this, toxicity appears (nausea, vision changes with yellow-green halos, dangerous arrhythmias). Pharmacists must counsel on exact dosing and never doubling a missed dose casually.
- **Drug interactions:** Diuretics (which lower potassium) + digoxin = much higher toxicity risk, because low potassium lets digoxin bind the pump more strongly. Always check potassium.
- **Antidote:** Digoxin immune Fab (antibody fragments) is the antidote for life-threatening digoxin poisoning — a classic exam point.
- **Monitoring:** Kidney function must be checked for digoxin dosing; liver function for bosentan (it can raise liver enzymes — monthly liver tests are standard practice).
- **Counselling:** Patients on bosentan must avoid pregnancy (harmful to the foetus) — a key counselling point.
- **Formulation note:** Nesiritide is a peptide — it would be digested if swallowed, so it is given only by IV infusion.

## 3.14 India Context

- Digoxin is one of the cheapest heart medicines in India and is widely available as tablets and injections in every hospital pharmacy — a mainstay for CHF and atrial fibrillation in Indian practice.
- *Digitalis purpurea* (the digitoxin plant) grows in the Himalayan regions, linking this drug class to Indian medicinal-plant heritage, though modern digoxin is manufactured synthetically/purified industrially.
- Nesiritide is very expensive and needs IV infusion with monitoring, so it is rarely used in Indian hospitals; Indian practice relies more on diuretics, ACE inhibitors, and digoxin for acute heart failure.
- Bosentan is available in India for pulmonary arterial hypertension, a condition seen in young Indian patients including those with congenital heart disease; its liver-monitoring requirement is an important pharmacist role.
- Because digoxin toxicity is common where monitoring is limited, Indian pharmacists play a big role in spotting early signs (loss of appetite, nausea, visual colour changes) and checking interacting drugs.

## 3.15 Key Points

1. CHF drugs here work by two ideas: strengthen the beat (glycosides) or lighten the workload (nesiritide, ERAs).
2. Cardiac glycosides = steroid + unsaturated 5-membered lactone (cardenolide) + digitoxose sugars at 3β-OH.
3. Mechanism: inhibit Na+/K+-ATPase → ↑ intracellular Na+ → ↑ intracellular Ca2+ → positive inotropy.
4. SAR essentials: unsaturated lactone at C-17β is a must; 3β-OH needed; sugars boost activity; cis (5β) ring fusion needed.
5. Digoxin has a 12β-OH (digitoxin does not) → digoxin is less lipophilic, shorter half-life (~36 h), kidney-cleared; digitoxin is more lipophilic, half-life ~7 days, liver-cleared.
6. Uses: CHF + atrial fibrillation/flutter (rate control).
7. Toxicity: narrow index — GI upset, arrhythmias, yellow-green vision; antidote = digoxin immune Fab.
8. Nesiritide = recombinant human BNP (32 amino acids), IV only, for acute decompensated HF; raises cGMP.
9. Bosentan = dual ETA/ETB antagonist, benzenesulfonamide + bipyrimidine scaffold, used in pulmonary arterial hypertension.
10. Tezosentan = dual ETA/ETB antagonist, pyrimidine-sulfonamide with tetrazolyl-pyridine, experimental for acute HF — trials showed no benefit.

## 3.16 Common Confusions

- **Digoxin vs digitoxin:** Both are cardenolides with 3 digitoxose sugars; the difference is the 12β-OH on digoxin only — this one –OH changes solubility, half-life, and elimination route.
- **Cardenolide vs bufadienolide:** Cardenolide = 5-membered lactone (our drugs); bufadienolide = 6-membered lactone (e.g., toad venom compounds — not in syllabus).
- **Inotrope vs chronotrope:** Inotrope changes force; chronotrope changes rate. Digoxin is a positive inotrope but slows rate (negative chronotrope via vagus) — both can be true at once.
- **Nesiritide is not a small molecule:** Students sometimes draw it like a normal drug structure — it is a 32-amino-acid peptide.
- **Bosentan's use:** It is mainly for pulmonary arterial hypertension, not routine CHF — do not list it as a first-line CHF drug.
- **Endothelin antagonists do not strengthen the heartbeat:** They only relax vessels; they are not inotropes.

## 3.17 Common Mistakes

1. Writing that digoxin "blocks calcium channels" — wrong; it blocks the Na+/K+ pump, and calcium rises indirectly.
2. Drawing the lactone as saturated — the C=C unsaturation in the 5-membered lactone is essential for activity.
3. Forgetting the sugar chain — the genin alone is far less active; always include digitoxose units.
4. Saying nesiritide is given orally — peptides are digested; it is IV only.
5. Mixing up half-lives — digoxin ~36 hours (shorter), digitoxin ~7 days (longer).
6. Listing tezosentan as an established CHF treatment — it is experimental; trials failed to show benefit.

## 3.18 Mnemonics

- **"DIG sells SUGAR with LACTONE on STEROID": D**igoxin = **S**teroid + **S**ugar (digitoxose) + **L**actone (unsaturated). The three parts of every cardiac glycoside.
- **"12 makes it LIVER-free":** Digoxin has the 12-OH → less fat-soluble → cleared by KIDNEY (not liver). Digitoxin (no 12-OH) → cleared by LIVER.
- **"Na stays, Ca plays":** Na+ stays inside → Ca2+ rises → heart plays (contracts) stronger.
- **"ENDO-BLOCK opens the road":** ENDOthelin BLOCKers (bosentan, tezosentan) open vessel roads.
- **Toxicity signs — "GAV": G**I upset, **A**rrhythmia, **V**ision (yellow-green halos).

## 3.19 Exam Summary

Congestive heart failure is treated by strengthening contraction or reducing workload. Cardiac glycosides (digoxin from *Digitalis lanata*, digitoxin from *Digitalis purpurea*) are cardenolides: a steroid aglycone with an unsaturated 5-membered lactone at C-17β and digitoxose sugars at 3β-OH. They inhibit Na+/K+-ATPase, raising intracellular Na+ and then Ca2+, producing a positive inotropic effect plus vagal slowing — used in CHF and atrial fibrillation/flutter. SAR: unsaturated lactone essential, 3β-OH essential, sugars enhance activity, 5β (cis) fusion required. Digoxin (12β-OH) has a ~36 h half-life and renal clearance; digitoxin (no 12β-OH) has a ~7-day half-life and hepatic clearance. Narrow therapeutic index; toxicity shows GI, cardiac, and visual effects; antidote is digoxin immune Fab. Nesiritide is recombinant human BNP (32-amino-acid peptide) given IV for acute decompensated HF; it raises cGMP causing vasodilation and diuresis. Bosentan (benzenesulfonamide–bipyrimidine) and tezosentan (pyrimidine-sulfonamide with tetrazolyl-pyridine) are dual ETA/ETB endothelin receptor antagonists; bosentan is used in pulmonary arterial hypertension, while tezosentan remains experimental for acute HF after unsuccessful trials.

## 3.20 One-Minute Revision

- 3 classes: glycosides (digoxin, digitoxin) | peptide (nesiritide) | endothelin blockers (bosentan, tezosentan).
- Glycoside structure: steroid + unsaturated 5-membered lactone (C-17) + digitoxose sugars (C-3).
- Mechanism: block Na+/K+ pump → ↑Na+ → ↑Ca2+ → stronger beat.
- Digoxin = 12-OH, kidney, 36 h. Digitoxin = no 12-OH, liver, 7 days.
- Toxicity: nausea, arrhythmia, yellow-green vision. Antidote: digoxin immune Fab.
- Nesiritide: lab-made BNP, 32 amino acids, IV, acute HF, ↑cGMP.
- Bosentan: PAH drug, dual ERA, sulfonamide scaffold. Tezosentan: experimental, trials failed.

## 3.21 Exam Questions

### Short-answer questions

1. Define a cardiac glycoside and draw its general structure with labels.
2. Why is digoxin cleared by the kidney while digitoxin is cleared by the liver?
3. State the mechanism by which cardiac glycosides increase the force of contraction.
4. What is nesiritide? Why can it not be given orally?
5. Name the two endothelin receptor antagonists in this chapter and give one use of each.

### Long-answer questions

1. Describe the chemical structure of cardiac glycosides. Discuss the SAR (structure–activity relationship) of cardiac glycosides with special reference to the lactone ring, the 3β-OH group, and the sugar chain.
2. Explain the mechanism of action of cardiac glycosides in congestive heart failure. Compare digoxin and digitoxin under: source, structure, half-life, and route of elimination.
3. Write notes on: (a) Nesiritide, (b) Bosentan — covering chemical class, structure features, mechanism, and uses.

### MCQs (with answers)

1. The lactone ring in digoxin is: (a) 5-membered saturated (b) 5-membered unsaturated (c) 6-membered unsaturated (d) absent. **Answer: (b)**
2. Cardiac glycosides act by inhibiting: (a) Ca2+ channels (b) Na+/K+-ATPase (c) Beta receptors (d) ACE. **Answer: (b)**
3. The sugar present in digoxin is: (a) glucose (b) digitoxose (c) rhamnose (d) fructose. **Answer: (b)**
4. Which statement about digoxin vs digitoxin is correct? (a) Digitoxin has a 12β-OH (b) Digoxin has a longer half-life (c) Digoxin has a 12β-OH and is renally cleared (d) Both are bufadienolides. **Answer: (c)**
5. Nesiritide is: (a) a steroid (b) recombinant human BNP, a 32-amino-acid peptide (c) a sulfonamide (d) a calcium blocker. **Answer: (b)**
6. Bosentan is used mainly in: (a) pulmonary arterial hypertension (b) epilepsy (c) diabetes (d) tuberculosis. **Answer: (a)**
7. Antidote for digoxin poisoning: (a) naloxone (b) flumazenil (c) digoxin immune Fab (d) protamine. **Answer: (c)**
8. Tezosentan blocks: (a) only ETA (b) only ETB (c) both ETA and ETB (d) angiotensin receptors. **Answer: (c)**

### Viva questions

1. What plant does digoxin come from? (*Digitalis lanata*.)
2. What does "cardenolide" mean? (5-membered unsaturated lactone cardiac glycoside.)
3. Why does low potassium increase digoxin toxicity? (K+ competes with digoxin at the pump; less K+ = more digoxin binding.)
4. How many amino acids are in nesiritide? (32.)
5. Why is bosentan's scaffold described as a sulfonamide? (It contains a benzenesulfonamide group.)

### Application-based questions

1. A CHF patient on digoxin is started on a thiazide diuretic and develops nausea and visual colour changes. Explain the likely cause and the pharmacist's role. (Diuretic causes K+ loss → increased digoxin binding → toxicity. Pharmacist: monitor K+, counsel on symptoms, alert prescriber, know the antidote.)
2. A patient with kidney failure needs a cardiac glycoside. Which is safer — digoxin or digitoxin — and why? (Digitoxin, because it is cleared by the liver, not the kidney. But its long half-life needs caution.)
3. Why must nesiritide be given by IV infusion rather than as a tablet? (It is a peptide and would be digested in the gut.)

## 3.22 References


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# Chapter 4 — Anti-arrhythmic Drugs (Class I–IV)

## 4.1 Learning Objectives

After studying this chapter, you will be able to:

1. Define arrhythmia and explain the Vaughan–Williams classification (Classes I, II, III, IV, with Ia/Ib/Ic).
2. Draw the classification table showing which drug belongs to which class and what each class does to the cardiac action potential.
3. Describe the chemical structure (scaffold + key substituents) and uses of all ten drugs: quinidine sulphate, procainamide, disopyramide, phenytoin, lidocaine, tocainide, mexiletine, lorcainide, amiodarone, sotalol.
4. Write the complete synthesis of disopyramide with every step, reagent, and intermediate.
5. Explain the SAR highlights of lidocaine and its analogues (amide link, ortho-methyl groups, hydrophilic amine).
6. Answer short, long, MCQ, viva, and application-based exam questions on this chapter.

## 4.2 Definitions

- **Arrhythmia:** Any abnormality of heart rhythm — too fast, too slow, or irregular. (Normal rhythm is called *sinus rhythm*.)
- **Vaughan–Williams classification:** The standard system that groups anti-arrhythmic drugs by which ion channel or receptor they block: Class I = sodium channel blockers, Class II = beta-blockers, Class III = potassium channel blockers, Class IV = calcium channel blockers.
- **Action potential:** The wave of electrical change that travels through heart muscle and makes it contract. It has phases 0 (upstroke, Na+ in), 1–2 (plateau, Ca2+ in), 3 (repolarisation, K+ out), 4 (resting).
- **Refractory period:** The time after a beat during which the heart cell cannot be excited again. Lengthening it prevents extra abnormal beats.
- **Automaticity:** The ability of some heart cells to fire on their own. Too much automaticity causes extra beats (arrhythmia).
- **Proarrhythmic:** A property where an anti-arrhythmic drug itself causes a new arrhythmia — an important risk of these drugs.

## 4.3 Terminology

- **Ia / Ib / Ic:** Subclasses of Class I based on how strongly they slow conduction and what they do to repolarisation: Ia = moderate slowing + prolongs repolarisation; Ib = weak slowing + shortens repolarisation; Ic = marked slowing + little change in repolarisation.
- **Use-dependence:** The drug blocks channels more when the heart beats faster — so it acts mainly on the abnormal fast rhythm, not the normal beat.
- **Amide link:** The –CO–NH– connection between the aromatic ring part and the amine part in lidocaine-like drugs.
- **Ortho-methyls:** Methyl groups at the 2 and 6 positions (next to the attachment point) of the phenyl ring in lidocaine — they shield the amide from being broken down.
- **Hydrophilic amine:** The water-loving nitrogen part (e.g., diethylamino) that becomes positively charged at body pH and binds inside the sodium channel.
- **Aryloxypropanolamine:** The common scaffold of beta-blockers: aromatic ring–O–CH2–CH(OH)–CH2–NH–. Sotalol contains it.
- **Benzofuran:** A fused benzene + furan ring system — the core of amiodarone.
- **Hydantoin:** A 5-membered ring with two nitrogens and two carbonyls (imidazolidine-2,4-dione) — the core of phenytoin.

## 4.4 Explanations

**What is an arrhythmia, simply?** Technical concept: A disturbance of impulse formation or conduction producing abnormal rate or rhythm. Simple explanation: The heart has its own electrical wiring. If the wiring fires too fast, too slow, or chaotically, the pump cannot fill and squeeze properly. Example: Atrial fibrillation — the top chambers quiver uselessly at 400+ times a minute instead of beating. Key takeaway: Arrhythmia = faulty heart electricity; drugs fix it by blocking the faulty currents.

**Why classify by ion channel?** Technical concept: Each phase of the cardiac action potential is driven by a specific ion current, so blocking a channel predictably changes the electrical wave. Simple explanation: The heartbeat's electrical wave is made of sodium rushing in (start), calcium holding the plateau (middle), and potassium leaving (end). Drugs that block each of these "doors" change the wave in a predictable way — that is the whole Vaughan–Williams system. Example: Block sodium doors → the upstroke is slower → fast abnormal beats cannot keep up. Key takeaway: Channel blocked = phase changed = rhythm corrected.

**Why is Class I split into Ia, Ib, Ic?** Technical concept: The subclasses differ in dissociation kinetics from the sodium channel and in effects on action potential duration. Simple explanation: All three block sodium, but they "hold the door" for different lengths of time. Ia holds moderately and also delays the wave's end; Ib holds briefly and shortens the wave; Ic grips hardest and slows the wave's start dramatically. Example: Lidocaine (Ib) jumps on and off quickly — good for emergency ventricular beats. Lorcainide (Ic) grips hard — powerful but riskier. Key takeaway: Ia = moderate + longer wave; Ib = fast + shorter wave; Ic = strong + slower start.

## 4.5 Classifications — The Vaughan–Williams System

| Class | What it blocks | Effect on action potential | Drugs in our syllabus | Typical use pattern |
|---|---|---|---|---|
| Ia | Na+ channels (moderate, slow dissociation) | Slows phase 0; PROLONGS repolarisation (longer APD) | Quinidine sulphate, Procainamide, Disopyramide | Atrial and ventricular arrhythmias |
| Ib | Na+ channels (fast on/off; bind inactivated channels) | Slows phase 0 slightly; SHORTENS repolarisation | Phenytoin, Lidocaine, Tocainide, Mexiletine | Ventricular arrhythmias, especially after heart attack or digoxin toxicity |
| Ic | Na+ channels (marked slowing) | Markedly slows phase 0; little effect on repolarisation | Lorcainide | Ventricular arrhythmias (potent, use with caution) |
| II | Beta-adrenergic receptors | Slows SA/AV node; reduces automaticity | (Sotalol also belongs here) | Rate control, supraventricular arrhythmias |
| III | K+ channels | PROLONGS repolarisation and refractory period | Amiodarone, Sotalol | Broad: atrial fibrillation + ventricular arrhythmias |
| IV | Ca2+ channels (L-type) | Slows SA/AV node conduction | (Verapamil, diltiazem — not in our drug list) | Supraventricular arrhythmias |

Memory hook: **I = Na (IN), II = Beta (BLOCK), III = K (KEEP the wave long), IV = Ca (CALM the nodes).**

## 4.6 Mechanisms of Action

**Class I (all):** Block the fast sodium channels responsible for phase 0. The upstroke becomes slower and smaller, abnormal fast impulses cannot propagate, and automaticity falls. Because of use-dependence, faster (abnormal) tissue is blocked more than normal tissue.

**Class Ia in detail:** Also block potassium channels somewhat → action potential duration and refractory period get LONGER → the heart needs more time before the next beat → re-entrant circuits (loops of abnormal electricity) are broken.

**Class Ib in detail:** Bind preferentially to inactivated (recently fired) channels and leave quickly → they shorten the action potential → ideal for damaged, fast-firing ventricular tissue; less effect on normal tissue.

**Class II:** Block beta-1 receptors → less adrenaline effect → SA node fires slower, AV node conducts slower → controls fast supraventricular rhythms.

**Class III:** Block potassium channels → repolarisation (phase 3) is delayed → action potential and refractory period lengthen → abnormal beats find the tissue still "resting" and die out. (Sotalol does this AND blocks beta receptors.)

**Class IV:** Block L-type calcium channels in the SA and AV nodes → conduction through the AV node slows → fast atrial impulses are filtered before reaching the ventricles.

**Amiodarone — the "all-rounder":** Mainly Class III (K+ blockade), but also blocks Na+ channels, beta receptors, and Ca2+ channels — which is why it works on almost every arrhythmia.

## 4.7 Diagrams (describe so they can be drawn)

**Diagram 1 — Cardiac action potential with drug class actions.** Draw the classic action potential shape: sharp upstroke (label "0: Na+ in"), small notch ("1"), flat plateau ("2: Ca2+ in"), downward slope ("3: K+ out"), flat resting line ("4"). Add arrows: Class I drugs flatten the phase-0 upstroke; Class III drugs stretch phases 2–3 wider; Class IV drugs act on a small inset drawing of the SA/AV node; Class II drugs put a brake symbol on an adrenaline arrow pointing at the node.

**Diagram 2 — Re-entry circuit and how drugs break it.** Draw a circular track (like a running track) with an electrical spark going round and round — label "re-entry loop causes tachycardia". Show Class Ia/III drugs placing a "road closed — refractory" barrier across the track (longer refractory period stops the loop). Show Class I drugs narrowing the track (slower conduction).

**Diagram 3 — Disopyramide synthesis scheme (boxes and arrows).** Box 1 "Phenylacetonitrile" + Box "2-chloropyridine" with arrow labelled "sodamide (NaNH2)" → Box 2 "α-phenyl-α-(2-pyridyl)acetonitrile" → arrow labelled "Cl–CH2–CH2–N(i-Pr)2 (2-(diisopropylamino)ethyl chloride)" → Box 3 "α-[2-(diisopropylamino)ethyl]-α-phenyl-2-pyridineacetonitrile" → arrow labelled "conc. H2SO4 (nitrile hydrolysis)" → Box 4 "Disopyramide (amide)" → arrow labelled "phosphoric acid" → Box 5 "Disopyramide phosphate (final drug)".

**Diagram 4 — Lidocaine SAR map.** Draw lidocaine as three blocks joined: [2,6-dimethylphenyl] —(amide link)– [CH2] — [N(Et)2]. Label each block: aromatic ring = lipophilic anchor (ortho-methyls protect the amide); amide = essential link (ester would be destroyed quickly); CH2 bridge = correct spacing; tertiary amine = hydrophilic, charged at pH 7.4, binds inside the channel.

## 4.8 Flowcharts

**Flowchart 1 — Choosing the class (exam logic).** Abnormal rhythm detected → Is it ventricular and acute (e.g., after MI)? → YES → Class Ib (lidocaine IV). → Is digoxin toxicity causing ventricular beats? → YES → Phenytoin (Ib). → Is it atrial fibrillation needing rhythm control? → Consider Ia (quinidine/procainamide) or III (amiodarone/sotalol). → Is broad, difficult arrhythmia (both atrial + ventricular)? → Amiodarone (Class III + others). → Is AV node conduction the target? → Class II or IV.

**Flowchart 2 — Disopyramide synthesis (reagents only, quick recall).** Phenylacetonitrile + 2-chloropyridine --(NaNH2)--> nitrile intermediate --(ClCH2CH2N(iPr)2)--> substituted nitrile --(conc. H2SO4)--> amide (disopyramide) --(H3PO4)--> disopyramide phosphate.

## 4.9 Infographic Concept Box

**"The 10 Drugs on One Card"**

- **Ia — the prolongers:** Quinidine (cinchona alkaloid), Procainamide (benzamide), Disopyramide (pyridine-amide). Slow Na+ + LONGER wave.
- **Ib — the quick hitters:** Phenytoin (hydantoin), Lidocaine (acetanilide), Tocainide (oral lidocaine), Mexiletine (ether cousin). Fast Na+ block, SHORTER wave, best for ventricles.
- **Ic — the strong gripper:** Lorcainide (chlorophenyl anilide). Hardest Na+ block.
- **III — the wave stretchers:** Amiodarone (iodinated benzofuran, does everything), Sotalol (sulfonamide beta-blocker). Block K+ → LONGER refractory period.
- **Golden rule:** Ia and III lengthen the wave; Ib shortens it; Ic just slows the start.

## 4.10 Master Table — Drug → Class → Key Structure → Uses

| Drug | Vaughan–Williams class | Key structure (scaffold + substituents) | Main uses |
|---|---|---|---|
| Quinidine sulphate | Ia | Cinchona alkaloid: 6-methoxyquinoline ring joined to a quinuclidine ring bearing a vinyl group and a secondary alcohol; diastereomer of quinine; used as sulphate salt | Atrial fibrillation/flutter, paroxysmal supraventricular tachycardia, maintenance of normal sinus rhythm |
| Procainamide | Ia | p-Aminobenzamide: benzene ring with a para-amino group and a –CO–NH–CH2–CH2–N(Et)2 side chain | Ventricular arrhythmias; atrial arrhythmias (IV/oral) |
| Disopyramide* | Ia | Phenyl-pyridyl-butyramide: quaternary carbon bearing a phenyl ring, a 2-pyridyl ring, a primary amide (–CONH2), and a –CH2–CH2–N(i-Pr)2 (diisopropylaminoethyl) chain; used as phosphate salt | Ventricular arrhythmias (oral) |
| Phenytoin | Ib | Hydantoin: imidazolidine-2,4-dione ring with two phenyl groups at C-5 (5,5-diphenylhydantoin) | Arrhythmias caused by digoxin toxicity; ventricular arrhythmias; also an antiepileptic |
| Lidocaine (lignocaine) | Ib | Acetanilide: 2,6-dimethylphenyl ring joined via an amide link (–NH–CO–CH2–) to a diethylamino group | Acute ventricular arrhythmias (especially after heart attack); IV only |
| Tocainide | Ib | Like lidocaine but with a primary amine: 2,6-dimethylphenyl–NH–CO–CH(CH3)–NH2 (chiral) | Ventricular arrhythmias; oral alternative to lidocaine |
| Mexiletine | Ib | Ether analogue: 2,6-dimethylphenoxy–CH2–CH(CH3)–NH2 (oxygen replaces the amide nitrogen of tocainide) | Ventricular arrhythmias; oral |
| Lorcainide | Ic | Benzeneacetamide (anilide): phenyl–CH2–CO–N(4-chlorophenyl)–(1-isopropylpiperidin-4-yl); contains p-chlorophenyl and isopropyl-piperidine groups | Ventricular arrhythmias (potent; limited clinical use) |
| Amiodarone | III (also I, II, IV actions) | Benzofuran core: (2-butylbenzofuran-3-yl) ketone linked to a 3,5-diiodophenyl ring bearing a 2-diethylaminoethoxy side chain | Broad-spectrum: ventricular tachycardia/fibrillation, atrial fibrillation, supraventricular arrhythmias |
| Sotalol | III + II | Aryloxypropanolamine with methanesulfonamide: 4-(1-hydroxy-2-isopropylaminoethyl)phenyl–NH–SO2–CH3 | Atrial fibrillation, ventricular arrhythmias; also a non-selective beta-blocker |

## 4.11 Drug-by-Drug Structure Notes (scaffold + substituents + uses)

1. **Quinidine sulphate (Ia):** Scaffold = quinoline + quinuclidine (cinchona alkaloid). Key substituents: 6-methoxy on quinoline, vinyl group on quinuclidine, secondary –OH at the bridge. The sulphate salt improves solubility for tablets/injection. Uses: converting atrial fibrillation/flutter back to normal rhythm and keeping it normal.
2. **Procainamide (Ia):** Scaffold = benzamide (benzoic acid + amine). Key substituents: para-amino group on the ring; N-(2-diethylaminoethyl) side chain. The para-amino is acetylated in the liver to N-acetylprocainamide (also active, Class III-like). Uses: ventricular arrhythmias; watch for lupus-like syndrome on long use.
3. **Disopyramide* (Ia):** Scaffold = butyramide with a fully substituted (quaternary) α-carbon. Key substituents: phenyl + 2-pyridyl + primary amide + diisopropylaminoethyl chain. Full synthesis below. Uses: oral treatment of ventricular arrhythmias; strong anticholinergic (dry mouth, urinary difficulty) and negative inotropic effects.
4. **Phenytoin (Ib):** Scaffold = hydantoin (imidazolidine-2,4-dione). Key substituents: two phenyl rings at C-5. Uses: arrhythmias from digoxin toxicity (it suppresses the abnormal automaticity without worsening conduction), ventricular arrhythmias.
5. **Lidocaine (Ib):** Scaffold = acetanilide (phenyl + amide). Key substituents: 2,6-dimethyl on phenyl (ortho-methyls); diethylamino tertiary amine two carbons from the amide. Uses: emergency IV drug for acute ventricular arrhythmias post-MI; not effective orally (heavy first-pass metabolism).
6. **Tocainide (Ib):** Scaffold = same acetanilide as lidocaine. Key difference: a primary amine (–NH2) on the α-carbon instead of lidocaine's tertiary amine, and it is chiral. Uses: oral lidocaine-like drug for chronic ventricular arrhythmias.
7. **Mexiletine (Ib):** Scaffold = phenoxypropanamine (ether, not amide). Key substituents: 2,6-dimethylphenoxy + isopropylamine chain. The ether link resists liver breakdown → oral activity. Uses: chronic ventricular arrhythmias, oral.
8. **Lorcainide (Ic):** Scaffold = benzeneacetamide anilide. Key substituents: p-chlorophenyl on nitrogen; 1-isopropylpiperidin-4-yl on nitrogen. Uses: potent ventricular anti-arrhythmic (Class Ic); clinical use limited because Ic drugs need careful patient selection.
9. **Amiodarone (III):** Scaffold = benzofuran ketone. Key substituents: 2-butyl on benzofuran; 3,5-diiodo on the phenyl ring (iodine → thyroid side effects); diethylaminoethoxy side chain (like Class I amine). Uses: the broadest anti-arrhythmic — VT, VF, atrial fibrillation, SVT. Watch: thyroid, lung, liver, eye (corneal deposits), blue-grey skin.
10. **Sotalol (III + II):** Scaffold = aryloxypropanolamine (beta-blocker backbone) + methanesulfonamide (–NH–SO2–CH3) on the ring. Uses: atrial fibrillation and ventricular arrhythmias; the sulfonamide part gives Class III K+ blockade while the backbone gives beta-blockade.

## 4.12 Synthesis of Disopyramide* (starred — every step, reagent, intermediate)

Technical concept: Build the quaternary carbon in two alkylations on phenylacetonitrile, then convert the nitrile to the amide. Simple explanation: Start with a small nitrile, attach the pyridine ring, then attach the amine chain, then turn the nitrile into an amide — the drug. Finally make the phosphate salt.

**Step 1 — Attach the pyridine ring.** Reagents: phenylacetonitrile (C6H5–CH2–CN) + 2-chloropyridine, base = sodamide (NaNH2). Reaction: The –CH2– between phenyl and –CN is acidic; sodamide removes a proton, and the resulting carbanion displaces chloride from 2-chloropyridine. Intermediate: α-phenyl-α-(2-pyridyl)acetonitrile [2-phenyl-2-(pyridin-2-yl)acetonitrile].

**Step 2 — Attach the amine side chain.** Reagent: 2-(diisopropylamino)ethyl chloride [Cl–CH2–CH2–N(i-Pr)2]. Reaction: Alkylation of the same α-carbon (still has one acidic proton) with the chloroethylamine. Intermediate: α-[2-(diisopropylamino)ethyl]-α-phenyl-2-pyridineacetonitrile (the fully substituted nitrile).

**Step 3 — Nitrile to amide.** Reagent: concentrated sulphuric acid (H2SO4), controlled hydrolysis. Reaction: Partial hydrolysis of –CN stops at the amide stage (–CONH2). Product: α-[2-(diisopropylamino)ethyl]-α-phenyl-2-pyridineacetamide = **disopyramide** (racemic base).

**Step 4 — Salt formation.** Reagent: phosphoric acid (H3PO4). Product: **disopyramide phosphate** (the marketed oral form; freely water-soluble).

Key takeaway: nitrile → (pyridine attached) → (amine chain attached) → amide → phosphate salt. Four transformations, each intermediate named above.

## 4.13 SAR Highlights — Lidocaine and Analogues

1. **The amide link is essential.** Replace –NH–CO– with an ester (–O–CO–) and the drug is destroyed in minutes by esterases (that is why procaine is short-acting). The amide survives long enough to work.
2. **Ortho-methyl groups (2,6-dimethyl) protect the amide.** The two methyl groups sit like guards on either side of the amide bond, sterically blocking enzymes that would hydrolyse it, and they add lipophilicity so the drug reaches the channel.
3. **Lipophilic ring + hydrophilic amine, two carbons apart.** The aromatic ring anchors in the fatty channel wall; the tertiary amine (diethylamino, pKa ~7.9) is partly positively charged at blood pH and plugs the inside of the sodium channel. Wrong spacing = poor fit.
4. **Smaller, less bulky amines dissociate faster.** Lidocaine's diethylamino group lets it hop on and off the channel quickly → Class Ib behaviour (fast kinetics, shortens APD). Bulkier amines hold longer (more Ia-like).
5. **Tocainide/mexiletine keep the same ends, change the middle.** Tocainide keeps the amide but uses a primary amine (oral activity, chiral centre); mexiletine swaps the amide for an ether (–O–) which the liver cannot cut easily → both are orally active lidocaine cousins.

## 4.14 Examples

1. **Quinidine:** A patient with atrial fibrillation is given quinidine to restore normal sinus rhythm; the doctor watches the ECG because Ia drugs can themselves prolong the QT interval.
2. **Procainamide:** IV procainamide terminates a run of ventricular tachycardia in an emergency ward.
3. **Disopyramide:** A patient with recurrent ventricular ectopic beats takes disopyramide phosphate capsules; he is warned about dry mouth and difficulty in urination (anticholinergic effects).
4. **Phenytoin:** A patient on digoxin develops dangerous ventricular beats from digoxin toxicity; phenytoin controls the rhythm without further depressing conduction.
5. **Lidocaine:** Immediately after a heart attack, a patient develops ventricular tachycardia; IV lidocaine is the classic emergency drug.
6. **Tocainide/mexiletine:** A patient stabilised on IV lidocaine is switched to oral mexiletine for long-term prevention.
7. **Lorcainide:** A case of resistant ventricular arrhythmia where a potent Class Ic sodium blocker is considered under specialist supervision.
8. **Amiodarone:** A patient with both atrial fibrillation and ventricular tachycardia receives amiodarone — one drug covering both because of its multi-class action.
9. **Sotalol:** A patient with atrial fibrillation who also needs beta-blockade receives sotalol, which does both jobs.

## 4.15 Analogies

- **Sodium channel blockers:** A speed breaker on a road — fast (abnormal) vehicles are slowed much more than slow (normal) ones (use-dependence).
- **Class Ia vs Ib:** Ia is like a long red traffic light (lengthens the wait = longer refractory period); Ib is a quick speed bump (brief slowdown, shorter wave).
- **Potassium blockers (Class III):** Keeping the shop shutters down longer after closing — the next customer (abnormal beat) finds the shop still closed (refractory).
- **Amiodarone:** A Swiss-army knife — one tool with a blade (Na+ block), scissors (K+ block), and screwdriver (beta + Ca2+ block).
- **Lidocaine's ortho-methyls:** Two bodyguards flanking a VIP (the amide bond) so attackers (enzymes) cannot reach it.
- **Re-entry circuit:** Children running in circles in a playground; Class Ia/III drugs lock the gate for longer so the circle breaks.

## 4.16 Pharmacy Relevance

- **Proarrhythmia counselling:** Every anti-arrhythmic can cause arrhythmia — pharmacists must stress ECG monitoring and reporting palpitations, dizziness, or fainting.
- **Quinidine/procainamide:** Can cause cinchonism (ringing in ears, headache) and lupus-like syndrome (procainamide) — counsel patients on warning signs.
- **Disopyramide:** Strong anticholinergic effects — warn about dry mouth, blurred vision, urinary retention (especially elderly men with prostate enlargement); also worsens heart failure (negative inotrope).
- **Lidocaine:** IV only, narrow use window; toxicity shows as drowsiness, confusion, seizures — infusion must be rate-controlled.
- **Amiodarone:** The highest counselling burden — thyroid tests, liver tests, chest X-ray/lung function, eye checks, and strict sun protection (photosensitivity + blue-grey skin). Its half-life is weeks, so effects linger long after stopping.
- **Sotalol:** Beta-blocker warnings apply — do not stop suddenly (rebound), caution in asthma and diabetes.
- **Salt forms matter:** Quinidine sulphate and disopyramide phosphate are the marketed salts — the salt improves solubility and absorption; dose is expressed accordingly.

## 4.17 India Context

- Quinidine, procainamide, and disopyramide are older drugs now less commonly stocked in Indian retail pharmacies, but they remain exam-important and are still used in tertiary cardiac centres.
- Lidocaine (lignocaine) injection is available in every Indian emergency room and is also the country's most common local anaesthetic — students already know it from dental/pharmacy practice, which helps memory.
- Amiodarone is the workhorse anti-arrhythmic in Indian hospitals — cheap, oral and IV forms available, used widely for atrial fibrillation, which is common in India's rheumatic heart disease patients.
- Sotalol is available in India and used for atrial fibrillation rhythm control.
- Phenytoin's dual role (epilepsy + digoxin-toxicity arrhythmia) makes it a favourite Indian exam question linking two chapters.
- Because ECG monitoring is limited in rural India, pharmacists are often the first to spot amiodarone's thyroid/lung warning signs during refill visits.

## 4.18 Key Points

1. Vaughan–Williams: I = Na+ blockers (Ia/Ib/Ic), II = beta-blockers, III = K+ blockers, IV = Ca2+ blockers.
2. Ia prolongs the action potential; Ib shortens it; Ic mainly slows conduction.
3. Quinidine = cinchona alkaloid (quinoline + quinuclidine), diastereomer of quinine; sulphate salt.
4. Procainamide = p-aminobenzamide; metabolite N-acetylprocainamide also active; lupus risk.
5. Disopyramide = phenyl + 2-pyridyl + amide + diisopropylaminoethyl on one quaternary carbon; phosphate salt; synthesis = sodamide coupling → alkylation → H2SO4 hydrolysis → H3PO4 salt.
6. Phenytoin = 5,5-diphenylhydantoin; drug of choice for digoxin-toxicity arrhythmias.
7. Lidocaine = 2,6-dimethylphenyl + amide + diethylamino; IV only; post-MI ventricular arrhythmias.
8. Tocainide (primary amine, chiral) and mexiletine (ether) = oral lidocaine analogues.
9. Lorcainide = Class Ic chlorophenyl anilide; potent Na+ blockade.
10. Amiodarone = iodinated benzofuran; mainly Class III but acts on all four classes; broadest use, most side effects.
11. Sotalol = beta-blocker backbone + methanesulfonamide; Class II + III.
12. Lidocaine SAR: amide link essential; ortho-methyls shield it; lipophilic ring + charged amine two carbons apart; fast on/off = Ib profile.

## 4.19 Common Confusions

- **Ia vs III:** Both prolong the action potential, but Ia does it as a side effect of Na+ blockade while III does it by direct K+ blockade. Quinidine/procainamide/disopyramide = Ia; amiodarone/sotalol = III.
- **Sotalol in two classes:** It is BOTH Class II (beta-blocker backbone) and Class III (K+ blockade from the sulfonamide part) — this dual listing is correct, not a mistake.
- **Lidocaine the anaesthetic vs anti-arrhythmic:** Same drug, same sodium-channel blockade — on nerves it stops pain signals, on heart it stops abnormal beats.
- **Tocainide vs mexiletine:** Both oral Ib analogues of lidocaine; tocainide keeps the amide (primary amine), mexiletine replaces it with an ether.
- **Amiodarone's iodine:** The two iodine atoms are part of the structure (not an impurity) and cause the thyroid side effects.
- **Disopyramide's anticholinergic effects:** Come from the bulky diisopropylamino group, not from the anti-arrhythmic action itself.

## 4.20 Common Mistakes

1. Putting lidocaine in Class Ia — it is Ib (shortens, not prolongs, the action potential).
2. Writing the disopyramide synthesis without sodamide in step 1 or without conc. H2SO4 in step 3 — both reagents are exam-marked.
3. Forgetting the phosphate salt — the marketed drug is disopyramide phosphate, not the free base.
4. Saying amiodarone is "only Class III" — mention its Class I, II, and IV actions for full marks.
5. Drawing lidocaine without the 2,6-dimethyl groups — the ortho-methyls are the key SAR feature.
6. Confusing quinidine with quinine — they are diastereomers (same formula, different 3D arrangement); quinidine is the anti-arrhythmic.
7. Listing verapamil/diltiazem as syllabus drugs — they are Class IV examples but NOT in our 10-drug list.

## 4.21 Mnemonics

- **"I-a, I-b, I-c: Prolong, Brief, Clamp": Ia** prolongs the wave, **Ib** is brief (shortens), **Ic** clamps conduction hard.
- **"QPD for Ia": Q**uinidine, **P**rocainamide, **D**isopyramide — the three Ia drugs.
- **"PLTM for Ib": P**henytoin, **L**idocaine, **T**ocainide, **M**exiletine — the four Ib drugs.
- **"Lorcainide Lingers Longest on the channel"** — Ic = strongest/slowest sodium blockade.
- **"A-S for III": A**miodarone, **S**otalol — the two K+ blockers. ("A-S = Action potential Stretched".)
- **Disopyramide synthesis — "PAN-P": P**henylacetonitrile + 2-chloropyridine → (sod**A**mide) → **N**itrile intermediate → amine chain → (H2SO4) amide → (**P**hosphoric acid) phosphate.
- **Lidocaine SAR — "MAP": M**ethyls (ortho) protect, **A**mide link essential, **P**lug (charged amine) blocks the channel.

## 4.22 Exam Summary

Arrhythmia is abnormal heart rhythm, classified for treatment by the Vaughan–Williams system: Class I blocks Na+ channels (Ia: quinidine sulphate, procainamide, disopyramide — moderate block, prolonged repolarisation; Ib: phenytoin, lidocaine, tocainide, mexiletine — fast block, shortened repolarisation; Ic: lorcainide — marked conduction slowing), Class II blocks beta receptors, Class III blocks K+ channels (amiodarone, sotalol — prolonged refractory period), Class IV blocks Ca2+ channels. Quinidine is a cinchona alkaloid (methoxyquinoline + quinuclidine, quinine's diastereomer); procainamide is a p-aminobenzamide; disopyramide is a phenyl-pyridyl-butyramide (quaternary carbon with phenyl, 2-pyridyl, amide, diisopropylaminoethyl) made by sodamide-mediated coupling of phenylacetonitrile with 2-chloropyridine, alkylation with 2-(diisopropylamino)ethyl chloride, conc. H2SO4 hydrolysis to the amide, and phosphoric acid salt formation; phenytoin is 5,5-diphenylhydantoin, preferred in digoxin-toxicity arrhythmias; lidocaine is a 2,6-dimethyl acetanilide with a diethylamino group, IV-only for acute ventricular arrhythmias; tocainide (primary amine) and mexiletine (ether) are its oral analogues; lorcainide is a chlorophenyl anilide (Ic); amiodarone is a diiodinated benzofuran with multi-class action and the broadest uses; sotalol combines beta-blockade with K+ blockade via its methanesulfonamide group. Lidocaine SAR: essential amide link, ortho-methyl shielding, lipophilic–hydrophilic balance with correct two-carbon spacing, and fast channel kinetics giving the Ib profile.

## 4.23 One-Minute Revision

- I = Na: Ia (QPD — prolong), Ib (PLTM — shorten), Ic (lorcainide — clamp).
- II = beta-blockers; III = K blockers (amiodarone, sotalol — stretch the wave); IV = Ca blockers.
- Disopyramide synthesis: phenylacetonitrile + 2-chloropyridine (NaNH2) → nitrile → + ClCH2CH2N(iPr)2 → substituted nitrile → (conc. H2SO4) → amide → (H3PO4) → phosphate.
- Lidocaine SAR: amide essential, 2,6-dimethyl guards, charged amine plugs channel.
- Phenytoin = digoxin-toxicity arrhythmia drug. Amiodarone = broadest, most side effects (thyroid/lung/eye/skin). Sotalol = II + III.

## 4.24 Exam Questions

**Short-answer questions**

1. State the Vaughan–Williams classification with one example drug for each class/subclass.
2. How do Class Ia and Class Ib differ in their effect on the action potential duration?
3. Draw the structure of lidocaine and label the three SAR regions.
4. Why is phenytoin preferred for arrhythmias caused by digoxin toxicity?
5. Name the reagents and intermediates in any two steps of the disopyramide synthesis.

### Long-answer questions

1. Write the complete synthesis of disopyramide, giving the structure of every intermediate and the reagent used in each step. Mention its class and uses.
2. Classify anti-arrhythmic drugs as per Vaughan–Williams. Describe the structure (scaffold + key substituents) and uses of quinidine, procainamide, and amiodarone.
3. Discuss the SAR of lidocaine and its analogues (tocainide, mexiletine). Why are tocainide and mexiletine orally active while lidocaine is not?

### MCQs (with answers)

1. Which drug is Class Ib? (a) Quinidine (b) Lidocaine (c) Lorcainide (d) Sotalol. **Answer: (b)**
2. Class III anti-arrhythmics act by blocking: (a) Na+ (b) K+ (c) Ca2+ (d) Cl−. **Answer: (b)**
3. In disopyramide synthesis, sodamide is used in the step: (a) nitrile hydrolysis (b) coupling of phenylacetonitrile with 2-chloropyridine (c) salt formation (d) alkylation with the amine chloride. **Answer: (b)**
4. The marketed salt of disopyramide is the: (a) sulphate (b) hydrochloride (c) phosphate (d) maleate. **Answer: (c)**
5. The ortho-methyl groups in lidocaine mainly: (a) increase water solubility (b) protect the amide from hydrolysis (c) block potassium channels (d) add beta-blocking activity. **Answer: (b)**
6. Drug of choice for digoxin-induced ventricular arrhythmia: (a) verapamil (b) phenytoin (c) sotalol (d) lorcainide. **Answer: (b)**
7. Amiodarone's characteristic side effects are due to: (a) the benzofuran ring (b) iodine atoms (c) the phosphate group (d) the vinyl group. **Answer: (b)**
8. Sotalol belongs to classes: (a) I only (b) II and III (c) III and IV (d) I and II. **Answer: (b)**
9. Tocainide differs from lidocaine by having: (a) an ether link (b) a primary amine and a chiral centre (c) two iodine atoms (d) a quinuclidine ring. **Answer: (b)**
10. Quinidine is the — of quinine: (a) enantiomer (b) diastereomer (c) salt (d) metabolite. **Answer: (b)**

### Viva questions

1. Expand "Vaughan–Williams" classes in one line each. (I = Na+ block, II = beta-block, III = K+ block, IV = Ca2+ block.)
2. Which reagent converts the nitrile to the amide in disopyramide synthesis? (Concentrated sulphuric acid.)
3. Why is lidocaine not given orally? (Heavy first-pass metabolism; also it is formulated for IV emergency use.)
4. Name the two oral analogues of lidocaine. (Tocainide and mexiletine.)
5. What makes amiodarone "broad-spectrum"? (It has Class I, II, III, and IV actions.)
6. Which structural feature gives sotalol its Class III activity? (The methanesulfonamide group; the backbone gives beta-blockade.)

### Application-based questions

1. A patient stabilised on IV lidocaine after a heart attack needs long-term oral therapy. Which two drugs could the doctor choose, and what structural change makes them orally active? (Tocainide — primary amine analogue; mexiletine — ether instead of amide, resisting liver metabolism.)
2. A patient on disopyramide complains of dry mouth and difficulty passing urine. Explain and advise. (Anticholinergic effect of the bulky diisopropylamino group. Advise: report urinary retention, especially elderly males; maintain hydration; do not stop abruptly without doctor's advice.)
3. A patient on long-term amiodarone develops cough and breathlessness. What should the pharmacist suspect and do? (Possible amiodarone lung toxicity — pulmonary fibrosis. Refer urgently to the prescriber; do not advise stopping on one's own; note the drug's weeks-long half-life.)

## 4.25 References


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