BP405T · B.PHARM THEORY

BP405T Systemic Pharmacology I

Unit II — Drugs Acting on the Cardiovascular System

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B.Pharm Semester IV · Unit II · 10 Hours

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Chapter 1: Cardiac Hemodynamics & Electrophysiology Basics

(Syllabus topic a: Introduction to cardiovascular hemodynamics and cardiac electrophysiology)

1.1 Learning Objectives

By the end of this chapter, you will be able to:

1. Define hemodynamics and list the main hemodynamic terms (cardiac output, stroke volume, heart rate, preload, afterload, contractility).
2. Explain the formula Cardiac Output = Heart Rate × Stroke Volume in simple words.
3. Explain preload, afterload and contractility using everyday examples.
4. State the Frank–Starling law in your own words and give one clinical example.
5. List the determinants of blood pressure and explain Blood Pressure = Cardiac Output × Total Peripheral Resistance.
6. Describe the phases (0–4) of the cardiac action potential and the ions moving in each phase.
7. Differentiate fast-response and slow-response action potentials.
8. Explain pacemaker activity of the SA node in simple words (funny current concept).
9. Trace the normal conduction pathway: SA node → AV node → Bundle of His → Purkinje fibres.
10. Define absolute and relative refractory periods and explain their importance.
11. Name the basic ECG waves (P, QRS, T) and state what electrical event each wave represents.
12. Answer exam questions on hemodynamics and electrophysiology with correct examples.

1.2 Definitions

Hemodynamics — the study of how blood flows through the heart and blood vessels, and what controls that flow. Simple meaning: the "physics of blood circulation" — how much blood the heart pumps, how hard it must push, and what resists the flow.

Cardiac output (CO) — the total volume of blood pumped by one ventricle (usually the left) per minute. Simple meaning: how many litres of blood the heart pushes out every minute. Normal resting value is roughly 5 litres per minute (about one bucket of water per minute).

Stroke volume (SV) — the volume of blood pumped out by one ventricle in a single heartbeat (one "stroke" of the pump). Roughly 70 mL per beat at rest in an adult.

Heart rate (HR) — the number of heartbeats per minute. Normal resting range is roughly 60–100 beats per minute.

Preload — the amount of stretch on the heart muscle just before it contracts, decided by how much blood fills the ventricle during diastole (resting phase). Simple meaning: "how full the pump is before it squeezes."

Afterload — the resistance or pressure the heart must push against to eject blood, mainly the pressure in the arteries. Simple meaning: "how heavy the load is that the pump must lift."

Contractility (inotropic state) — the inherent strength or force of heart muscle contraction, independent of preload and afterload. Simple meaning: "how powerfully the pump's motor can squeeze."

Frank–Starling law — the rule that the more the heart muscle is stretched by incoming blood (within limits), the more forcefully it contracts and the more blood it pumps out. Simple meaning: "the fuller the pump, the stronger the squeeze."

Blood pressure (BP) — the force/pressure that flowing blood exerts on the walls of arteries. It is determined by cardiac output and the resistance of blood vessels: BP = CO × TPR (total peripheral resistance).

Cardiac action potential — the sequence of electrical voltage changes across the heart muscle cell membrane during one heartbeat. It has 5 phases numbered 0 to 4.

Pacemaker — a heart cell that can generate its own electrical impulse repeatedly without any outside signal. The SA node is the heart's natural pacemaker.

Refractory period — a short time after an electrical impulse during which a heart cell cannot be excited again (or needs a stronger stimulus). It prevents the heart from beating too fast and chaotically.

ECG (electrocardiogram) — a recording of the heart's electrical activity from the body surface. Its waves (P, QRS, T) represent the spread of electrical impulses through the heart.

1.3 Terminology

- **Systole** — the contraction (squeezing) phase of the heart when blood is pumped out.
- **Diastole** — the relaxation (filling) phase of the heart when blood flows in.
- **Ejection fraction (EF)** — the percentage of blood in the ventricle that is pumped out with each beat. Normal is roughly 55–70%. Low EF (for example, below 40%) means a weak pump — a key concept in heart failure.
- **Chronotropy** — effect on heart rate (positive chronotropic = increases rate; negative = decreases rate).
- **Inotropy** — effect on force of contraction (positive inotropic = stronger squeeze).
- **Dromotropy** — effect on speed of conduction through the AV node (negative dromotropic = slows conduction).
- **Bathmotropy** — effect on excitability of heart muscle.
- **Mean arterial pressure (MAP)** — the average pressure in arteries during one cardiac cycle; the main driving force pushing blood to organs.
- **Pulse pressure** — the difference between systolic and diastolic pressure.
- **Fast-response action potential** — the type seen in atrial/ventricular muscle and Purkinje fibres; phase 0 is very fast (sodium rushes in).
- **Slow-response action potential** — the type seen in SA and AV nodes; phase 0 is slow (calcium trickles in, not sodium).
- **Pacemaker potential (phase 4 depolarization)** — the slow, spontaneous drifting upward of voltage in SA node cells during rest, which triggers the next heartbeat automatically.
- **Funny current (If)** — a special inward current (sodium and potassium mix) in pacemaker cells that starts the slow phase-4 drift. Called "funny" because it behaves unusually (opens when the cell is at rest voltage).
- **Automaticity** — the ability of pacemaker cells to fire impulses on their own.
- **Absolute refractory period (ARP)** — no stimulus, however strong, can excite the cell.
- **Relative refractory period (RRP)** — only a stronger-than-normal stimulus can excite the cell.
- **P wave** — atrial depolarization (atria contract).
- **QRS complex** — ventricular depolarization (ventricles contract); the tall spike on ECG.
- **T wave** — ventricular repolarization (ventricles relax electrically).
- **PR interval** — time for the impulse to travel from atria through the AV node to ventricles.
- **Ectopic beat** — a heartbeat starting from an abnormal site instead of the SA node.

1.4 Explanation (Main Teaching)

The heart is a pump — start here. Everything in this chapter becomes easy if you keep one picture in mind: the heart is a muscular pump, the blood vessels are pipes, and blood is the fluid flowing through the pipes. A pump's job is decided by three things: how much fluid it moves per minute, how full it gets before each squeeze, and how hard it must push against the pipes. Cardiology and cardiovascular pharmacology are mostly about these three things.

Cardiac output: the master formula. Cardiac Output = Heart Rate × Stroke Volume (CO = HR × SV). In words: the litres pumped per minute equals beats per minute multiplied by litres pumped per beat. Example: if the heart beats 70 times per minute and pushes 70 mL each beat, CO = 70 × 70 mL = 4,900 mL ≈ 5 litres per minute. During heavy exercise, heart rate can roughly double and stroke volume can increase, so cardiac output can rise several-fold — the pump works harder when the body demands more.

What controls stroke volume? Three factors: preload, afterload, contractility.

Preload — "how full the pump is." When more blood returns to the heart through the veins (venous return), the ventricle fills more and its muscle fibres stretch more before contracting. A stretched muscle contracts more forcefully — this is the Frank–Starling law (explained below). Things that increase preload: more blood volume, venoconstriction (veins squeezing blood toward the heart), lying down. Drugs that reduce preload (like nitrates and diuretics) help a failing, overloaded heart by "unloading" it.

Afterload — "how heavy the load is." After the ventricle starts squeezing, it must open the aortic valve and push blood into the high-pressure aorta. The resistance it faces is the afterload, decided mainly by arterial blood pressure and vessel tightness (peripheral resistance). High blood pressure = high afterload = the pump must work harder. Drugs that dilate arteries (like ACE inhibitors) reduce afterload and make the heart's job easier.

Contractility — "how strong the motor is." This is the muscle's own squeezing power, controlled by the sympathetic nervous system (adrenaline/noradrenaline increase it) and by calcium inside the cells. Drugs like digoxin (positive inotropic) increase contractility; beta blockers reduce it.

Frank–Starling law — the rubber band rule. Stretch a rubber band a little and let go — it snaps back weakly. Stretch it more (within limits) — it snaps back strongly. Heart muscle behaves the same way: more filling (more stretch) → stronger contraction → more blood pumped out. This is the heart's built-in self-adjustment: if extra blood arrives, the heart automatically pumps the extra out, so blood does not pile up. Clinical example: when you stand up quickly after lying down, venous return changes and the Frank–Starling mechanism instantly adjusts stroke volume. In heart failure, the heart is stretched too far for too long and this mechanism fails — the pump is overstretched like an old rubber band that has lost its snap.

Blood pressure determinants. Blood Pressure = Cardiac Output × Total Peripheral Resistance (BP = CO × TPR). Two multipliers decide BP: (1) how much blood the heart pumps (CO — itself decided by heart rate, stroke volume, blood volume), and (2) how tight/narrow the blood vessels are (TPR — decided by vessel diameter; sympathetic tone constricts vessels, and hormones like angiotensin II constrict them). This one formula explains nearly every blood pressure drug: diuretics reduce blood volume (↓CO), beta blockers reduce heart rate and contractility (↓CO), ACE inhibitors/ARBs/CCBs relax vessels (↓TPR). Hypertension treatment is applied hemodynamics.

The heart's electricity: action potential phases 0–4. A heart muscle cell at rest is negatively charged inside (about −90 mV). When stimulated, its voltage changes in a fixed sequence:

- **Phase 0 — rapid upstroke (firing):** Sodium channels fly open; Na^+ rushes INTO the cell; voltage shoots upward. This is the "spark" that starts contraction. (In fast-response cells.)
- **Phase 1 — early notch (brief dip):** Sodium channels close; a brief outward flow of K^+ causes a small dip. A short transitional phase.
- **Phase 2 — plateau (the flat top):** Calcium channels open; Ca^{2+} flows IN while K^+ flows OUT — the two balance, so voltage stays flat like a plateau. This long plateau (unique to heart muscle) is what keeps the heart contracted long enough to pump, and it creates the long refractory period that prevents chaotic re-excitation.
- **Phase 3 — repolarization (coming down):** Calcium channels close; K^+ rushes OUT; voltage falls back to resting level. The cell relaxes.
- **Phase 4 — resting (or pacemaker drift):** In ordinary muscle cells, voltage sits quietly at rest while pumps (Na^+/K^+ ATPase) restore ion balance. In pacemaker cells (SA node), phase 4 is not quiet — voltage slowly drifts upward on its own until it hits the firing threshold, and the next beat starts automatically.

Fast vs slow response. Ordinary atrial/ventricular muscle and Purkinje fibres show the FAST response: phase 0 is a steep spike driven by fast Na^+ channels. The SA node and AV node show the SLOW response: there are almost no fast Na^+ channels there, so phase 0 is a gentle slope driven by slow Ca^{2+} channels. Why does this matter? Because drugs act differently on the two types: calcium channel blockers (verapamil) slow the SA and AV nodes (slow-response tissue) but do little to ordinary ventricular muscle; sodium channel blockers (Class I antiarrhythmics) act on fast-response tissue. This single distinction explains half of antiarrhythmic pharmacology.

Pacemaker activity of the SA node — the heart's clock. SA node cells never truly rest. During phase 4, three currents work together: (1) the funny current (If) lets positive ions drift in; (2) T-type Ca^{2+} channels open briefly; (3) K^+ outward flow decreases. Net effect: the voltage slowly climbs like water rising in a tank until it reaches threshold — then Ca^{2+} channels open (slow phase 0), the cell fires, and the impulse spreads. The sympathetic system (adrenaline) speeds the drift (faster heart rate); the parasympathetic system (vagal, acetylcholine) slows it. This is why beta blockers slow the heart (block sympathetic speed-up) and why ivabradine (a newer drug) slows the heart by blocking the funny current directly.

The conduction system — the house wiring. The electrical impulse must spread through the heart in the correct order (atria first, then ventricles) with a small delay between. The wiring path:

1. **SA node** (top of right atrium) — generates the impulse; the main switch of the house.
2. **Atrial muscle** — impulse spreads across both atria; atria contract (P wave).
3. **AV node** (between atria and ventricles) — the impulse is DELAYED here (~0.1 second). This delay lets the atria finish squeezing blood into the ventricles before the ventricles contract. Like a deliberate pause in the wiring.
4. **Bundle of His** — the only electrical bridge through the insulating wall between atria and ventricles; carries the impulse downward.
5. **Right and left bundle branches** — split the signal to each ventricle.
6. **Purkinje fibres** — a fast network spreading the impulse rapidly across ventricular muscle so both ventricles contract together powerfully (QRS complex).

> Analogy: the SA node is the main switch, atrial muscle is the ground-floor wiring, the AV node is a timer-switch that deliberately delays, the Bundle of His is the single cable through the concrete slab between floors, and Purkinje fibres are the room-by-room wiring that lights every bulb at once.

Refractory periods — the safety lock. After firing, a heart cell needs recovery time before it can fire again. The **absolute refractory period** (roughly phases 0–2) is a total lockout: no stimulus can re-excite the cell. The **relative refractory period** (phase 3) is a partial lockout: only an extra-strong stimulus works. The **effective/full refractory period** extends until the cell is fully reset. Importance: the long plateau (phase 2) gives heart muscle a long refractory period, so the heart cannot be re-stimulated while it is still contracting — this prevents tetanus (sustained cramp, which would stop pumping) and limits how fast dangerous rhythms can go. Many antiarrhythmic drugs work by LENGTHENING the refractory period.

Basic ECG waves — reading the heart's electricity. One heartbeat on ECG:

- **P wave** — small bump: atria depolarize and contract. (Atrial systole.)
- **QRS complex** — tall sharp spike: ventricles depolarize and contract. It is tall because ventricular muscle is thick and Purkinje conduction is fast.
- **T wave** — medium bump: ventricles repolarize (electrically reset, muscle relaxes).
- **PR interval** — from start of P to start of QRS: the AV nodal delay; if prolonged, conduction is slowed (AV block).
- **ST segment & QT interval** — relate to the plateau and total electrical recovery time; drugs that prolong QT (like some antiarrhythmics) can be pro-arrhythmic.

Key takeaway: Hemodynamics (CO = HR × SV; BP = CO × TPR; preload/afterload/contractility; Frank–Starling) tells you WHAT the pump is doing. Electrophysiology (phases 0–4, fast vs slow response, SA node pacemaker, conduction wiring, refractory periods, ECG waves) tells you HOW the pump's electricity works. Every drug in the next three chapters acts on one of these two stories.

1.5 Classifications

Classification of hemodynamic parameters:

1. **Pump output parameters:** cardiac output (CO), stroke volume (SV), ejection fraction (EF), cardiac index.
2. **Load parameters:** preload (filling load), afterload (ejection load).
3. **Muscle property:** contractility (inotropic state).
4. **Vascular parameters:** total peripheral resistance (TPR), blood volume, venous return.
5. **Pressure parameters:** systolic BP, diastolic BP, mean arterial pressure (MAP), pulse pressure.

Classification of factors increasing/decreasing cardiac output:

- **Increase CO:** increased heart rate (sympathetic stimulation, exercise), increased preload (more venous return), increased contractility (adrenaline, digoxin).
- **Decrease CO:** decreased heart rate (vagal stimulation, beta blockers), decreased preload (blood loss, diuretics), decreased contractility (heart failure, calcium channel blockers), increased afterload (severe hypertension).

Classification of cardiac action potentials:

1. **Fast-response action potential** — atrial muscle, ventricular muscle, Purkinje fibres; phase 0 via fast Na^+ channels; steep upstroke; long plateau.
2. **Slow-response action potential** — SA node, AV node; phase 0 via slow Ca^{2+} channels; gentle upstroke; prominent phase-4 pacemaker drift.

Classification of refractory periods:

1. **Absolute refractory period (ARP)** — phases 0 to mid-phase 2; no response to any stimulus.
2. **Relative refractory period (RRP)** — late phase 3; response only to strong stimulus.
3. **Effective refractory period (ERP)** — ARP + the part of RRP where a propagated response is impossible; the period most antiarrhythmics prolong.

Classification of ECG components:

1. **Depolarization waves:** P wave (atrial), QRS complex (ventricular).
2. **Repolarization waves:** T wave (ventricular); atrial repolarization is hidden inside QRS.
3. **Intervals/segments:** PR interval (AV conduction time), QRS duration (ventricular spread speed), QT interval (total ventricular electrical activity time), ST segment (plateau phase).

1.6 Mechanisms

Mechanism of contraction — excitation–contraction coupling (simple version): The electrical signal (action potential) travels along the cell membrane and dives into the cell through tiny tunnels (T-tubules). This opens L-type Ca^{2+} channels; a little Ca^{2+} enters. That little Ca^{2+} triggers the cell's internal store (sarcoplasmic reticulum) to release a LOT of Ca^{2+} — "calcium-induced calcium release." The flood of Ca^{2+} binds to the muscle filaments (troponin), the filaments slide past each other, and the cell shortens = contraction. When Ca^{2+} is pumped back into the store, the cell relaxes. More Ca^{2+} inside = stronger contraction. This is why calcium handling is the key to contractility, and why digoxin (which raises intracellular Ca^{2+}) strengthens the heartbeat.

Mechanism of the Frank–Starling law (at the muscle level): When the ventricle fills with more blood, each muscle fibre is stretched to a more optimal length. At this length, the contractile filaments (actin and myosin) overlap perfectly, so more gripping points (cross-bridges) can form — like two combs meshing better. More cross-bridges = more force. Additionally, stretch makes the filaments more sensitive to Ca^{2+}. Net result: the stretched heart ejects the extra blood it received. (Limit: overstretch beyond the optimal point weakens contraction — the failing, over-dilated heart.)

Mechanism of blood pressure regulation (short-term — baroreceptor reflex): Pressure sensors (baroreceptors) in the carotid sinus and aortic arch constantly measure BP. If BP falls → less stretch on sensors → signal to brainstem → sympathetic activation + vagal withdrawal → heart rate up, contractility up, vessels constrict → BP rises back. If BP rises → opposite. This reflex works within seconds. (Long-term control is by the kidney and RAAS — covered in Chapter 2.)

Ion movements in each action potential phase (fast-response cell):

- **Phase 0:** Fast Na^+ channels open → massive Na^+ INFLUX → rapid depolarization (upstroke).
- **Phase 1:** Fast Na^+ channels inactivate; transient outward K^+ current (Ito) → brief repolarization notch.
- **Phase 2 (plateau):** L-type Ca^{2+} channels open → Ca^{2+} INFLUX balanced by slow K^+ EFFLUX → flat voltage; Ca^{2+} entry triggers contraction.
- **Phase 3:** Ca^{2+} channels close; delayed rectifier K^+ channels open → rapid K^+ EFFLUX → repolarization to resting voltage.
- **Phase 4:** Resting; Na^+/K^+ ATPase pump (3 Na^+ out, 2 K^+ in) and Na^+/Ca^{2+} exchanger restore ion gradients quietly.

Pacemaker mechanism (SA node, slow-response cell): Phase 4 is unstable: funny current (If — mixed Na^+/K^+ inward) + T-type Ca^{2+} current flow inward while K^+ outward current fades → membrane slowly depolarizes → threshold reached → L-type Ca^{2+} channels open → slow phase-0 upstroke (no fast Na^+ here) → then K^+ efflux repolarizes (phase 3) → cycle repeats automatically. Sympathetic stimulation steepens the phase-4 slope (faster rate); vagal stimulation flattens it (slower rate).

Mechanism of orderly conduction: Gap junctions (electrical tunnels between neighbouring heart cells) let the impulse flow from cell to cell. Conduction is fast in Purkinje fibres (many gap junctions, fast Na^+ channels), slow in the AV node (few gap junctions, slow Ca^{2+} channels) — creating the useful AV delay.

1.7 Diagrams (Describe Textually So They Can Be Drawn)

Diagram 1 — The heart as a pump with preload and afterload. Draw a simple heart outline with two arrows: a wide blue arrow entering from veins labelled "PRELOAD — filling load (venous return stretches the ventricle)"; a red arrow leaving through the aorta pushing against a narrow pipe labelled "AFTERLOAD — ejection load (arterial pressure resists ejection)". Inside the heart wall write "CONTRACTILITY — muscle's own squeezing power". Below, write "CO = HR × SV".

Diagram 2 — Frank–Starling curve. X-axis: "Ventricular filling / preload (end-diastolic volume)"; Y-axis: "Stroke volume / force of contraction". Draw a curve rising steeply then flattening at the top. Mark three points: low filling → low output; normal filling → normal output; very high filling (failing heart) → curve flattens/falls. Caption: "More stretch → stronger beat, up to a limit."

Diagram 3 — Cardiac action potential with phases and ions (fast response). Draw voltage (Y) vs time (X): sharp spike up (0), tiny notch (1), long flat plateau (2), downward slope (3), flat baseline (4). Annotate: 0 = "Na^+ IN (fast)", 1 = "K^+ OUT briefly", 2 = "Ca^{2+} IN = K^+ OUT (plateau)", 3 = "K^+ OUT", 4 = "rest — pumps restore". Shade the ARP (phases 0–2) and RRP (phase 3) beneath.

Diagram 4 — Slow-response (SA node) action potential. Draw a gentle triangular wave with a sloping phase 4 rising to threshold, then a slow upstroke. Annotate phase 4: "If (funny current) + Ca^{2+} drift upward"; phase 0: "Ca^{2+} IN (slow, no fast Na^+)".

Diagram 5 — Conduction system map. Draw a heart outline; mark SA node (top right atrium) with a star "pacemaker — fires first"; arrows across atria; AV node marked with a clock symbol "delay ~0.1 s"; Bundle of His as a single line through the septum; left/right bundle branches; Purkinje network fanning over ventricles. Number the sequence 1→6.

Diagram 6 — Normal ECG with labels. Draw one P-QRS-T complex. Label: P = "atria contract", QRS = "ventricles contract (tall spike)", T = "ventricles reset". Mark PR interval with a bracket "AV node delay" and QT interval "total ventricular electrical time".

1.8 Flowcharts (Step-by-Step Text Flowcharts)

Flowchart 1 — What decides cardiac output:

```
Blood volume / venous return
        ↓
   Ventricular filling (PRELOAD)
        ↓
Frank-Starling: more stretch → stronger contraction
        ↓
STROKE VOLUME  ×  HEART RATE (SA node rate)
        ↓
CARDIAC OUTPUT (L/min)
        ↓
Reduced by: ↑ afterload (high BP), ↓ contractility (failing muscle)
Increased by: sympathetic stimulation, ↓ afterload
```

Flowchart 2 — What decides blood pressure:

```
CARDIAC OUTPUT (HR × SV)   ×   TOTAL PERIPHERAL RESISTANCE (vessel tightness)
        ↓
BLOOD PRESSURE
        ↓
CO raised by: ↑HR, ↑SV (↑preload, ↑contractility, ↑blood volume)
TPR raised by: sympathetic vasoconstriction, angiotensin II
Drugs lower BP by: ↓CO (diuretics, beta blockers) or ↓TPR (ACE-I, ARBs, CCBs)
```

Flowchart 3 — Baroreceptor reflex (seconds-fast BP control):

```
BP falls → carotid/aortic sensors stretched less
        ↓
Signal to brainstem
        ↓
Sympathetic ↑ + vagal ↓
        ↓
HR ↑, contractility ↑, vessels constrict
        ↓
BP restored toward normal
```

Flowchart 4 — Sequence of one heartbeat's electricity:

```
SA node fires (pacemaker, phase-4 drift hits threshold)
        ↓
Atria depolarize → P wave → atria contract
        ↓
AV node delays impulse (~0.1 s) — atria finish emptying
        ↓
Bundle of His → bundle branches → Purkinje fibres (fast spread)
        ↓
Ventricles depolarize → QRS complex → ventricles contract
        ↓
Ventricles repolarize → T wave → ventricles relax
        ↓
SA node fires again (next cycle)
```

Flowchart 5 — Fast-response action potential ion sequence:

```
Stimulus arrives → fast Na⁺ channels open
        ↓  PHASE 0: Na⁺ rushes IN → voltage spikes up
Na⁺ channels close; brief K⁺ outflow
        ↓  PHASE 1: small notch
L-type Ca²⁺ channels open; Ca²⁺ in = K⁺ out
        ↓  PHASE 2: plateau (long) → Ca²⁺ triggers contraction
Ca²⁺ channels close; K⁺ channels open wide
        ↓  PHASE 3: K⁺ rushes OUT → voltage falls
Resting: Na⁺/K⁺ pump restores gradients
        ↓  PHASE 4: quiet (or pacemaker drift in SA node)
```

1.9 Infographic Concept Box

🫀 THE HEART IN ONE PAGE

PUMP MATH: CO = HR × SV (how much per minute = beats × per beat) | BP = CO × TPR (pressure = pump flow × pipe tightness)

THREE PUMP CONTROLS: 🪣 **Preload** = how full before squeeze (venous return) | 🏋️ **Afterload** = how heavy the push (arterial pressure) | 💪 **Contractility** = motor strength (calcium + adrenaline)

RUBBER-BAND RULE (Frank–Starling): more filling → more stretch → stronger beat (up to a limit)

ELECTRICITY IN 5 PHASES: 0️⃣ Na^+ IN (spark) → 1️⃣ K^+ OUT (notch) → 2️⃣ Ca^{2+} IN (plateau = squeeze time) → 3️⃣ K^+ OUT (reset) → 4️⃣ rest (or SA node drift → next beat)

TWO ELECTRIC TYPES: ⚡ Fast (muscle + Purkinje: Na^+ spike) | 🐢 Slow (SA + AV node: Ca^{2+} slope — target of verapamil)

WIRING ORDER: SA node ⭐ → atria → AV node ⏱️ (delay) → His → branches → Purkinje → ventricles

ECG IN 3 WAVES: P = atria work | QRS = ventricles work (tall spike) | T = ventricles rest

SAFETY LOCK: long plateau → long refractory period → heart can't cramp (no tetanus) — antiarrhythmics lengthen this lock.

1.10 Tables

Table 1.1 — Hemodynamic parameters at a glance

Parameter	Symbol	Simple meaning	What increases it	What decreases it
Cardiac output	CO	Litres pumped/min (≈5 L)	↑HR, ↑SV, exercise, adrenaline	Heart failure, blood loss, beta blockers
Stroke volume	SV	mL pumped per beat (≈70 mL)	↑preload, ↑contractility	↑afterload, weak muscle
Heart rate	HR	Beats/min (60–100 rest)	Sympathetic, fever, exercise	Vagal, beta blockers, sleep
Preload	—	Filling/stretch before beat	↑blood volume, venoconstriction	Diuretics, nitrates, bleeding
Afterload	—	Resistance to ejection	Hypertension, vasoconstriction	ACE-I, ARBs, CCBs (vasodilation)
Contractility	—	Muscle's own strength	Adrenaline, digoxin, ↑Ca^{2+}	Heart failure, acidosis, CCBs
Total peripheral resistance	TPR	Tightness of vessels	Sympathetic, angiotensin II	Vasodilator drugs, heat
Ejection fraction	EF	% pumped out per beat (55–70%)	↑contractility	Heart failure (<40% = weak pump)

Table 1.2 — Fast-response vs slow-response action potentials

Feature	Fast response	Slow response
Found in	Atrial & ventricular muscle, Purkinje fibres	SA node, AV node
Phase 0 ion	Fast Na^+ influx (steep spike)	Slow Ca^{2+} influx (gentle slope)
Phase 4	Quiet resting	Pacemaker drift (automatic firing)
Conduction speed	Fast	Slow (useful AV delay)
Drug targets	Na^+ channel blockers (Class I antiarrhythmics)	Ca^{2+} channel blockers (verapamil), beta blockers, funny-current blocker (ivabradine)

Table 1.3 — Action potential phases and ion movements (fast response)

Phase	Name	Main ion movement	Effect on voltage
0	Upstroke	Na^+ rushes IN	Shoots up
1	Notch	K^+ flows OUT briefly	Small dip
2	Plateau	Ca^{2+} IN balances K^+ OUT	Stays flat (long)
3	Repolarization	K^+ rushes OUT	Falls down
4	Resting	Pumps restore balance	Flat baseline

Table 1.4 — ECG waves and what they mean

Wave/interval	Electrical event	Mechanical event
P wave	Atrial depolarization	Atria contract
PR interval	Conduction through AV node (delay)	Atria finish emptying into ventricles
QRS complex	Ventricular depolarization (fast via Purkinje)	Ventricles contract
ST segment	Ventricular plateau phase	Ventricles stay contracted
T wave	Ventricular repolarization	Ventricles relax
QT interval	Total ventricular electrical activity	Contraction + relaxation time

1.11 Examples

1. **CO calculation:** A patient's heart beats 80/min with stroke volume 70 mL → CO = 80 × 70 = 5,600 mL/min ≈ 5.6 L/min.
2. **Preload example:** Drinking 2 litres of water / receiving IV saline increases blood volume → more venous return → higher preload → (Frank–Starling) stronger beat → higher stroke volume.
3. **Afterload example:** A hypertensive patient with BP 180/110 has high afterload; the left ventricle must push against stiff, high-pressure arteries, so it thickens over time (hypertrophy).
4. **Contractility example:** During sudden fear, adrenaline increases contractility — the heart pounds harder and faster.
5. **Frank–Starling example:** After a large meal, extra blood flows to the gut; venous return rises slightly and the heart automatically pumps a little more per beat — no brain signal needed.
6. **Pacemaker example:** The SA node fires ~70 times/min at rest; if it fails, the AV node can take over at ~40–50/min (slower backup).
7. **AV delay example:** The ~0.1 s AV nodal delay is why atria contract first (P wave) and ventricles after (QRS) — without it, both would squeeze together and filling would fail.
8. **ECG example:** In a normal ECG, each P wave is followed by a QRS — one atrial beat, one ventricular beat, in order.

1.12 Analogies

1. **Heart = water pump; vessels = pipes; blood = water.** Every hemodynamic term maps to plumbing.
2. **Preload = how full the bucket is before you throw the water.** A fuller bucket throws more water.
3. **Afterload = throwing water uphill vs downhill.** High BP is uphill — harder work.
4. **Contractility = the strength of your arm throwing the water.** Same bucket, stronger arm = farther throw.
5. **Frank–Starling = rubber band.** Stretch more → snap harder (within limits); overstretch an old band → weak snap (failing heart).
6. **BP = CO × TPR is like water pressure = pump flow × how narrow the pipe nozzle is.** Narrow the nozzle (vasoconstriction) → pressure rises even with the same pump.
7. **Action potential = a wave in a stadium.** One section stands (depolarizes), then sits (repolarizes); the wave travels in order.
8. **SA node = the orchestra conductor.** Every musician (heart cell) can play, but all follow the conductor's beat.
9. **AV node = a speed-breaker (speed bump).** It deliberately slows the impulse so atria finish their work first.
10. **Purkinje fibres = express highway.** Fast lanes delivering the signal to every corner of the ventricles simultaneously.
11. **Refractory period = a camera flash recharging.** After one flash, you must wait before it can flash again — prevents chaotic rapid firing.
12. **Plateau phase = holding your breath.** The long flat phase keeps the muscle contracted long enough to actually pump blood out.

1.13 Pharmacy Relevance

- Every cardiovascular drug you will dispense acts on this chapter's concepts: diuretics and nitrates ↓ preload; ACE inhibitors/ARBs/CCBs ↓ afterload; digoxin ↑ contractility; beta blockers ↓ heart rate and contractility; antiarrhythmics modify phases/refractory periods.
- When counselling, translate: "this tablet reduces the load on your heart's pump" (afterload reducer) or "this helps your heart fill and pump more comfortably" (preload reducer).
- Digoxin toxicity risk rises when K^+ is low — the same Na^+/K^+ pump and ion gradients from this chapter explain why (Chapter 2).
- QT-prolonging drugs (some antiarrhythmics, antibiotics, antipsychotics) lengthen phase 3 — pharmacists must watch for dangerous arrhythmia (torsades de pointes) risk.
- Understanding the AV node as slow-response tissue explains why verapamil and beta blockers slow AV conduction — used in atrial fibrillation rate control and a counselling point for dizziness/fainting.

1.14 India Context

- Cardiovascular disease is among the leading causes of death in India, and hypertension affects roughly one in four adults — so the hemodynamic concepts in this chapter (BP = CO × TPR) are the daily reality of Indian pharmacy practice.
- Rheumatic heart disease (from untreated streptococcal throat infection in childhood) remains relevant in India; it damages heart valves, disturbs hemodynamics (valve stenosis raises afterload-type load; regurgitation raises preload-type load) and commonly causes atrial fibrillation — linking this chapter to digoxin and anticoagulant use in later chapters.
- The National List of Essential Medicines (NLEM) of India includes the basic cardiovascular drugs built on these concepts (furosemide, enalapril, atenolol, amlodipine, aspirin), and Jan Aushadhi (PMBJP) Kendras supply them as low-cost generics — a pharmacist should know which hemodynamic target each essential drug acts on.
- Simple BP and pulse measurement — taught in Indian pharmacy practicals — is applied hemodynamics: systolic/diastolic pressure, heart rate, and pulse rhythm directly reflect CO, TPR, SA node activity and conduction.

1.15 Key Points

1. CO = HR × SV; BP = CO × TPR — the two master formulas of cardiovascular pharmacology.
2. Stroke volume is decided by preload (filling), afterload (resistance) and contractility (muscle strength).
3. Frank–Starling law: more stretch (within limits) → stronger contraction → more output.
4. Cardiac action potential phases: 0 (Na^+ in), 1 (K^+ out notch), 2 (Ca^{2+} in plateau), 3 (K^+ out), 4 (rest/pacemaker drift).
5. Fast response (muscle/Purkinje, Na^+-driven) vs slow response (SA/AV node, Ca^{2+}-driven) — decides drug targets.
6. SA node pacemaker: funny current (If) drives phase-4 drift; sympathetic speeds it, vagal slows it.
7. Conduction order: SA node → atria → AV node (delay) → His → bundle branches → Purkinje → ventricles.
8. Long plateau → long refractory period → prevents tetanus and chaotic re-excitation; antiarrhythmics prolong it.
9. ECG: P = atrial depolarization, QRS = ventricular depolarization, T = ventricular repolarization; PR interval = AV nodal delay.
10. Excitation–contraction coupling: Ca^{2+} entry triggers massive Ca^{2+} release → contraction; more intracellular Ca^{2+} = stronger beat.

1.16 Common Confusions (with Corrections)

1. **Confusion:** Preload and afterload are the same thing. **Correction:** Preload is the filling load BEFORE contraction (venous return/stretch); afterload is the ejection load DURING contraction (arterial resistance). One is "how full", the other is "how hard to push".
2. **Confusion:** The T wave is atrial repolarization. **Correction:** T wave = ventricular repolarization. Atrial repolarization happens during the QRS and is hidden.
3. **Confusion:** The SA node and AV node have fast Na^+-driven upstrokes like muscle. **Correction:** They are slow-response (Ca^{2+}-driven) with gentle upstrokes — that is why verapamil affects nodes, not ventricles.
4. **Confusion:** More heart rate always means more cardiac output. **Correction:** CO = HR × SV; at very high rates, filling time shortens so SV falls — CO can actually drop (as in fast arrhythmias).
5. **Confusion:** The plateau phase is "rest". **Correction:** The plateau (phase 2) is active — Ca^{2+} entering keeps the muscle contracted; rest is phase 4.
6. **Confusion:** Ejection fraction and stroke volume are identical. **Correction:** SV is a volume (mL/beat); EF is the percentage of the filled ventricle ejected per beat.

1.17 Common Mistakes (with Corrections)

1. **Mistake:** Writing "BP = HR × SV". **Correction:** That is cardiac output. BP = CO × TPR.
2. **Mistake:** Labelling phase 0 as potassium influx. **Correction:** Phase 0 = Na^+ INFLUX (fast cells); K^+ moves OUT in phases 1 and 3.
3. **Mistake:** Saying the AV node speeds up conduction. **Correction:** The AV node DELAYS conduction (~0.1 s) — essential for sequential atrial-then-ventricular contraction.
4. **Mistake:** Drawing the QRS as atrial activity. **Correction:** QRS = ventricular depolarization; P = atrial.
5. **Mistake:** Stating refractory period lets the heart beat faster. **Correction:** It LIMITS rate and prevents re-excitation during contraction — a protective lock.

1.18 Mnemonics

1. **Master formulas:** "**C**ardiac **O**utput = **H**eart **R**ate × **S**troke **V**olume" → "**C**ows **H**ate **S**nowy **V**alleys" (CO = HR × SV). "**B**lood **P**ressure = **C**ardiac **O**utput × **T**otal **P**eripheral **R**esistance" → "**B**ig **P**umps **C**reate **T**remendous **P**ressure **R**ise".
2. **SV determinants:** "**P**reload, **A**fterload, **C**ontractility" → "**P**ump **A**djusts **C**arefully".
3. **AP phases ions:** "**0: Na**$^+$ IN (spark) → **1:** K^+ OUT (notch) → **2: Ca**$^{2+}$ IN (plateau) → **3:** K^+ OUT (down) → **4:** rest" → "**N**aughty **K**ids **C**limb **K**arefully, **R**esting" (Na, K, Ca, K, Rest).
4. **Fast vs slow:** "**F**ast = **F**our-letter **Na**$^+$ (muscle); **S**low = **S**A/**S**i… " → "**F**ast cells use **Na**$^+$; **S**low nodes use **Ca**$^{2+}$ — **F**-**N**, **S**-**C**".
5. **Conduction order:** "**S**A → **A**tria → **A**V (delay) → **H**is → **B**ranches → **P**urkinje" → "**S**end **A** **A**pple **H**ome **B**efore **P**arty".
6. **ECG waves:** "**P**umps **A**tria, **QRS** **V**entricles **S**queeze, **T**hey **R**est" (P = atrial depolarization, QRS = ventricular depolarization, T = ventricular repolarization).

1.19 Exam Summary

Hemodynamics studies blood flow physics: CO = HR × SV (≈5 L/min at rest); SV depends on preload (filling/stretch), afterload (arterial resistance) and contractility (muscle strength, Ca^{2+}-dependent); Frank–Starling law = more stretch → stronger beat (within limits); BP = CO × TPR, so BP drugs act by reducing CO (diuretics, beta blockers) or TPR (ACE-I, ARBs, CCBs). Cardiac action potential: phase 0 Na^+ influx (fast cells), phase 1 K^+ notch, phase 2 Ca^{2+} plateau (contraction time), phase 3 K^+ efflux, phase 4 rest. Fast-response (muscle/Purkinje, Na^+) vs slow-response (SA/AV node, Ca^{2+}). SA node pacemaker: funny current (If) drives phase-4 drift; sympathetic ↑ rate, vagal ↓ rate. Conduction: SA → atria → AV node (delay) → His → branches → Purkinje → ventricles. Long plateau gives long refractory period (ARP + RRP), preventing tetanus; antiarrhythmics prolong it. ECG: P (atrial depolarization), QRS (ventricular depolarization), T (ventricular repolarization); PR interval reflects AV nodal delay.

1.20 One-Minute Revision

- CO = HR × SV; BP = CO × TPR.
- SV = preload + afterload + contractility. Frank–Starling: stretch → stronger beat.
- AP phases: 0 Na^+ in → 1 K^+ notch → 2 Ca^{2+} plateau → 3 K^+ out → 4 rest.
- Fast (Na^+, muscle) vs slow (Ca^{2+}, SA/AV node).
- SA node: funny current → automatic phase-4 drift.
- Wiring: SA → AV (delay) → His → Purkinje → ventricles.
- ECG: P (atria), QRS (ventricles), T (ventricular reset).
- Long refractory period = safety lock against chaos.

1.21 Exam Questions

Short-answer questions:

1. Define cardiac output and give its formula with a solved example.
2. Define preload, afterload and contractility with one example each.
3. State the Frank–Starling law and give one clinical application.
4. Write the blood pressure formula and name two drug classes acting on each component.
5. List the ions moving in phases 0–4 of the fast-response cardiac action potential.
6. Differentiate fast-response and slow-response action potentials (any four points).
7. What is the funny current? Where is it found and what is its function?
8. Trace the normal cardiac conduction pathway in order.
9. Define absolute and relative refractory periods. Why is a long refractory period protective?
10. Name the ECG waves and state the electrical event each represents.

Long-answer questions:

1. Explain the determinants of cardiac output and blood pressure. Correlate each determinant with one class of cardiovascular drugs.
2. Describe the phases of the cardiac action potential in a ventricular muscle cell with ion movements, and differentiate it from the SA nodal action potential. Explain the significance of the plateau phase.
3. Describe the conduction system of the heart. Explain the physiological importance of the AV nodal delay and the refractory period.
4. Explain the Frank–Starling law at the muscle level and its role in matching ventricular output to venous return. What happens to this mechanism in heart failure?

MCQs (with answer key):

1. Cardiac output is calculated as:

a) HR + SV b) HR × SV c) BP × TPR d) SV ÷ HR

2. Normal resting cardiac output is approximately:

a) 0.5 L/min b) 5 L/min c) 15 L/min d) 50 L/min

3. Preload is best described as:

a) Arterial resistance to ejection b) Ventricular filling/stretch before contraction c) Muscle's own strength d) Heart rate

4. Frank–Starling law states that increased:

a) Afterload increases heart rate b) Preload (within limits) increases force of contraction c) Contractility decreases stroke volume d) TPR decreases cardiac output

5. Blood pressure = :

a) HR × SV b) CO × TPR c) SV × EF d) HR × TPR

6. Phase 0 of the fast-response action potential is due to:

a) K^+ efflux b) Na^+ influx c) Ca^{2+} influx d) Cl^- influx

7. The plateau (phase 2) is mainly due to:

a) Na^+ influx only b) Ca^{2+} influx balanced by K^+ efflux c) Funny current d) Na^+/K^+ pump

8. Slow-response action potentials are found in:

a) Ventricular muscle b) Purkinje fibres c) SA and AV nodes d) Atrial muscle

9. The funny current (If) is important for:

a) Ventricular contraction b) SA node pacemaker phase-4 drift c) AV nodal delay d) Repolarization

10. The AV nodal delay allows:

a) Ventricles to contract first b) Atria to finish emptying before ventricles contract c) Faster heart rate d) Stronger contraction

11. The QRS complex represents:

a) Atrial depolarization b) Ventricular depolarization c) Ventricular repolarization d) SA node firing

12. The T wave represents:

a) Atrial contraction b) Ventricular depolarization c) Ventricular repolarization d) AV conduction

Answers: 1-b, 2-b, 3-b, 4-b, 5-b, 6-b, 7-b, 8-c, 9-b, 10-b, 11-b, 12-c

Viva questions:

1. Why can't heart muscle develop tetanus like skeletal muscle?
2. A patient's heart rate doubles but cardiac output falls — explain using CO = HR × SV.
3. Why do calcium channel blockers slow the AV node but not ventricular muscle much?
4. What would happen if there were no AV nodal delay?
5. Which phase of the action potential is the target of Class III antiarrhythmics, and why?

Application-based questions:

1. A patient with severe blood loss has low BP. Using BP = CO × TPR, explain which component has fallen and name two drug/fluid measures that correct it.
2. A hypertensive patient's BP is 170/100. Explain in hemodynamic terms (CO vs TPR) two different drug strategies to lower it.
3. During a fever of 102°F, a patient's heart rate rises to 120/min. Explain the pacemaker mechanism behind this and predict the effect on cardiac output.

1.22 References

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Chapter 2: Drugs for Congestive Cardiac Failure + Anti-anginal & Newer Anti-ischemic Drugs

(Syllabus topics b and d)

2.1 Learning Objectives

By the end of this chapter, you will be able to:

1. Define congestive cardiac failure (heart failure) and explain why compensatory mechanisms become harmful.
2. Classify drugs used in heart failure and state the role of each class.
3. Explain the mechanism of action, uses and adverse effects of furosemide and spironolactone in heart failure.
4. Explain how ACE inhibitors (enalapril) and ARBs (losartan) help the failing heart, including their adverse effects (cough, hyperkalemia, angioedema).
5. Explain the paradox of beta blockers (carvedilol, metoprolol) in heart failure.
6. Describe digoxin's mechanism (Na^+/K^+ ATPase inhibition → increased intracellular Ca^{2+}), uses and toxicity with management.
7. State the role of hydralazine + isosorbide dinitrate combination in heart failure.
8. Explain the newer agents: sacubitril/valsartan (ARNI) and dapagliflozin (SGLT2 inhibitor) at concept level.
9. Define angina pectoris, list its types, and explain the oxygen supply–demand mismatch.
10. Explain the mechanism, uses and adverse effects of nitrates (nitroglycerin, ISDN/ISMN), including nitrate tolerance and its prevention.
11. Explain the role of beta blockers and calcium channel blockers (amlodipine, verapamil, diltiazem) in angina.
12. Describe newer anti-ischemic drugs (ranolazine, ivabradine, nicorandil, trimetazidine) at concept level.
13. Answer exam questions comparing drug classes with correct examples.

2.2 Definitions

Congestive cardiac failure (CCF / heart failure) — a condition in which the heart cannot pump enough blood to meet the body's needs, so blood "backs up" (congests) in the lungs and body. Simple meaning: a weak pump that leaves fluid piled up behind it — breathlessness (fluid in lungs), swollen feet (fluid in legs), tiredness (less blood to muscles).

Ejection fraction (EF) — percentage of ventricular blood pumped out per beat (recap from Chapter 1). Heart failure with reduced EF (HFrEF, roughly below 40%) = weak squeeze; heart failure with preserved EF (HFpEF) = stiff heart that cannot fill properly.

Preload/afterload (recap) — filling load and ejection load; heart failure drugs mainly reduce one or both ("unloading" the heart).

Neurohumoral activation — in heart failure, the body senses low output and switches on the sympathetic nervous system and the RAAS (renin–angiotensin–aldosterone system) to compensate. Short-term helpful, long-term harmful (remodelling, fluid retention).

Cardiac remodelling — harmful long-term change in heart size, shape and muscle (enlargement, fibrosis) driven by chronic neurohumoral activation. Modern heart failure drugs aim to stop remodelling, not just relieve symptoms.

Cardiac glycoside — a drug (e.g., digoxin, from the foxglove plant *Digitalis*) that strengthens heart contraction by inhibiting the Na^+/K^+ ATPase pump.

Positive inotropic — strengthening the force of heart muscle contraction (digoxin is the classic example).

Angina pectoris — chest pain or pressure caused by the heart muscle not getting enough oxygen-rich blood, usually because narrowed coronary arteries cannot meet increased demand. Simple meaning: the heart's own blood supply falls short when it works hard — like an engine starved of fuel on a steep climb.

Myocardial oxygen supply–demand mismatch — angina occurs when oxygen demand (raised by heart rate, contractility, wall tension) exceeds oxygen supply (limited by narrowed coronary arteries).

Nitrate tolerance — loss of nitrate effect when nitrates are used continuously without a break; prevented by a daily nitrate-free interval.

Newer anti-ischemic drugs — drugs that relieve heart-muscle ischemia by novel mechanisms (not the classic nitrate/beta-blocker/CCB routes): ranolazine, ivabradine, nicorandil, trimetazidine.

2.3 Terminology

- **Orthopnoea** — breathlessness when lying flat (fluid shifts to lungs); relieved by sitting up.
- **Paroxysmal nocturnal dyspnoea (PND)** — sudden breathlessness waking the patient at night.
- **Oedema** — swelling from fluid collection in tissues (ankle oedema in right-heart failure; lung congestion in left-heart failure).
- **RAAS** — renin–angiotensin–aldosterone system: kidney–hormone chain that raises BP and retains salt/water; overactive in heart failure.
- **Natriuretic peptides (ANP, BNP)** — helpful heart hormones that promote salt/water loss and vessel relaxation; broken down by the enzyme neprilysin.
- **Neprilysin** — enzyme that destroys natriuretic peptides; blocked by sacubitril.
- **ARNI** — angiotensin receptor–neprilysin inhibitor (sacubitril + valsartan): blocks harmful angiotensin while preserving helpful natriuretic peptides.
- **SGLT2 inhibitor** — originally a diabetes drug (blocks glucose reabsorption in kidney); now proven to help heart failure even without diabetes.
- **Digitalis toxicity** — poisoning by digoxin: nausea, visual colour changes (yellow-green vision), confusion, and dangerous arrhythmias.
- **Xanthopsia** — yellow vision, a classic digoxin toxicity symptom.
- **Stable angina** — predictable chest pain on exertion, relieved by rest/nitrate.
- **Unstable angina** — new, worsening or rest pain; a warning of impending heart attack.
- **Variant (Prinzmetal) angina** — pain at rest due to coronary artery spasm, not exertion.
- **Venodilator** — drug dilating veins mainly (reduces preload); nitrates are mainly venodilators.
- **Coronary steal** — a theoretical risk where a drug dilates healthy vessels and "steals" blood from diseased areas (a reason some vasodilators are avoided in angina).
- **Nitrate-free interval** — a daily 8–12 hour period without nitrate to prevent tolerance.

2.4 Explanation (Main Teaching)

PART A — HEART FAILURE

What is heart failure? The tired pump story. Imagine a water pump whose motor is weakening. At first it still moves water, but less per minute. The body's sensors notice "less flow" and panic: they switch on emergency systems — the sympathetic nervous system (adrenaline: beat faster, squeeze harder, tighten vessels) and the RAAS (retain salt and water to fill the pump more, constrict vessels to keep pressure up). For days this helps. But the emergency never switches off. Months of adrenaline exhaust and poison the muscle; months of salt/water retention overload the pump with fluid; months of vessel tightening raise the load. The heart enlarges, stiffens and scars — this is **remodelling**. So heart failure is a vicious cycle: weak pump → harmful compensation → weaker pump. Modern treatment breaks the cycle at its roots (block RAAS, block sympathetic overdrive, remove excess fluid), not just whip the tired horse harder.

Goals of heart failure drug therapy: (1) relieve congestion symptoms (breathlessness, oedema) — diuretics, (2) improve pumping efficiency by unloading (ACE-I/ARB/ARNI, hydralazine–nitrate), (3) block harmful neurohumoral activation to stop remodelling and prolong life (ACE-I/ARNI, beta blockers, spironolactone, SGLT2 inhibitors), (4) strengthen contraction when needed (digoxin), (5) control triggers like atrial fibrillation and hypertension.

Class 1 — Diuretics: "remove the extra water." A failing heart cannot handle normal blood volume — fluid backs into lungs (breathlessness) and legs (swelling). Diuretics make the kidneys excrete extra salt and water, reducing blood volume → reduced preload → less congestion → easier breathing.

- **Furosemide (Lasix)** — loop diuretic; blocks the Na^+-K^+-$2Cl^-$ transporter in the thick ascending loop of Henle → massive salt and water loss. Fast, powerful; given orally daily or IV in acute breathlessness ("it works within minutes IV, the patient can breathe easier the same hour"). Adverse effects: low potassium (hypokalemia → digoxin toxicity risk, cramps, arrhythmia), low sodium, dehydration, low BP, hearing effects at high IV doses (ototoxicity), raised uric acid (gout).
- **Spironolactone (Aldactone)** — potassium-sparing diuretic; blocks aldosterone receptors in the kidney's collecting duct → mild water loss WITHOUT potassium loss (it "spares" K^+). Two roles in heart failure: (a) counteracts furosemide-induced potassium loss, and (b) at low doses it blocks aldosterone's harmful remodelling/fibrosis effects on the heart — this mortality benefit is independent of its weak diuretic action. Adverse effects: high potassium (hyperkalemia — dangerous with ACE-I), gynaecomastia/breast tenderness in men (it also weakly blocks male hormone receptors), menstrual irregularities.

Class 2 — ACE inhibitors: "open the pipes and block the harmful hormone." Example: **enalapril (Enam)**. ACE (angiotensin-converting enzyme) does two things: converts angiotensin I → angiotensin II (a powerful vasoconstrictor that also triggers aldosterone → salt/water retention and drives remodelling), and destroys bradykinin (a natural vasodilator). Enalapril blocks ACE → LESS angiotensin II (vessels relax → afterload falls; less aldosterone → less salt/water retention → preload falls; less remodelling) + MORE bradykinin (extra vasodilation). Net: the failing heart pushes against lower resistance with less fluid overload, and remodelling slows — symptoms improve and life is prolonged. Adverse effects: dry persistent cough (bradykinin accumulation — the commonest reason to switch to an ARB), high potassium, low BP (first-dose hypotension), angioedema (rare swelling of lips/tongue — bradykinin-related, can be dangerous), worsening kidney function in susceptible patients, and foetal harm in pregnancy (absolutely contraindicated — all RAAS blockers).

Class 3 — ARBs: "the cough-free alternative." Example: **losartan (Losar)**. Instead of blocking ACE, ARBs block the angiotensin II receptor (AT1) directly. Same benefits as ACE-I (less vasoconstriction, less aldosterone, less remodelling) but NO bradykinin rise → NO cough, much less angioedema. Used when ACE-I cough is intolerable, or combined in some regimens. Adverse effects: hyperkalemia, hypotension, renal effects, pregnancy contraindication — same as ACE-I except cough.

Class 4 — Beta blockers: "the paradox — slowing a weak heart helps it." Examples: **carvedilol (Carloc)**, **metoprolol (Met XL / Betaloc)**. This confuses students: why give a drug that weakens contraction to a weak heart? Because chronic adrenaline overdrive is poisoning the heart — it raises oxygen demand, triggers dangerous rhythms and drives remodelling. Carefully started at LOW dose and slowly increased, beta blockers shield the heart from adrenaline, lower heart rate (more filling time, less oxygen demand), reduce arrhythmia risk and reverse remodelling — prolonging life. Rules: start low, go slow; never stop suddenly (rebound); avoid in acute decompensated (severely breathless, fluid-overloaded) failure — stabilize first. Carvedilol additionally blocks alpha receptors (extra vasodilation). Adverse effects: bradycardia, hypotension, fatigue, worsening breathlessness initially, masks low blood sugar signs in diabetics, bronchospasm (caution in asthma — use cardioselective metoprolol preferentially).

Class 5 — Cardiac glycosides: digoxin (Lanoxin) — "the old strengthener." Digoxin comes from the foxglove plant. Mechanism in three steps: (1) digoxin blocks the Na^+/K^+ ATPase pump on heart cell membranes → (2) sodium builds up inside the cell → the Na^+/Ca^{2+} exchanger (which normally throws Ca^{2+} out in exchange for Na^+ in) slows down → (3) calcium builds up inside → stronger contraction (positive inotropic). Bonus effects: it increases vagal (parasympathetic) tone → slows SA node and AV node — useful when heart failure coexists with atrial fibrillation (controls the fast ventricular rate). Uses: HFrEF with symptoms despite other drugs, especially with atrial fibrillation; narrow role today (symptom/rate control, not first-line for survival). Pharmacokinetic cautions: narrow therapeutic index (small gap between effective and toxic dose), excreted by kidneys (dose reduce in elderly/renal impairment), long half-life.

Digoxin toxicity — the most exam-asked topic in this chapter. Early signs: loss of appetite, nausea, vomiting, abdominal pain. Then: visual disturbances — blurred vision, yellow-green vision (xanthopsia), halos. Then: confusion, and CARDIAC — almost any arrhythmia, classically AV block, ventricular bigeminy, bidirectional VT. Factors increasing toxicity: LOW potassium (hypokalemia — K^+ competes with digoxin at the pump; low K^+ = more digoxin binding), low magnesium, high calcium, old age, kidney failure, hypothyroidism, and interactions (diuretics causing K^+ loss; verapamil/amiodarone raising digoxin levels). Management: stop digoxin; correct K^+ (give potassium, but carefully — if hyperkalemia with severe toxicity, different approach); manage arrhythmias; digoxin-specific antibody fragments (Fab) for life-threatening toxicity; dialysis does NOT remove digoxin (large volume of distribution). Prevention is the pharmacist's job: monitor K^+ in patients on furosemide + digoxin.

Class 6 — Vasodilators: hydralazine + isosorbide dinitrate. Hydralazine dilates arteries (↓ afterload); isosorbide dinitrate dilates veins (↓ preload). Together they unload both sides of the failing heart. Especially useful when ACE-I/ARBs cannot be used (e.g., severe renal impairment, hyperkalemia, angioedema history) — and this combination has proven benefit in patients of African ancestry with HFrEF. Adverse: hydralazine — headache, flushing, lupus-like syndrome on long use; ISDN — headache, hypotension, tolerance (see nitrates below).

Class 7 — Newer agents (concept level).

- **ARNI — sacubitril + valsartan (Entresto / Vymada):** Two-in-one tablet. Valsartan = ARB (blocks harmful angiotensin). Sacubitril = neprilysin inhibitor → neprilysin normally destroys helpful natriuretic peptides (ANP, BNP); blocking it raises these peptides → more salt/water excretion, vessel relaxation, less remodelling. So ARNI simultaneously blocks the bad hormone and boosts the good hormones. Used in HFrEF instead of ACE-I/ARB. Caution: never combine with an ACE-I (angioedema risk); needs a washout gap when switching.
- **SGLT2 inhibitors — dapagliflozin (Forxiga / Oxra):** Diabetes drugs (block glucose reabsorption in kidney → glucose lost in urine) that surprisingly reduce heart failure hospitalizations and death EVEN in non-diabetics. Concept: mild diuretic-like effect, reduced cardiac workload, improved heart energy use — now a pillar of HFrEF therapy alongside ACE-I/ARNI, beta blocker and spironolactone ("the fantastic four").

PART B — ANGINA & ANTI-ISCHEMIC DRUGS

Angina: supply vs demand. The heart muscle feeds itself through coronary arteries. Angina = chest pain when oxygen DEMAND exceeds SUPPLY. Demand rises with: heart rate, contractility, and wall tension (preload/afterload). Supply falls with: narrowed/ spasming coronary arteries. Three types: **stable** (predictable, on exertion, relieved by rest) — fixed narrowing; **unstable** (new/worsening/at rest — pre-heart-attack warning); **variant/Prinzmetal** (at rest, from coronary SPASM, often at night). All anti-anginal drugs fix the mismatch: either ↓ demand or ↑ supply (or both).

Nitrates — nitroglycerin (Nitrocontin / Angised), isosorbide dinitrate (Sorbitrate), isosorbide mononitrate. Mechanism: nitrates release nitric oxide (NO) in vessel walls → NO activates guanylate cyclase → ↑ cGMP → smooth muscle relaxation. Main effect: VENODILATION (veins relax and hold more blood → less blood returns to heart → ↓ preload → ↓ wall tension → ↓ oxygen demand). Also dilate coronary arteries (↑ supply, relieves spasm — key in variant angina) and at high doses arteries. Uses: acute attack — sublingual nitroglycerin (acts in 1–3 minutes; patient sits, one dose, repeat per advice); prevention — oral/isosorbide or patches. Adverse effects: throbbing headache (vessel dilation in head — commonest), flushing, hypotension, dizziness/fainting (especially standing — warn patients to sit), reflex tachycardia. **Nitrate tolerance:** continuous exposure depletes sulfhydryl groups needed to release NO (plus neurohumoral counter-regulation) → effect fades. Prevention: a daily **nitrate-free interval** (typically overnight, e.g., remove patch at bedtime). Dangerous interaction: NEVER combine nitrates with sildenafil-type drugs (both raise cGMP → severe hypotension) — a favourite exam trap and counselling point.

Beta blockers in angina: ↓ heart rate + ↓ contractility → ↓ oxygen demand. Also lengthen diastole (coronaries fill during diastole) → ↑ supply. First-line in stable angina, especially after heart attack. (Details as in heart failure section; avoid abrupt withdrawal — rebound angina.)

Calcium channel blockers in angina: Block L-type Ca^{2+} channels → vessel relaxation + (non-DHPs) reduced heart work.

- **Amlodipine (Amlopress)** — dihydropyridine (DHP): mainly VESSEL dilator (↓ afterload, coronary dilation); little heart-rate effect. Good in stable + variant angina (relieves spasm), and hypertension. Adverse: ankle swelling (oedema), flushing, headache, gum swelling.
- **Verapamil (Calaptin)** and **diltiazem (Dilzem / Angizem)** — non-DHPs: dilate vessels AND slow SA/AV nodes + reduce contractility (↓ demand three ways). Good when beta blockers unsuitable; verapamil/diltiazem also used in arrhythmias (Chapter 3). Adverse: bradycardia, AV block, constipation (verapamil classic), oedema; never combine verapamil with beta blockers casually (severe bradycardia risk).

Newer anti-ischemic drugs (concept level):

- **Ranolazine (Ranozex):** blocks the LATE sodium current in heart cells → less Na^+ overload → less Ca^{2+} overload → heart muscle relaxes better in diastole → less oxygen demand, without lowering heart rate or BP much. Add-on in chronic stable angina.
- **Ivabradine (Ivabrad):** blocks the funny current (If) in the SA node (Chapter 1!) → slows heart rate WITHOUT weakening contraction or lowering BP. For stable angina (and HFrEF) when heart rate stays high despite beta blockers or when beta blockers are unsuitable.
- **Nicorandil (Nikoran):** dual action — nitrate-like (NO donor → vasodilation) + potassium-channel opener (arterial dilation). Used in stable angina; also has some heart-protective (preconditioning-like) concept.
- **Trimetazidine (Flavedon):** metabolic modulator — shifts heart energy use from fatty-acid burning toward glucose burning (more oxygen-efficient) → same work with less oxygen. Add-on in stable angina; no effect on heart rate/BP.

Key takeaway: Heart failure therapy = unload the pump (diuretics ↓ preload; ACE-I/ARB ↓ afterload) + block the harmful compensation (ACE-I/ARB/ARNI, beta blockers, spironolactone, SGLT2i) + strengthen when needed (digoxin). Angina therapy = fix supply–demand mismatch: nitrates (↓ preload, dilate coronaries), beta blockers (↓ demand), CCBs (dilate + ↓ demand), plus newer agents with novel mechanisms.

2.5 Classifications

Classification of drugs used in congestive cardiac failure:

1. **Diuretics:** loop — furosemide; K^+-sparing/aldosterone antagonist — spironolactone.
2. **RAAS blockers:** ACE inhibitors — enalapril; ARBs — losartan; ARNI — sacubitril + valsartan.
3. **Sympathetic blockers:** beta blockers — carvedilol, metoprolol.
4. **Positive inotropes:** cardiac glycosides — digoxin.
5. **Vasodilators:** hydralazine + isosorbide dinitrate combination.
6. **Newer/metabolic:** SGLT2 inhibitors — dapagliflozin.

Classification by hemodynamic action in heart failure:

- ↓ Preload: diuretics (furosemide), nitrates/venodilators (ISDN), ACE-I/ARB (mild).
- ↓ Afterload: ACE-I (enalapril), ARB (losartan), ARNI, hydralazine, CCBs.
- ↑ Contractility: digoxin (dobutamine/dopamine IV in acute — Chapter 4 shock).
- Block neurohumoral harm: ACE-I, ARB, ARNI, beta blockers, spironolactone, SGLT2 inhibitors.

Classification of anti-anginal drugs:

1. **Nitrates (NO donors):** nitroglycerin, isosorbide dinitrate, isosorbide mononitrate.
2. **Beta blockers:** metoprolol, atenolol, propranolol.
3. **Calcium channel blockers:** DHP — amlodipine, nifedipine; non-DHP — verapamil, diltiazem.
4. **Newer anti-ischemic:** ranolazine (late Na^+ blocker), ivabradine (If blocker), nicorandil (nitrate + K^+-channel opener), trimetazidine (metabolic modulator).

Classification of angina:

1. Stable (exertional) — fixed coronary narrowing; demand-driven.
2. Unstable — plaque rupture/thrombus; rest or worsening pain; medical emergency.
3. Variant (Prinzmetal) — coronary spasm at rest; nitrates/CCBs best.

2.6 Mechanisms

RAAS in heart failure (the chain to block): Low cardiac output → kidneys release renin → renin converts angiotensinogen → angiotensin I → ACE converts it → angiotensin II → (a) constricts vessels (↑ afterload), (b) releases aldosterone from adrenals → kidneys retain Na^+/water (↑ preload) and lose K^+, (c) directly drives cardiac fibrosis/hypertrophy (remodelling), (d) stimulates sympathetic activity. ACE-I breaks the chain at ACE; ARBs block the AT1 receptor; ARNI adds neprilysin blockade to preserve natriuretic peptides.

Digoxin mechanism (3 steps): (1) inhibits membrane Na^+/K^+ ATPase → (2) intracellular Na^+ rises → Na^+/Ca^{2+} exchanger slows (less Ca^{2+} thrown out) → (3) intracellular Ca^{2+} rises → stronger actin–myosin interaction → positive inotropy. Vagal effect: ↑ parasympathetic tone → ↓ SA node rate, ↓ AV conduction (useful in atrial fibrillation).

Nitrate mechanism: organic nitrate → releases NO in vascular smooth muscle → activates guanylate cyclase → ↑ cGMP → ↓ intracellular Ca^{2+} → relaxation. Veins >> arteries at low doses → venous pooling → ↓ preload → ↓ ventricular wall tension → ↓ myocardial O_2 demand; coronary dilation → ↑ O_2 supply.

Nitrate tolerance mechanism: continuous nitrate → depletion of sulfhydryl (–SH) groups needed to generate NO + activation of counter-regulatory vasoconstrictor systems → diminished response. Solved by intermittent dosing with a nitrate-free interval.

Beta blocker mechanism (angina + HF): block β1 receptors → ↓ heart rate, ↓ contractility, ↓ AV conduction → ↓ myocardial O_2 demand; longer diastole → better coronary filling → ↑ supply. In HF, chronic blockade reverses adrenaline-driven remodelling.

CCB mechanism: block L-type Ca^{2+} channels → less Ca^{2+} entry → vascular smooth muscle relaxes (all CCBs → ↓ afterload, coronary dilation); in SA/AV node and myocardium (non-DHPs verapamil/diltiazem only) → ↓ heart rate, ↓ conduction, ↓ contractility.

Ranolazine: inhibits late inward Na^+ current (INaL) → ↓ intracellular Na^+ → ↓ Ca^{2+} overload via Na^+/Ca^{2+} exchanger → improved diastolic relaxation → ↓ O_2 demand; minimal HR/BP change.

Ivabradine: selectively blocks If (funny current) in SA node → flattens phase-4 slope → slower heart rate; no effect on contractility or BP.

Nicorandil: NO-donor moiety (venodilation like nitrates) + opens ATP-sensitive K^+ channels (arterial dilation) → ↓ preload and ↓ afterload.

Trimetazidine: inhibits fatty-acid oxidation enzymes → shifts myocardial metabolism toward glucose oxidation → more ATP per oxygen molecule → ischemia tolerated better.

2.7 Diagrams (Describe Textually So They Can Be Drawn)

Diagram 1 — The heart failure vicious cycle. Draw a circle of boxes with arrows: "Weak pump (↓CO)" → "Body senses low flow" → "Sympathetic ↑ + RAAS ↑" → "Vessel tightening (↑afterload) + salt/water retention (↑preload) + direct heart damage" → "Remodelling: bigger, stiffer, scarred heart" → back to "Weaker pump". Mark drug break-points on arrows: ACE-I/ARB/ARNI on RAAS arrow; beta blockers on sympathetic arrow; diuretics on fluid-retention arrow; digoxin boosting the pump box.

Diagram 2 — RAAS cascade with drug block points. Vertical chain: "Renin → Angiotensin I → [ACE] → Angiotensin II → AT1 receptor → vasoconstriction + aldosterone → Na^+/water retention". Mark: "enalapril blocks ACE here ×"; "losartan blocks AT1 receptor here ×"; "spironolactone blocks aldosterone receptor here ×"; side branch: "neprilysin destroys natriuretic peptides — sacubitril blocks neprilysin × (peptides preserved)".

Diagram 3 — Digoxin mechanism (3 steps). Three panels: (1) cell membrane with Na^+/K^+ pump crossed out "digoxin blocks pump"; (2) "Na^+ builds up inside" with Na^+/Ca^{2+} exchanger slowed; (3) "Ca^{2+} builds up inside → stronger squeeze". Add note: "Low K^+ outside → digoxin binds pump MORE → toxicity".

Diagram 4 — Angina supply–demand seesaw. Draw a seesaw: left side "OXYGEN DEMAND" with weights labelled "heart rate, contractility, wall tension (preload/afterload)"; right side "OXYGEN SUPPLY" with "coronary blood flow" weight shortened by a clamp labelled "narrowed artery". Show drug actions as hands: beta blockers removing demand weights; nitrates/CCBs lifting the supply side.

Diagram 5 — Nitrate action on vessels. Draw a vein (wide, thin wall) and an artery: nitrate/NO arrows → vein dilates markedly ("blood pools here → ↓ preload"), coronary artery dilates ("spasm relieved → ↑ supply"), small arterial effect at high dose.

Diagram 6 — Nitrate tolerance and free interval. Timeline bar: "8 am patch ON → effect strong" … "evening effect fading (tolerance)" … "10 pm patch OFF → nitrate-free interval overnight" … "8 am patch ON → effect restored". Caption: "A daily break restores sensitivity."

2.8 Flowcharts (Step-by-Step Text Flowcharts)

> **Flowchart 1 — Heart failure drug strategy:**

```
SYMPTOM RELIEF (congestion: breathlessness, oedema)
        → Diuretics: furosemide (± spironolactone for K⁺)
DISEASE-MODIFYING (block harmful compensation, prolong life)
        → ACE-I (enalapril) or ARB (losartan) or ARNI (sacubitril/valsartan)
        → Beta blocker (carvedilol / metoprolol): start low, go slow
        → Spironolactone (low dose): blocks aldosterone remodelling
        → SGLT2 inhibitor (dapagliflozin): even without diabetes
STRENGTHEN + RATE CONTROL (selected patients)
        → Digoxin: HFrEF with AF or persistent symptoms
        → Hydralazine + ISDN: if ACE-I/ARB unsuitable
```

Flowchart 2 — Digoxin: from pump block to stronger beat:

```
Digoxin binds Na⁺/K⁺ ATPase → pump inhibited
        ↓
Na⁺ accumulates inside cell
        ↓
Na⁺/Ca²⁺ exchanger slows (less Ca²⁺ expelled)
        ↓
Intracellular Ca²⁺ rises
        ↓
Stronger contraction (positive inotropic)
PLUS: ↑ vagal tone → slower SA/AV node (rate control in AF)
```

Flowchart 3 — Digoxin toxicity: risk → signs → action:

```
RISK FACTORS: old age, renal failure, low K⁺ (furosemide!), low Mg²⁺,
              interacting drugs (verapamil, amiodarone)
        ↓
EARLY SIGNS: anorexia → nausea/vomiting → visual changes (yellow-green, halos)
        ↓
DANGEROUS: confusion + any arrhythmia (AV block, ventricular rhythms)
        ↓
ACTION: stop digoxin → correct K⁺/Mg²⁺ → treat arrhythmia →
        antibody fragments (Fab) if life-threatening; dialysis does NOT help
```

Flowchart 4 — Nitrate use and tolerance prevention:

```
ACUTE ATTACK: sublingual nitroglycerin → NO released → venodilation
        → ↓ preload → ↓ O₂ demand → pain relieved in minutes
        ↓
PREVENTION: oral ISDN/ISMN or patch
        ↓
TOLERANCE RISK with continuous use → give NITRATE-FREE INTERVAL daily
        (e.g., patch off overnight)
        ↓
NEVER combine with sildenafil-type drugs → severe hypotension
```

Flowchart 5 — Choosing anti-anginal by type:

```
STABLE angina (exertional, predictable)
   → Beta blocker first (↓ demand) ± nitrate for attacks; add CCB/ranolazine if needed
UNSTABLE angina (rest/worsening pain)
   → Emergency: aspirin + heparin + nitrates + beta blocker; hospital care
VARIANT angina (rest pain, spasm)
   → Nitrates or CCBs (relieve spasm); AVOID non-selective beta blockers alone
      (unopposed alpha → worse spasm)
```

2.9 Infographic Concept Box

💔 HEART FAILURE & ANGINA — ONE-PAGE MAP

HF = weak pump + fluid backup + harmful compensation. Break the cycle at 4 points:

Target	Drug	Brand hint
💧 Remove fluid (↓preload)	Furosemide	Lasix
🔓 Open pipes, block RAAS (↓afterload)	Enalapril / Losartan	Enam / Losar
🛡️ Block adrenaline harm	Carvedilol / Metoprolol	Carloc / Met XL
💪 Strengthen squeeze	Digoxin	Lanoxin
🆕 New pillars	Sacubitril/valsartan (ARNI), Dapagliflozin (SGLT2i)	Vymada / Forxiga
🧂 Spare K^+, block aldosterone	Spironolactone	Aldactone

DIGOXIN TOXICITY — "VIG-AD": **V**isual (yellow-green), **I**ntestinal (nausea), **G** — GI upset first, **A**rrhythmia (any!), **D**eath risk. Worse with LOW K^+. Fix: stop drug, correct K^+, Fab antibodies.

ANGINA = demand > supply. Fix it 3 classic ways + 4 new: **N**itrates (↓preload, open coronaries) • **B**eta blockers (↓demand) • **C**CBs (open vessels ± slow heart) → "**NBC** — the angina news channel"

🆕 **Ranolazine** (late-Na^+ block) • **Ivabradine** (funny-current block → ↓HR only) • **Nicorandil** (nitrate + K^+-channel) • **Trimetazidine** (better fuel use)

⚠️ **Nitrate rules:** tolerance needs a daily FREE interval; NEVER with sildenafil.

2.10 Tables

Table 2.1 — Heart failure drugs: mechanism, effects, uses, adverse effects

Drug (brand)	Mechanism	Key effects	Uses in HF	Adverse effects
Furosemide (Lasix)	Blocks Na^+-K^+-$2Cl^-$ in loop of Henle	Powerful salt/water loss → ↓preload	Congestion, acute breathlessness	Hypokalemia, dehydration, hypotension, ototoxicity (high IV dose), gout
Spironolactone (Aldactone)	Blocks aldosterone receptor	Mild diuresis, K^+ spared; blocks remodelling	Add-on in HFrEF; counters K^+ loss	Hyperkalemia, gynaecomastia, menstrual changes
Enalapril (Enam)	ACE inhibitor	↓angiotensin II + ↑bradykinin → ↓afterload & preload, ↓remodelling	HFrEF first-line, prolongs life	Dry cough, hyperkalemia, hypotension, angioedema, foetal harm
Losartan (Losar)	ARB (blocks AT1)	Like ACE-I without bradykinin rise	ACE-I cough/intolerance	Hyperkalemia, hypotension (no cough)
Carvedilol (Carloc)	β + α1 blocker	↓HR, ↓remodelling, mild vasodilation	HFrEF (start low, go slow)	Bradycardia, hypotension, fatigue, bronchospasm caution
Metoprolol (Met XL)	β1-selective blocker	↓HR, ↓O_2 demand, ↓remodelling	HFrEF, post-MI	Same as above; safer in asthma than non-selective
Digoxin (Lanoxin)	Na^+/K^+ ATPase inhibitor → ↑Ca^{2+}	↑contractility; vagal → slows AV node	HFrEF with AF / persistent symptoms	Anorexia, nausea, xanthopsia, arrhythmias (narrow index!)
Hydralazine + ISDN	Arterial + venous dilator	↓afterload + ↓preload	ACE-I unsuitable; proven in African-ancestry HFrEF	Headache, lupus-like syndrome (hydralazine), nitrate tolerance
Sacubitril/valsartan (Vymada)	ARNI: neprilysin inhibitor + ARB	↑natriuretic peptides + ↓angiotensin	HFrEF instead of ACE-I/ARB	Hypotension, hyperkalemia, angioedema risk (never with ACE-I)
Dapagliflozin (Forxiga)	SGLT2 inhibitor	Glucose/water loss, ↓cardiac workload	HFrEF with or without diabetes	Genital fungal infections, dehydration, rare ketoacidosis

Table 2.2 — Anti-anginal drugs compared

Drug/class (brand)	Main mechanism	Demand or supply?	Best for	Key adverse effects
Nitroglycerin (Angised)	NO → venodilation	↓demand (↓preload); ↑supply (coronary dilation)	Acute attack (sublingual); variant angina	Headache, hypotension, tolerance
ISDN/ISMN (Sorbitrate)	NO donor, longer acting	Same as above	Prevention	Same; needs free interval
Beta blockers (Met XL)	β1 block → ↓HR, ↓contractility	↓demand	Stable angina, post-MI	Bradycardia, fatigue, bronchospasm
Amlodipine (Amlopress)	DHP CCB → vessel dilation	↑supply + ↓demand (↓afterload)	Stable + variant angina	Ankle oedema, flushing, headache
Verapamil (Calaptin)	Non-DHP CCB → vessel + heart effects	↓demand (↓HR, ↓contractility) + ↑supply	Stable angina; also arrhythmias	Bradycardia, AV block, constipation
Diltiazem (Dilzem)	Non-DHP CCB (intermediate)	Like verapamil, milder heart effects	Stable angina	Bradycardia, oedema
Ranolazine (Ranozex)	Late Na^+ current block	↓demand (better relaxation)	Add-on chronic angina	Dizziness, nausea, QT caution
Ivabradine (Ivabrad)	If (funny current) block	↓demand (↓HR only)	Angina/HF with high HR	Bradycardia, visual brightness (phosphenes)
Nicorandil (Nikoran)	NO donor + K^+-channel opener	↓demand + ↑supply	Stable angina add-on	Headache, hypotension, mouth ulcers
Trimetazidine (Flavedon)	Metabolic: glucose > fatty acid use	Tolerates ↓supply better	Add-on chronic angina	GI upset, parkinsonism-like symptoms (caution)

Table 2.3 — Digoxin toxicity: factors, signs, management

Aspect	Details
Risk factors	Old age, kidney failure, hypokalemia (furosemide!), hypomagnesemia, hypercalcemia, verapamil/amiodarone interaction
Early signs	Loss of appetite, nausea, vomiting, abdominal pain
Visual	Blurred vision, yellow-green vision (xanthopsia), halos around lights
Cardiac	Almost ANY arrhythmia: AV block, atrial/ventricular ectopics, bigeminy
Management	Stop digoxin; correct K^+/Mg^{2+}; treat arrhythmia; Fab antibody fragments if life-threatening; dialysis NOT useful
Prevention	Monitor K^+ with loop diuretics; dose-adjust in elderly/renal impairment

Table 2.4 — Stable vs unstable vs variant angina

Feature	Stable	Unstable	Variant (Prinzmetal)
Trigger	Exertion, predictable	Rest or minimal exertion, worsening	Rest (often night), coronary spasm
Relief	Rest / nitrate	Not easily relieved	Nitrate / CCB
Cause	Fixed narrowing	Plaque rupture + clot	Artery spasm
Danger	Chronic	Pre-heart-attack emergency	Usually responds to vasodilators
Drug choice	Beta blocker ± nitrate/CCB	Hospital: aspirin, heparin, nitrates	Nitrates, CCBs (avoid beta blocker alone)

2.11 Examples

1. **Furosemide:** A breathless heart failure patient gets IV furosemide; within an hour urine output surges, lung congestion eases, and breathing improves — preload reduced.
2. **Spironolactone:** A patient on furosemide + enalapril develops low potassium; adding low-dose spironolactone corrects K^+ and adds remodelling protection.
3. **Enalapril cough:** A patient on enalapril develops a dry irritating cough for weeks with normal chest X-ray; switching to losartan stops the cough — classic ACE-I adverse effect.
4. **Beta blocker paradox:** A stable HFrEF patient starts carvedilol 3.125 mg twice daily; over months the dose is doubled stepwise, breathlessness lessens and EF improves — shielding from adrenaline helps.
5. **Digoxin + furosemide danger:** A patient on digoxin + furosemide without K^+ check develops nausea, yellow vision and ventricular bigeminy; K^+ is found low — textbook toxicity precipitated by hypokalemia.
6. **Hydralazine + ISDN:** A heart failure patient with high creatinine cannot take enalapril; hydralazine + ISDN unloads the heart without worsening kidneys.
7. **ARNI:** A HFrEF patient on enalapril is switched to sacubitril/valsartan (after a washout gap) with improved symptoms — newer guideline pillar.
8. **Sublingual nitrate:** A man with stable angina feels chest pressure climbing stairs; one sublingual nitroglycerin under the tongue relieves it in 2 minutes — sit down first to avoid fainting.
9. **Nitrate tolerance:** A patient wearing a nitroglycerin patch 24 hours daily finds it stops working; removing the patch overnight (free interval) restores effect.
10. **Nitrate + sildenafil:** A patient on isosorbide mononitrate takes sildenafil — severe hypotension and collapse; the combination is absolutely contraindicated.
11. **Verapamil constipation:** An elderly angina patient on verapamil complains of constipation — classic non-DHP adverse effect.
12. **Ivabradine:** A stable angina patient intolerant to beta blockers (asthma) with resting HR 90 gets ivabradine; heart rate falls, angina episodes reduce, BP unchanged.

2.12 Analogies

1. **Failing heart = tired old water pump.** Diuretics = draining excess water from the tank; ACE-I = widening the outlet pipe; beta blockers = stopping someone from whipping the tired pump; digoxin = oiling the motor for a stronger push.
2. **RAAS = a panic committee.** Low flow alarms it; it orders "retain water, tighten pipes" — helpful for a day, ruinous for a year. ACE-I/ARBs = disbanding the panic committee.
3. **Remodelling = a house settling on a weak foundation.** Walls crack and rooms warp over time; beta blockers and RAAS blockers = foundation repair, not just repainting (symptom relief).
4. **Digoxin mechanism = blocking the drain.** Na^+/K^+ pump is a drain throwing Na^+ out; block it → Na^+ piles up → Ca^{2+} piles up → stronger squeeze. Like damming a stream to raise the waterwheel's power.
5. **Angina = engine starved of fuel uphill.** Demand (speed, load) exceeds fuel line capacity (narrowed pipe). Nitrates = widening the fuel line + lightening the load; beta blockers = driving slower.
6. **Nitrate tolerance = a nose going numb to a smell.** Constant exposure dulls the response; a break (free interval) restores sensitivity.
7. **Coronary spasm (variant angina) = a sudden cramp in the fuel pipe.** Nitrates/CCBs = relaxing the cramp.
8. **ARNI = two workers in one tablet.** Valsartan blocks the villain (angiotensin); sacubitril protects the hero (natriuretic peptides).
9. **Ivabradine = dimming the conductor's baton.** It slows the SA node's beat without touching the musicians' strength (contractility).
10. **Trimetazidine = switching the engine to a more mileage-efficient fuel.** Same distance, less fuel (oxygen) burned.

2.13 Pharmacy Relevance

- Heart failure regimens are multi-drug: the pharmacist checks for the "fantastic four" (ACE-I/ARNI + beta blocker + spironolactone + SGLT2i) plus diuretic, and watches K^+ (ACE-I/ARB/spironolactone raise it; furosemide lowers it — the combination needs monitoring).
- Digoxin has a narrow therapeutic index: counsel on signs of toxicity (nausea, visual colour changes, confusion, palpitations), ensure K^+/renal monitoring, and flag interactions (diuretics, verapamil, amiodarone).
- ACE-I counselling: warn about dry cough (switch to ARB, don't just stop), first-dose dizziness (take at bedtime initially), and absolute avoidance in pregnancy.
- Nitrate counselling: sit/lie down when taking sublingual nitrate; carry it always; check expiry; never combine with sildenafil-type drugs; explain the nitrate-free interval for patches.
- Beta blocker counselling: never stop suddenly (rebound angina/HF worsening); take at same time daily; report unusual breathlessness, very slow pulse, or wheezing.
- Pharmacists in India commonly dispense fixed-dose combinations (e.g., losartan + hydrochlorothiazide, metoprolol + amlodipine) — know each component's role from this chapter.

2.14 India Context

- Heart failure in India often follows untreated hypertension, diabetes-related coronary disease, and rheumatic valvular disease — so the drugs in this chapter (ACE-I, beta blockers, diuretics, digoxin) are daily-dispensed medicines in Indian pharmacies.
- Ischemic heart disease is a leading cause of death in India, striking at younger ages than in Western populations; affordable anti-anginals (nitrates like Sorbitrate, beta blockers, amlodipine) are on the NLEM and widely available as low-cost generics through Jan Aushadhi Kendras.
- Digoxin remains relevant in India because rheumatic heart disease commonly causes atrial fibrillation with heart failure — a classic digoxin indication (rate control + inotropy).
- Newer agents (sacubitril/valsartan as Vymada, dapagliflozin as Oxra/Forxiga generics) are increasingly available in India, including Indian-manufactured affordable versions — pharmacists should know they are now guideline pillars, not luxuries.
- Counselling in Indian languages about salt restriction, daily weight monitoring (fluid overload sign), and never stopping beta blockers abruptly is core pharmacist work in heart failure clinics.

2.15 Key Points

1. Heart failure = weak pump + congestion + harmful neurohumoral compensation → vicious cycle of remodelling.
2. Furosemide (loop) powerfully ↓ preload; watch hypokalemia. Spironolactone spares K^+ and blocks aldosterone-driven remodelling; watch hyperkalemia.
3. Enalapril (ACE-I): ↓ angiotensin II + ↑ bradykinin → ↓ afterload/preload, ↓ remodelling; dry cough is the signature adverse effect.
4. Losartan (ARB): same benefits without cough; use when ACE-I intolerable.
5. Beta blockers (carvedilol, metoprolol) paradoxically help HF by blocking chronic adrenaline harm — start low, go slow, never stop suddenly.
6. Digoxin: Na^+/K^+ ATPase block → ↑ intracellular Ca^{2+} → ↑ contractility + vagal slowing; narrow index; toxicity = GI + visual (xanthopsia) + any arrhythmia; worse with low K^+.
7. Hydralazine + ISDN: dual unloading when ACE-I/ARB unsuitable.
8. ARNI (sacubitril/valsartan): blocks angiotensin + preserves natriuretic peptides; never with ACE-I.
9. Dapagliflozin (SGLT2i): helps HFrEF even without diabetes.
10. Angina = O_2 demand > supply. Nitrates (NO → venodilation, ↓ preload) relieve attacks; tolerance prevented by nitrate-free interval; NEVER with sildenafil.
11. Beta blockers ↓ demand; CCBs: amlodipine (vessel), verapamil/diltiazem (vessel + heart).
12. Newer anti-ischemic: ranolazine (late Na^+), ivabradine (funny current, ↓HR only), nicorandil (nitrate + K^+ channel), trimetazidine (metabolic).

2.16 Common Confusions (with Corrections)

1. **Confusion:** Beta blockers are contraindicated in all heart failure. **Correction:** They are life-prolonging in STABLE chronic HFrEF (carvedilol, metoprolol, bisoprolol); only avoided/used cautiously in ACUTE decompensated failure.
2. **Confusion:** Digoxin is the first-line drug for heart failure. **Correction:** Modern first-line = ACE-I/ARNI + beta blocker + spironolactone + SGLT2i; digoxin is add-on for symptoms/AF rate control.
3. **Confusion:** ACE-I cough means allergy — stop all RAAS drugs. **Correction:** Cough is bradykinin-related, not allergy; switch to ARB (no bradykinin rise).
4. **Confusion:** Nitrates mainly dilate arteries. **Correction:** At usual doses nitrates are mainly VENODILATORS (↓ preload); arterial/coronary dilation is secondary.
5. **Confusion:** Amlodipine and verapamil are interchangeable. **Correction:** Amlodipine (DHP) = mainly vessels; verapamil (non-DHP) = vessels + slows heart + ↓ contractility; different adverse effects and interactions.
6. **Confusion:** Ivabradine weakens the heart like beta blockers. **Correction:** Ivabradine only slows SA node rate (funny current); contractility and BP are largely unchanged.

2.17 Common Mistakes (with Corrections)

1. **Mistake:** Prescribing/counselling nitrates with sildenafil. **Correction:** Absolute contraindication — both raise cGMP → life-threatening hypotension.
2. **Mistake:** Stopping a beta blocker suddenly after long use. **Correction:** Taper slowly — abrupt stop causes rebound angina, arrhythmia, HF worsening.
3. **Mistake:** Giving digoxin without checking K^+/renal function. **Correction:** Hypokalemia and renal impairment precipitate toxicity — monitor both.
4. **Mistake:** Using a nitrate patch 24 hours continuously. **Correction:** Needs a daily nitrate-free interval to prevent tolerance.
5. **Mistake:** Starting a beta blocker at full dose in heart failure. **Correction:** Start very low, double slowly only if tolerated ("start low, go slow").
6. **Mistake:** Combining ACE-I with ARNI (sacubitril/valsartan). **Correction:** Never together — angioedema risk; observe a washout gap when switching.

2.18 Mnemonics

1. **HF drug pillars — "ABCD + S": A**CE-I/ARNI, **B**eta blocker, **C** (aldosterone antagonist — spironolactone; 'C' for its metabolite canrenone), **D**iuretic (loop), **S**GLT2 inhibitor → "**A B**ig **C**ardiac **D**efence **S**quad".
2. **Digoxin toxicity signs — "VIG-AD": V**isual (xanthopsia), **I**ntestinal/GI (anorexia, nausea), **G** — GI comes first, **A**rrhythmia (any), **D**anger — worse with low K^+.
3. **Digoxin mechanism — "3 steps: Block, Build, Boost":** Block Na^+/K^+ pump → Na^+ Builds up → Ca^{2+} Boosts contraction.
4. **ACE-I adverse effects — "CAPTOPRIL" (works for the class): C**ough, **A**ngioedema, **P**otassium ↑, **T**aste change, **O**rthostatic hypotension, **P**regnancy contraindicated, **R**enal impairment, **I**ndry cough… (use as: Cough, Angioedema, Potassium high, Taste loss, hypotension, Pregnancy — no, Renal watch).
5. **Anti-anginal triad — "NBC": N**itrates, **B**eta blockers, **C**alcium channel blockers — "the NBC news channel for chest pain".
6. **Nitrate tolerance — "Take a Holiday":** a daily nitrate-FREE interval keeps nitrates working.
7. **Newer anti-ischemic — "RINT": R**anolazine, **I**vabradine, **N**icorandil, **T**rimetazidine → "RINT — rinse ischemia away".
8. **CCB split — "DHP = Dilates Hypertension Pipes"** (vessels mainly: amloDIPine); **"non-DHP = Delays Heart Pulse"** (verapamil/diltiazem slow the heart too).

2.19 Exam Summary

Heart failure: weak pump + congestion + harmful sympathetic/RAAS compensation → remodelling vicious cycle. Treatment: furosemide (loop diuretic, ↓ preload; hypokalemia risk) + spironolactone (K^+-sparing, anti-remodelling; hyperkalemia, gynaecomastia) + enalapril (ACE-I: ↓ angiotensin II, ↑ bradykinin; cough, hyperkalemia, angioedema, pregnancy contraindicated) or losartan (ARB, no cough) + carvedilol/metoprolol (beta blockers paradoxically prolong life; start low go slow) + digoxin (Na^+/K^+ ATPase inhibition → ↑ Ca^{2+} → ↑ contractility + vagal slowing; narrow index; toxicity = GI + xanthopsia + arrhythmias, worse with low K^+) + hydralazine/ISDN (dual unloading) + newer ARNI sacubitril/valsartan and SGLT2i dapagliflozin (pillars even without diabetes). Angina = O_2 demand > supply (stable/unstable/variant). Nitrates (nitroglycerin, ISDN/ISMN): NO → venodilation → ↓ preload; tolerance needs nitrate-free interval; never with sildenafil. Beta blockers ↓ demand; CCBs — amlodipine (vessels), verapamil/diltiazem (vessels + heart). Newer: ranolazine (late Na^+ block), ivabradine (If block, HR only), nicorandil (nitrate + K^+ channel), trimetazidine (metabolic switch to glucose).

2.20 One-Minute Revision

- HF cycle: weak pump → RAAS/sympathetic panic → remodelling → weaker pump.
- Unload: furosemide (↓preload), enalapril/losartan (↓afterload).
- Protect: beta blocker + spironolactone + dapagliflozin + ARNI.
- Digoxin: block Na^+/K^+ pump → ↑Ca^{2+} → stronger beat; toxicity = VIG-AD, worse in low K^+.
- Angina: demand > supply. NBC: Nitrates, Beta blockers, CCBs.
- Nitrates: NO → veins dilate → ↓preload; free interval beats tolerance; no sildenafil.
- New: ranolazine, ivabradine (funny current), nicorandil, trimetazidine.

2.21 Exam Questions

Short-answer questions:

1. Define heart failure and explain the vicious cycle of neurohumoral activation with a flowchart.
2. Explain the mechanism of action of furosemide and its adverse effects in heart failure.
3. Why is spironolactone called a potassium-sparing diuretic? Give its two roles in heart failure.
4. Explain how enalapril helps a failing heart. List four adverse effects.
5. Why does enalapril cause dry cough but losartan does not?
6. Explain the "beta blocker paradox" in heart failure with dosing rules.
7. Describe digoxin's mechanism of action in three steps.
8. List the signs of digoxin toxicity and four factors that increase its risk.
9. What is the role of hydralazine + isosorbide dinitrate in heart failure?
10. Explain the ARNI concept (sacubitril + valsartan) in simple words.
11. Why are SGLT2 inhibitors now used in heart failure without diabetes?
12. Define angina and explain the oxygen supply–demand mismatch with examples.
13. Explain the mechanism of nitrates in angina. Why are they mainly venodilators?
14. What is nitrate tolerance? How is it prevented?
15. Why should nitrates never be combined with sildenafil?
16. Differentiate amlodipine from verapamil (any four points).
17. Write the concept-level mechanism of any two newer anti-ischemic drugs.

Long-answer questions:

1. Classify drugs used in congestive cardiac failure. Explain the mechanism, therapeutic uses and adverse effects of ACE inhibitors and digoxin in detail.
2. Describe the mechanism of digoxin toxicity, its clinical features, predisposing factors and management. Why is hypokalemia dangerous in a patient on digoxin?
3. Classify anti-anginal drugs. Explain the mechanism of action, uses and adverse effects of nitrates, including nitrate tolerance and its prevention.
4. Compare beta blockers and calcium channel blockers in angina. Add a note on newer anti-ischemic drugs (ranolazine, ivabradine, nicorandil, trimetazidine).

MCQs (with answer key):

1. Furosemide acts by blocking:

a) Aldosterone receptor b) Na^+-K^+-$2Cl^-$ transporter in loop of Henle c) ACE d) Funny current

2. Spironolactone's mortality benefit in HF is mainly due to:

a) Strong diuresis b) Aldosterone blockade reducing remodelling c) Heart rate slowing d) Vasodilation

3. Dry cough with enalapril is due to accumulation of:

a) Angiotensin II b) Bradykinin c) Aldosterone d) Natriuretic peptides

4. An ACE-I-intolerant (cough) heart failure patient should receive:

a) Higher ACE-I dose b) ARB like losartan c) Digoxin alone d) Stop all therapy

5. Beta blockers help chronic HF mainly by:

a) Increasing contractility b) Blocking chronic sympathetic harm and remodelling c) Causing diuresis d) Dilating coronaries

6. Digoxin strengthens contraction by:

a) Opening K^+ channels b) Inhibiting Na^+/K^+ ATPase → ↑ intracellular Ca^{2+} c) Blocking beta receptors d) Releasing NO

7. Digoxin toxicity is worsened by:

a) High potassium b) Low potassium c) High sodium intake d) Beta blockers

8. Xanthopsia means:

a) Double vision b) Yellow-green vision c) Night blindness d) Tunnel vision

9. Sacubitril in ARNI works by:

a) Blocking ACE b) Inhibiting neprilysin → preserving natriuretic peptides c) Blocking calcium channels d) Increasing heart rate

10. Nitrates relieve angina mainly by:

a) Increasing heart rate b) Venodilation → ↓ preload → ↓ O_2 demand c) Blocking beta receptors d) Thinning blood

11. Nitrate tolerance is prevented by:

a) Increasing the dose b) A daily nitrate-free interval c) Adding sildenafil d) Continuous infusion

12. Nitrates + sildenafil causes:

a) Severe hypertension b) Severe hypotension c) Bradycardia d) No interaction

1. Amlodipine is a:

a) Non-DHP CCB acting mainly on heart b) DHP CCB acting mainly on vessels c) Beta blocker d) Nitrate

14. Verapamil's classic non-cardiac adverse effect is:

a) Cough b) Constipation c) Ankle oedema d) Gynaecomastia

15. Ivabradine lowers:

a) Blood pressure mainly b) Heart rate via funny current, without ↓ contractility c) Cholesterol d) Blood glucose

16. Ranolazine's concept mechanism is:

a) Beta blockade b) Late sodium current inhibition c) ACE inhibition d) Diuresis

Answers: 1-b, 2-b, 3-b, 4-b, 5-b, 6-b, 7-b, 8-b, 9-b, 10-b, 11-b, 12-b, 13-b, 14-b, 15-b, 16-b

Viva questions:

1. Why is spironolactone combined with furosemide in heart failure?
2. A patient on enalapril develops lip swelling — what is it and what will you do?
3. Why must digoxin dose be reduced in an elderly patient with renal impairment?
4. Explain why beta blockers are started "low and slow" in heart failure.
5. A patient asks why the nitrate patch is removed at night — explain.
6. Why is verapamil avoided with a beta blocker in the same patient?

Application-based questions:

1. A 65-year-old heart failure patient on furosemide + digoxin presents with nausea, yellow vision and ventricular bigeminy. Lab shows K^+ 2.8 mEq/L. Explain the chain of events and outline management.
2. A hypertensive diabetic patient with HFrEF (EF 32%) is on enalapril, carvedilol and furosemide. The doctor adds dapagliflozin though the patient has no diabetes. Justify using chapter concepts.
3. A 55-year-old with stable angina uses sublingual nitroglycerin 3–4 times daily and also takes sildenafil occasionally. Identify the drug interaction risk and counsel the patient.
4. A patient on a 24-hour nitroglycerin patch reports it "stopped working." Explain tolerance and advise a regimen fix.

2.22 References

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Chapter 3: Anti-arrhythmic Drugs

(Syllabus topic c)

3.1 Learning Objectives

By the end of this chapter, you will be able to:

1. Define cardiac arrhythmia and explain the two basic mechanisms (abnormal impulse formation, reentry).
2. State the Vaughan–Williams classification of antiarrhythmics and the ion channel/receptor each class targets.
3. Differentiate Class Ia, Ib and Ic drugs with examples.
4. Explain the mechanism, uses and adverse effects of quinidine, procainamide, lidocaine, flecainide and propafenone.
5. Explain the role of Class II (beta blockers) in arrhythmias.
6. Explain the mechanism, uses and adverse effects of amiodarone and sotalol (Class III).
7. Explain the mechanism, uses and adverse effects of verapamil and diltiazem (Class IV).
8. Describe the roles of adenosine, digoxin and magnesium in arrhythmia management.
9. Correlate each class with the action potential phases from Chapter 1.
10. Answer exam questions on antiarrhythmic classification with correct examples.

3.2 Definitions

Cardiac arrhythmia — any abnormality of heart rhythm: too fast, too slow, or irregular. Simple meaning: the heart's electrical wiring misfires — the conductor (SA node) loses control or a short-circuit loop forms.

Reentry — the commonest arrhythmia mechanism: an electrical impulse goes around in a circle (loop) re-stimulating heart tissue repeatedly, causing rapid rhythm. Simple meaning: an electrical "roundabout" with no exit — the signal keeps circling.

Abnormal automaticity — pacemaker-like firing from cells that should not fire on their own (e.g., damaged ventricular cells firing during phase 4).

Triggered activity — abnormal extra beats caused by afterdepolarizations (oscillations after the action potential), often from calcium overload (e.g., digoxin toxicity).

Vaughan–Williams classification — the standard 4-class system for antiarrhythmics based on which ion channel or receptor the drug blocks: Class I = Na^+ channels, Class II = beta receptors, Class III = K^+ channels, Class IV = Ca^{2+} channels.

Use-dependence — a property where a drug blocks channels MORE when the heart beats faster (blocks open channels); useful because it targets fast abnormal rhythms while sparing normal slow rhythm.

Pro-arrhythmic effect — when an antiarrhythmic drug itself CAUSES a new arrhythmia (all antiarrhythmics can do this — an important exam concept).

Supraventricular arrhythmia — rhythm starting above the ventricles (atria or AV node), e.g., atrial fibrillation, PSVT.

Ventricular arrhythmia — rhythm starting in the ventricles, e.g., ventricular tachycardia, ventricular fibrillation (more dangerous).

3.3 Terminology

- **Atrial fibrillation (AF)** — chaotic, rapid atrial firing (≈300–600/min) with irregular ventricular response; clots can form in atria → stroke risk.
- **Atrial flutter** — rapid but organized atrial rhythm (≈300/min, "sawtooth" ECG).
- **PSVT (paroxysmal supraventricular tachycardia)** — sudden rapid regular rhythm from above ventricles, often via reentry through AV node.
- **Ventricular tachycardia (VT)** — fast ventricular rhythm (≈150–250/min); can degenerate to VF.
- **Ventricular fibrillation (VF)** — chaotic ventricular quivering; no pumping; cardiac arrest — needs immediate defibrillation.
- **AV block** — impulse fails to pass through AV node (delayed or blocked); severe forms need pacemaker.
- **Torsades de pointes** — a dangerous polymorphic VT ("twisting of points") linked to QT prolongation (Class Ia/III drugs, low K^+/Mg^{2+}).
- **Cardioversion/defibrillation** — electric shock to reset rhythm (not a drug, but mentioned with adenosine/amiodarone contexts).
- **Rate control vs rhythm control** — two AF strategies: slow the ventricular rate (beta blocker, verapamil, digoxin) vs restore normal sinus rhythm (amiodarone, cardioversion).

3.4 Explanation (Main Teaching)

Why do arrhythmias happen? Two mechanisms. (1) **Abnormal impulse formation:** cells fire when they shouldn't — either abnormal automaticity (a damaged cell's phase 4 drifts up on its own) or triggered activity (afterdepolarizations from Ca^{2+} overload, as in digoxin toxicity). (2) **Reentry:** the impulse travels down one path, finds the tissue ahead still excitable (because refractory periods differ), loops back up another path, and circles forever — like a rumor going around a village and coming back to start. Requirements for reentry: two pathways + one-way (unidirectional) block + slow conduction. Most tachyarrhythmias (AF, PSVT, VT) involve reentry.

How antiarrhythmics fix rhythms — three strategies: (a) **Slow conduction / block the abnormal pathway** (Na^+ blockers, Ca^{2+} blockers in AV node); (b) **Lengthen the refractory period** so the circling impulse hits "locked" tissue and dies (K^+ blockers — Class III); (c) **Suppress abnormal firing** — reduce automaticity (beta blockers reduce sympathetic drive; Na^+ blockers reduce excitability).

The Vaughan–Williams map — "Naughty Boys Kick Cats": Class **I** blocks **Na**$^+$ channels; Class **II** blocks **B**eta receptors; Class **III** blocks **K**$^+$ channels; Class **IV** blocks **Ca**$^{2+}$ channels. Numbers 1-2-3-4 = Na-β-K-Ca. Every drug below fits this map.

CLASS I — Sodium channel blockers (act on phase 0 of fast-response cells). They slow the upstroke and conduction, suppress excitability, and most are use-dependent (work harder on fast rhythms). Subdivided by effect on action potential duration (APD):

- **Ia — "Intermediate": quinidine, procainamide.** Block Na^+ channels AND prolong APD/refractory period (they also block K^+ channels → longer phase 3). Uses: atrial fibrillation/flutter, PSVT, VT. Adverse: quinidine — cinchonism (ringing in ears, headache, visual disturbance; quinidine comes from cinchona bark), GI upset, hypotension, QT prolongation → torsades risk, thrombocytopenia; procainamide — lupus-like syndrome on long use, hypotension, QT prolongation. (Both prolong QT — pro-arrhythmic caution.)
- **Ib — "Brief": lidocaine (Xylocaine).** Blocks Na^+ channels but SHORTENS APD (fast on/off binding; prefers damaged/ischemic tissue). Uses: VENTRICULAR arrhythmias only (post-heart-attack VT/VF) — IV drug, emergency use. Little effect on atria. Adverse: CNS — drowsiness, confusion, seizures at high levels; hypotension. (Short APD = mnemonic "Ib = brief".)
- **Ic — "Complete/strongest": flecainide, propafenone.** Strongest Na^+ blockade, markedly slow conduction, NO change in APD. Uses: AF, PSVT, WPW syndrome (an extra electrical pathway) — in structurally NORMAL hearts. Critical caution: can WORSEN mortality in patients with structural heart disease/post-MI (learned from trials) — never used casually. Adverse: pro-arrhythmic (can convert AF to slow atrial flutter with fast ventricular conduction — usually combined with AV nodal blocker), dizziness, visual disturbance (flecainide), metallic taste/bronchospasm caution (propafenone has mild beta-blocking activity).

CLASS II — Beta blockers. Block sympathetic drive → ↓ automaticity (flatter phase-4 slope), ↓ AV conduction (slow-response tissue), ↓ triggered activity. Uses: rate control in AF, PSVT, VT prevention post-MI, exercise-induced arrhythmias. Examples: metoprolol, esmolol (ultra-short-acting IV for emergencies), propranolol. Adverse: bradycardia, AV block, hypotension, bronchospasm, fatigue.

CLASS III — Potassium channel blockers (act on phase 3; prolong APD and refractory period). By blocking K^+ efflux, repolarization takes longer → the refractory "lock" lasts longer → reentry circuits die when they hit refractory tissue.

- **Amiodarone (Cordarone)** — the "broad-spectrum antibiotic of arrhythmias": actually has Class I + II + III + IV actions (blocks Na^+, beta, K^+, Ca^{2+} channels). Uses: BOTH supraventricular (AF) and ventricular (VT/VF) arrhythmias — most versatile antiarrhythmic, IV in emergencies. Catches: very long half-life (weeks–months), MANY adverse effects — thyroid (hypo- or hyperthyroidism; contains iodine), lung fibrosis (cough/breathlessness — monitor), liver, corneal deposits, skin photosensitivity (blue-grey discoloration), bradycardia, QT prolongation. Needs regular monitoring (thyroid, lung, liver, eye).
- **Sotalol** — K^+ blocker + beta blocker (Class III + II). Uses: AF, VT. Adverse: bradycardia, QT prolongation → torsades risk (dose-related), bronchospasm caution.

CLASS IV — Calcium channel blockers: verapamil (Calaptin), diltiazem (Dilzem). Block L-type Ca^{2+} channels in SLOW-response tissue (SA/AV node — Chapter 1!) → slow AV conduction, slow SA rate. Uses: SUPRAVENTRICULAR arrhythmias — rate control in AF, PSVT termination (verapamil IV). NO use in ventricular arrhythmias (ventricles are fast-response, Na^+-driven). Adverse: bradycardia, AV block, hypotension, constipation (verapamil); never combine casually with beta blockers (additive AV block).

Beyond the four classes:

- **Adenosine (Adenocard)** — drug of choice to TERMINATE PSVT: ultra-short-acting (seconds) — given as rapid IV bolus, it transiently BLOCKS the AV node completely, breaking the reentry circuit that uses the AV node. Feels: brief chest flushing, breathlessness, sense of doom — but it passes in seconds. Caution in asthma (bronchospasm) and heart transplant patients.
- **Digoxin (Lanoxin)** — not a classic antiarrhythmic but slows AV nodal conduction via vagal effect → ventricular RATE control in atrial fibrillation (especially with heart failure). Does not convert AF to normal rhythm.
- **Magnesium (IV magnesium sulfate)** — membrane stabilizer; drug of choice for torsades de pointes (with QT prolongation), and useful in digoxin-toxicity arrhythmias with low Mg^{2+}. Corrects the ionic instability driving afterdepolarizations.

Key takeaway: Map every drug to Chapter 1: Na^+ blockers hit phase 0 (fast tissue), K^+ blockers stretch phase 3 (longer refractory lock), Ca^{2+} blockers + beta blockers + adenosine hit the slow-response AV node, and digoxin slows AV conduction vagally. The Vaughan–Williams classes are just applied cardiac electrophysiology.

3.5 Classifications

Vaughan–Williams classification (with subdivisions):

1. **Class I — Na^+ channel blockers:**

- Ia (prolong APD): quinidine, procainamide, disopyramide.
- Ib (shorten APD): lidocaine, mexiletine, phenytoin.
- Ic (no APD change, strongest conduction slowing): flecainide, propafenone.

2. **Class II — beta blockers:** metoprolol, esmolol, propranolol, atenolol.
3. **Class III — K^+ channel blockers (prolong APD/refractory):** amiodarone, sotalol, dofetilide, ibutilide.
4. **Class IV — Ca^{2+} channel blockers (slow-response tissue):** verapamil, diltiazem.
5. **Others:** adenosine (AV nodal blocker), digoxin (vagal AV slowing), magnesium (membrane stabilizer), atropine/isoproterenol for bradycardia (raise rate — opposite action).

Classification by arrhythmia site:

- **Supraventricular (AF, flutter, PSVT):** beta blockers, verapamil/diltiazem, digoxin (rate control); amiodarone, sotalol, flecainide, propafenone, adenosine (rhythm/termination).
- **Ventricular (VT, VF):** lidocaine, amiodarone, sotalol; (flecainide avoided in structural disease).

Classification by effect on APD:

- Prolong APD/refractory: Ia, III.
- Shorten APD: Ib.
- No APD change: Ic.
- Slow AV nodal conduction: II, IV, adenosine, digoxin.

3.6 Mechanisms

Class I mechanism: bind fast Na^+ channels (preferentially open/inactivated states → use-dependence) → ↓ phase-0 upstroke velocity → slowed conduction + reduced excitability → abnormal impulses and reentry circuits suppressed. Ia/Ib/Ic differ in binding speed and added K^+-channel effects (Ia blocks K^+ too → longer APD; Ib speeds K^+-related repolarization → shorter APD; Ic pure strong Na^+ block).

Class II mechanism: β1 blockade → ↓ sympathetic stimulation → flatter SA phase-4 slope (↓ automaticity), slowed AV nodal conduction (slow-response tissue), reduced Ca^{2+}-mediated triggered activity.

Class III mechanism: block delayed-rectifier K^+ channels → ↓ K^+ efflux in phase 3 → prolonged repolarization → longer APD + longer effective refractory period → reentry impulse encounters refractory tissue and extinguishes.

Class IV mechanism: block L-type Ca^{2+} channels in SA/AV nodal cells → slower phase-0 upstroke and slower phase-4 drift in nodes → ↓ sinus rate, prolonged AV nodal refractory period → slowed AV conduction.

Adenosine mechanism: activates A1 receptors → opens K^+ channels + closes Ca^{2+} channels in AV node → transient complete AV block (half-life seconds) → breaks AV-node-dependent reentry.

Digoxin mechanism (rhythm aspect): ↑ vagal tone → ↓ AV nodal conduction velocity + prolonged AV refractory period → fewer atrial impulses reach ventricles in AF (rate control).

Magnesium mechanism: stabilizes membranes by antagonizing Ca^{2+}-driven afterdepolarizations and supporting Na^{+}/K^{+} ATPase function → suppresses triggered activity (torsades).

3.7 Diagrams (Describe Textually So They Can Be Drawn)

Diagram 1 — Reentry circuit. Draw a circular loop of heart tissue with an arrow going around. Mark: "slow conduction zone", "unidirectional block (impulse can't go back up)", and a "gap of excitable tissue" ahead of the wavefront. Show the wavefront chasing its tail around the loop. Caption: "Two paths + one-way block + slow conduction = endless circling."

Diagram 2 — Vaughan–Williams map on the action potential. Draw one fast-response AP; mark class actions: Class I arrow on phase 0 ("slows upstroke"), Class III bracket over phase 3 ("stretches repolarization → longer refractory"), and a separate small SA/AV nodal AP with Class II, IV, adenosine arrows ("slow the nodes"). Caption: "Every class maps to a phase from Chapter 1."

Diagram 3 — Ia vs Ib vs Ic on APD. Draw three APs side by side: Ia = wider (prolonged plateau), Ib = narrower (shortened), Ic = same width but flattened/slowed upstroke. Label drugs under each.

Diagram 4 — AF rate control concept. Draw atria firing chaotically (many small arrows, "350/min") → AV node as a gate/funnel letting only some through ("verapamil/beta blocker/digoxin tighten the gate") → ventricles beating regularly at "80/min". Caption: "Rate control: don't fix the atria, guard the gate."

Diagram 5 — Adenosine breaking PSVT. Draw a reentry loop passing through the AV node; show adenosine as a barrier slamming the AV node shut ("block for seconds") → loop broken → sinus rhythm restored.

3.8 Flowcharts (Step-by-Step Text Flowcharts)

Flowchart 1 — Choosing an antiarrhythmic by rhythm:

```
SUPRAVENTRICULAR:
  AF with fast rate → RATE CONTROL: beta blocker / verapamil / diltiazem / digoxin
  AF rhythm control → amiodarone / sotalol / flecainide (normal heart)
  PSVT attack → adenosine IV (first choice) → verapamil if needed
VENTRICULAR:
  VT/VF emergency → IV amiodarone or lidocaine (+ defibrillation for VF)
  Chronic VT prevention → amiodarone / sotalol
AVOID: Ic drugs (flecainide) in structural heart disease/post-MI
```

Flowchart 2 — How Class III kills reentry:

```
K⁺ channels blocked → phase 3 repolarization slowed
        ↓
Action potential duration prolonged
        ↓
Effective refractory period prolonged ("lock" lasts longer)
        ↓
Circling reentry impulse hits refractory tissue → cannot pass
        ↓
Circuit extinguished → normal sinus rhythm resumes
```

Flowchart 3 — Amiodarone monitoring:

```
Start amiodarone → baseline: thyroid, liver, lung, eye, ECG (QT, bradycardia)
        ↓
Ongoing: repeat thyroid/liver periodically; watch cough/breathlessness (lung fibrosis)
        ↓
Adverse signs → dose review / switch (long half-life: effects linger weeks)
```

3.9 Infographic Concept Box

⚡ **ANTIARRHYTHMICS — ONE-PAGE MAP**

"Naughty Boys Kick Cats": I = **Na**$^{+}$ block | **II** = **B**eta block | **III** = **K**$^{+}$ block | **IV** = **Ca**$^{2+}$ block

Class	APD effect	Key drugs	Best for
Ia	Prolongs	Quinidine, procainamide	AF, VT (QT caution!)
Ib	Shortens	Lidocaine	Ventricular (post-MI), IV
Ic	No change	Flecainide, propafenone	AF/PSVT in NORMAL hearts only
II	— (nodes)	Metoprolol, esmolol	Rate control, post-MI
III	Prolongs	Amiodarone, sotalol	AF + VT/VF (broadest)
IV	— (nodes)	Verapamil, diltiazem	Supraventricular rate control

🆘 **Adenosine** = PSVT terminator (seconds-long AV block) | **Digoxin** = AF rate control (vagal) | **Magnesium** = torsades fixer

⚠️ **All antiarrhythmics can be pro-arrhythmic.** Ia/III prolong QT → torsades. Ic dangerous in damaged hearts.

📍 **Map to Chapter 1:** Na^{+} blockers → phase 0 (fast tissue) • K^{+} blockers → phase 3 (refractory lock) • Ca^{2+}/beta/adenosine → slow AV node.

3.10 Tables

Table 3.1 — Vaughan–Williams classes: full drug profiles

Class/drug (brand)	Target	APD effect	Main uses	Key adverse effects
Ia: Quinidine	Na^+ (+ K^+)	Prolongs	AF, flutter, VT	Cinchonism (tinnitus, headache), GI upset, QT prolongation, thrombocytopenia
Ia: Procainamide	Na^+ (+ K^+)	Prolongs	AF, VT (IV)	Lupus-like syndrome, hypotension, QT prolongation
Ib: Lidocaine (Xylocaine)	Na^+ (fast on/off)	Shortens	Ventricular arrhythmias post-MI (IV)	CNS: drowsiness, confusion, seizures
Ic: Flecainide	Na^+ (strong)	No change	AF/PSVT (normal hearts)	Pro-arrhythmic in structural disease, dizziness, visual disturbance
Ic: Propafenone	Na^+ (+ mild β block)	No change	AF/PSVT	Metallic taste, dizziness, bronchospasm caution
II: Metoprolol/Esmolol	β1	—	AF rate control, post-MI VT prevention	Bradycardia, AV block, hypotension, bronchospasm
III: Amiodarone (Cordarone)	K^+ (+ Na^+, β, Ca^{2+})	Prolongs	AF, VT/VF (broadest)	Thyroid, lung fibrosis, liver, cornea, skin, QT, bradycardia
III: Sotalol	K^+ + β	Prolongs	AF, VT	QT → torsades, bradycardia
IV: Verapamil (Calaptin)	Ca^{2+} (nodes)	—	SVT rate control, PSVT	Bradycardia, AV block, hypotension, constipation
IV: Diltiazem (Dilzem)	Ca^{2+} (nodes)	—	Same as verapamil	Bradycardia, AV block, oedema

Table 3.2 — Non-classified agents

Drug	Mechanism	Use	Cautions
Adenosine (Adenocard)	A1 agonist → transient AV block	Terminate PSVT (IV bolus)	Seconds-long flushing/dyspnoea; caution in asthma
Digoxin (Lanoxin)	Vagal → slows AV conduction	AF rate control (+ HF)	Toxicity (see Chapter 2); narrow index
Magnesium sulfate (IV)	Membrane stabilizer, ↓ triggered activity	Torsades de pointes; low-Mg^{2+} arrhythmias	Hypotension, flushing with rapid IV

Table 3.3 — Ia vs Ib vs Ic

Feature	Ia	Ib	Ic
Examples	Quinidine, procainamide	Lidocaine	Flecainide, propafenone
APD	Prolonged	Shortened	Unchanged
Conduction slowing	Moderate	Mild	Marked
Main site	Atria + ventricles	Ventricles (ischemic tissue)	Atria (SVT)
Signature risk	QT prolongation → torsades	CNS toxicity	Pro-arrhythmia in structural heart disease

3.11 Examples

1. **PSVT termination:** A young patient with sudden regular palpitations at 180/min gets rapid IV adenosine; within seconds the rhythm snaps back to normal — AV-node reentry broken.
2. **AF rate control:** An elderly AF patient with ventricular rate 140/min receives IV diltiazem; rate falls to 85/min — atria still fibrillate, but the gate is guarded.
3. **Post-MI VT:** A heart attack patient develops VT; IV lidocaine suppresses the ventricular ectopy — Ib prefers ischemic tissue.
4. **Amiodarone breadth:** A patient with both AF and VT episodes is controlled on oral amiodarone — the broadest-spectrum choice.
5. **Flecainide caution:** Flecainide is chosen for AF in a patient with a structurally normal heart on echo — but would be avoided after MI with low EF.
6. **Quinidine cinchonism:** A patient on quinidine reports ringing ears and headache — cinchonism, from its cinchona-bark origin.
7. **Torsades:** A patient on sotalol with low K^+ develops polymorphic VT with twisting QRS — QT-prolongation-related torsades; IV magnesium given.
8. **Digoxin in AF:** A heart failure + AF patient gets digoxin; ventricular rate slows via vagal AV effect while contractility improves.

3.12 Analogies

1. **Reentry = rumor circling a village.** It keeps coming back unless someone (longer refractory period) refuses to pass it on.
2. **Refractory period = a "do not disturb" sign on a hotel door.** Class III drugs hang the sign for longer — the circling impulse can't enter.
3. **Use-dependence = a speed camera.** It only flashes (blocks) the fast drivers (rapid abnormal beats), ignoring slow normal traffic.
4. **AV node drugs = a strict security gate.** Beta blockers, verapamil, digoxin, adenosine all tighten the gate so fewer chaotic atrial impulses reach the ventricles.
5. **Amiodarone = a Swiss Army knife.** One tool with four blades (I + II + III + IV actions) — versatile but heavy to carry (many adverse effects).
6. **Adenosine = pulling the plug for one second.** The whole AV-node circuit reboots and normal rhythm returns.
7. **Lidocaine = a fire extinguisher for the ventricles only.** Works where the fire is (ischemic ventricular tissue), not elsewhere.
8. **Flecainide in a damaged heart = putting racing tires on a cracked road.** Strong conduction slowing becomes dangerous when the heart is structurally abnormal.

3.13 Pharmacy Relevance

- Antiarrhythmics have narrow therapeutic indices and pro-arrhythmic potential — the pharmacist must ensure ECG/QT, electrolyte (K^+, Mg^{2+}) and drug-interaction checks before dispensing.
- Amiodarone needs a monitoring plan (thyroid, liver, lung, eye, ECG) — pharmacists counsel on photosensitivity, blue-grey skin, and reporting new cough/breathlessness.
- Many common drugs prolong QT (certain antibiotics, antipsychotics) — adding them to Class Ia/III antiarrhythmics multiplies torsades risk; the pharmacist is the safety net.
- Adenosine must be given as a RAPID IV bolus (seconds half-life) — a practical point for hospital pharmacy.
- Counsel sotalol/flecainide patients to report syncope, palpitations, or dizziness immediately.

3.14 India Context

- Atrial fibrillation is increasingly detected in India with wider ECG access; rate-control drugs (metoprolol, diltiazem, digoxin) are NLEM-listed and available as low-cost Jan Aushadhi generics.
- Rheumatic heart disease — still significant in India — causes mitral valve disease → left atrial enlargement → AF; these patients need rate control (digoxin/beta blocker) plus anticoagulation (stroke prevention, Chapter 4/Unit III).
- Amiodarone (Cordarone and Indian generics) is widely used in Indian hospitals for both AF and VT; its thyroid and lung monitoring is a pharmacist-counselling opportunity.
- Lidocaine (Xylocaine) is the familiar emergency drug in Indian casualty/ICU settings for post-MI ventricular arrhythmias, and adenosine is standard for PSVT termination.

3.15 Key Points

1. Arrhythmias arise from abnormal impulse formation or reentry (two pathways + one-way block + slow conduction).
2. Vaughan–Williams: I = Na^+, II = beta, III = K^+, IV = Ca^{2+} ("Naughty Boys Kick Cats").
3. Ia prolongs APD (quinidine, procainamide — QT/torsades risk); Ib shortens APD (lidocaine — ventricular, IV); Ic no APD change, strongest block (flecainide — normal hearts only).
4. Class II (beta blockers): ↓ automaticity + slow AV node; rate control, post-MI.
5. Class III (amiodarone, sotalol): block K^+ → longer refractory → kills reentry; amiodarone is broadest-spectrum with many organ toxicities.
6. Class IV (verapamil, diltiazem): slow-response AV node only — supraventricular use, never ventricular.
7. Adenosine: seconds-long AV block terminates PSVT. Digoxin: vagal AV slowing for AF rate control. Magnesium: treats torsades.
8. All antiarrhythmics can be pro-arrhythmic — respect QT, K^+, Mg^{2+} and structural heart disease.

3.16 Common Confusions (with Corrections)

1. **Confusion:** Class Ic drugs are safest because they don't change APD. **Correction:** Ic drugs are the most dangerous in structural heart disease — strong conduction slowing can be lethal post-MI.
2. **Confusion:** Verapamil can treat ventricular tachycardia. **Correction:** Verapamil acts on slow-response nodal tissue; VT is ventricular (fast-response) — verapamil is ineffective and can cause collapse in VT.
3. **Confusion:** Digoxin converts AF to normal rhythm. **Correction:** Digoxin only SLOWS the ventricular rate (rate control); it does not restore sinus rhythm.
4. **Confusion:** Longer refractory period makes arrhythmias worse. **Correction:** Longer refractory period TERMINATES reentry (the impulse hits locked tissue) — the basis of Class III action.
5. **Confusion:** Adenosine works for minutes. **Correction:** Its half-life is seconds — given as rapid IV bolus; effects (flushing, dread) pass almost immediately.

3.17 Common Mistakes (with Corrections)

1. **Mistake:** Giving flecainide to a post-MI patient with low EF. **Correction:** Ic drugs are contraindicated with structural heart disease — use amiodarone/sotalol instead.
2. **Mistake:** Combining verapamil with a beta blocker casually. **Correction:** Additive AV block/bradycardia — dangerous combination.
3. **Mistake:** Ignoring QT-prolonging co-medications with sotalol/amiodarone. **Correction:** Check every added drug for QT risk; keep K^+/Mg^{2+} normal.
4. **Mistake:** Using adenosine as a slow IV infusion. **Correction:** Rapid IV bolus only — it vanishes in seconds.
5. **Mistake:** Stopping amiodarone and expecting immediate washout. **Correction:** Half-life is weeks–months; effects and interactions linger.

3.18 Mnemonics

1. **Classes:** "**N**aughty **B**oys **K**ick **C**ats" = **I**-Na^+, **II**-Beta, **III**-K^+, **IV**-Ca^{2+}.
2. **Ia/Ib/Ic APD:** "**I**ncreases, **d**ecreases (**b**rief), **u**nchanged (**c**onstant)" → "**Ia = lA**rger APD, **Ib = B**rief APD, **Ic = C**onstant APD".
3. **Ia drugs:** "**Q**uinidine, **P**rocainamide" → "**Q**uite **P**rolonged (QT)".
4. **Ic caution:** "**I**c = **I**nfarct **C**ontraindicated" (avoid in structural/post-MI hearts).
5. **Amiodarone toxicities:** "**T**hyroid, **L**ung, **L**iver, **C**ornea, **S**kin, **B**radycardia" → "**T**he **L**ungs **L**ove **C**lean **S**afe **B**eats" — monitor all.
6. **Adenosine:** "**A**denosine **A**bolishes **A**V-node reentry in **A**n instant" (PSVT terminator).

3.19 Exam Summary

Arrhythmias = abnormal impulse formation or reentry (two pathways, one-way block, slow conduction). Vaughan–Williams: Class I (Na^+ blockers): Ia (quinidine, procainamide — prolong APD, QT/torsades risk, cinchonism/lupus), Ib (lidocaine — shortens APD, ventricular post-MI, IV, CNS toxicity), Ic (flecainide, propafenone — no APD change, strongest block, AF/PSVT in normal hearts only, dangerous post-MI). Class II (beta blockers): ↓ automaticity, slow AV node — AF rate control, post-MI. Class III (K^+ blockers): prolong refractory, kill reentry — amiodarone (broadest I+II+III+IV, many toxicities: thyroid/lung/liver/cornea/skin) and sotalol (also beta blocker, torsades risk). Class IV (verapamil, diltiazem): slow AV node only — supraventricular. Others: adenosine (seconds-long AV block, terminates PSVT), digoxin (vagal AV slowing, AF rate control), magnesium (torsades). All antiarrhythmics can be pro-arrhythmic.

3.20 One-Minute Revision

- Reentry needs: 2 paths + one-way block + slow conduction.
- I-Na, II-beta, III-K, IV-Ca. Ia prolongs, Ib shortens, Ic unchanged APD.
- Quinidine: cinchonism + QT. Lidocaine: ventricles, IV. Flecainide: normal hearts only.
- Amiodarone: broadest, most toxicities. Sotalol: III + II, torsades risk.
- Verapamil/diltiazem: AV node only — supraventricular.
- Adenosine: PSVT killer (seconds). Digoxin: AF rate control. Mg^{2+}: torsades.

3.21 Exam Questions

Short-answer questions:

1. Define arrhythmia and explain the reentry mechanism with a diagram.
2. State the Vaughan–Williams classification with one example per class.
3. Differentiate Class Ia, Ib and Ic antiarrhythmics (APD effect + example + use).
4. Explain why quinidine prolongs QT and what danger this creates.
5. Why is lidocaine used only for ventricular arrhythmias?
6. Why is flecainide avoided in post-MI patients?
7. Explain the "broad-spectrum" actions of amiodarone and list five adverse effects.
8. Why do verapamil and diltiazem work on supraventricular but not ventricular arrhythmias?
9. Explain how adenosine terminates PSVT.
10. What is the role of magnesium in arrhythmia management?
11. Differentiate rate control from rhythm control in atrial fibrillation with drug examples.

Long-answer questions:

1. Describe the Vaughan–Williams classification of antiarrhythmic drugs. Explain the mechanism, uses and adverse effects of one drug from each class.
2. Explain the mechanism of action, therapeutic uses and adverse effects of amiodarone. Why does it need multi-organ monitoring?
3. Compare Class I subdivisions (Ia, Ib, Ic) with examples. Explain the concept of pro-arrhythmic effects with examples.

MCQs (with answer key):

1. Class I antiarrhythmics block:

a) K^+ channels b) Na^+ channels c) Ca^{2+} channels d) Beta receptors

2. "Naughty Boys Kick Cats" maps classes I–IV to:

a) K^+, Na^+, Ca^{2+}, beta b) Na^+, beta, K^+, Ca^{2+} c) Ca^{2+}, K^+, Na^+, beta d) Beta, Na^+, Ca^{2+}, K^+

3. Which drug SHORTENS action potential duration?

a) Quinidine b) Lidocaine c) Amiodarone d) Sotalol

4. Cinchonism is an adverse effect of:

a) Lidocaine b) Quinidine c) Verapamil d) Adenosine

5. Flecainide is contraindicated in:

a) Normal hearts with AF b) Post-MI structural heart disease c) PSVT d) WPW syndrome

6. Amiodarone's action includes:

a) Only K^+ blockade b) Na^+, beta, K^+ and Ca^{2+} blockade c) Only beta blockade d) Only Na^+ blockade

7. Drug of choice to terminate PSVT:

a) Digoxin b) Adenosine (rapid IV bolus) c) Furosemide d) Lidocaine

8. Verapamil is useful in:

a) Ventricular tachycardia b) Supraventricular arrhythmias (AV node) c) VF d) Bradycardia

9. Torsades de pointes is treated with IV:

a) Calcium b) Magnesium sulfate c) Potassium chloride d) Sodium bicarbonate

1. Digoxin controls AF by:

a) Converting to sinus rhythm b) Vagal slowing of AV conduction (rate control) c) Blocking Na^+ channels d) Prolonging QT

11. Sotalol's dangerous adverse effect is:

a) Cinchonism b) QT prolongation → torsades c) Lupus syndrome d) Corneal deposits

12. Which combination is dangerous?

a) Verapamil + beta blocker b) Amiodarone + monitoring c) Lidocaine + VT d) Adenosine + PSVT

Answers: 1-b, 2-b, 3-b, 4-b, 5-b, 6-b, 7-b, 8-b, 9-b, 10-b, 11-b, 12-a

Viva questions:

1. Why is adenosine given as a rapid IV bolus and not an infusion?
2. A patient on amiodarone develops a new cough — what do you suspect and advise?
3. Why must K^+ and Mg^{2+} be normal before starting sotalol?
4. Explain use-dependence with a Class I example.
5. Why can't digoxin terminate PSVT like adenosine?

Application-based questions:

1. A 30-year-old with structurally normal heart has recurrent PSVT. The doctor prescribes flecainide for prevention and advises rapid IV adenosine for attacks. Justify both choices and state one caution for each.
2. A post-MI patient with EF 30% develops AF. Explain why flecainide is inappropriate and suggest a safer rhythm-control option with monitoring plan.
3. A patient on quinidine + erythromycin (a QT-prolonging antibiotic) develops syncope with polymorphic VT on ECG. Explain the mechanism and immediate management.

3.22 References

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Chapter 4: Anti-hypertensive Drugs + Shock Management + Stroke Management

(Syllabus topics e, f and g)

4.1 Learning Objectives

By the end of this chapter, you will be able to:

1. Define hypertension and explain it using BP = CO × TPR.
2. Classify anti-hypertensive drugs and state the hemodynamic target of each class.
3. Explain the mechanism, uses and adverse effects of thiazide/loop/K^+-sparing diuretics, ACE inhibitors, ARBs, CCBs, beta blockers, prazosin, clonidine, methyldopa, hydralazine, minoxidil and sodium nitroprusside.
4. Define hypertensive emergency vs urgency and outline management principles.
5. Define shock, classify its types, and explain the basic pathophysiology of each.
6. List the drugs used in shock (IV fluids, noradrenaline, dopamine, dobutamine, adrenaline, vasopressin, corticosteroids) with their roles.
7. Differentiate ischemic from hemorrhagic stroke.
8. List the drugs used in stroke management (thrombolytics, antiplatelets, anticoagulants, statins) and explain why thrombolysis is contraindicated in hemorrhagic stroke.
9. Answer exam questions across all three topics with correct examples.

4.2 Definitions

Hypertension — persistently raised arterial blood pressure. Simple meaning: the pipes are under too much pressure for too long, damaging the heart, brain, kidneys and eyes silently over years ("the silent killer").

Essential (primary) hypertension — high BP with no single identifiable cause (the vast majority of cases); managed with lifestyle + drugs.

Secondary hypertension — high BP due to an identifiable cause (kidney disease, hormonal tumour, certain drugs); treat the cause.

Hypertensive emergency — severe BP rise WITH acute organ damage (brain, heart, kidney, eye) — needs immediate IV BP lowering in hospital.

Hypertensive urgency — severe BP rise WITHOUT acute organ damage — managed with oral drugs, not emergency IV drops (rapid lowering can harm).

Shock — a life-threatening state where blood flow (perfusion) to organs is too low to meet their needs, so organs begin to fail. Simple meaning: the pump/pipe system collapses — organs starve for blood. Low BP alone is not shock; shock = poor organ perfusion (cold clammy skin, low urine, confusion, fast weak pulse).

Stroke — sudden loss of brain function because brain blood supply is interrupted. **Ischemic stroke** (≈4 in 5 strokes): a clot BLOCKS a brain artery. **Hemorrhagic stroke**: a brain artery RUPTURES and bleeds into the brain.

Thrombolytic (clot-buster) — a drug that dissolves blood clots (e.g., alteplase, streptokinase); useful only in ischemic stroke within a short time window.

Perfusion — blood flow delivering oxygen/nutrients to tissues; the central concept of shock.

4.3 Terminology

- **ABCD rule (hypertension):** A = ACE-I/ARB, B = beta blocker, C = calcium channel blocker, D = diuretic (thiazide) — the four first-line classes.
- **Thiazide diuretics:** hydrochlorothiazide, chlorthalidone — first-line in uncomplicated hypertension; mild, long-acting.
- **Loop diuretics:** furosemide — reserved for hypertension with heart/kidney failure or fluid overload.
- **K^+-sparing diuretics:** spironolactone, amiloride, triamterene — weak BP effect alone; used in resistant hypertension or with thiazides to balance K^+.
- **First-dose hypotension:** sharp BP fall after the first ACE-I dose — start low, give at bedtime.
- **Orthostatic (postural) hypotension:** BP drop on standing → dizziness/fainting; typical of prazosin, clonidine.
- **Rebound hypertension:** dangerous BP surge if clonidine is stopped suddenly.
- **Resistant hypertension:** BP uncontrolled on 3+ drugs — often needs spironolactone added.
- **Vasopressor:** drug that tightens vessels to raise BP in shock (noradrenaline, vasopressin).
- **Inotrope:** drug that strengthens heart contraction in shock (dobutamine, dopamine, adrenaline).
- **Crystalloids:** salt-water IV fluids (normal saline, Ringer's lactate) — first-line volume replacement in shock.
- **MAP (mean arterial pressure):** the key perfusion number targeted in shock management.
- **FAST (stroke):** Face drooping, Arm weakness, Speech difficulty, Time to act — public awareness tool.
- **Time window:** thrombolysis in ischemic stroke only helps within a few hours of symptom onset — "time is brain."
- **Hemorrhagic transformation:** bleeding into an ischemic stroke area — one reason thrombolysis is risky late.

4.4 Explanation (Main Teaching)

PART A — ANTI-HYPERTENSIVES

Hypertension through the BP formula. BP = CO × TPR (Chapter 1). Every anti-hypertensive lowers BP by reducing cardiac output, reducing vessel resistance, or both:

- ↓ **CO (less pump flow):** diuretics (↓ blood volume), beta blockers (↓ heart rate + contractility).
- ↓ **TPR (looser pipes):** ACE-I, ARBs, CCBs, alpha blockers, central agents, direct vasodilators.

1. Diuretics — "drain some water from the pipes."

- **Thiazides (hydrochlorothiazide, chlorthalidone):** block Na^+-Cl^- reabsorption in the distal tubule → mild salt/water loss → ↓ blood volume → ↓ CO → ↓ BP. First-line in uncomplicated hypertension, especially elderly and salt-sensitive patients; long-acting, cheap, once daily. Adverse: hypokalemia, hyponatremia, raised uric acid (gout), raised glucose/lipids slightly, erectile dysfunction.
- **Loop (furosemide — Lasix):** too powerful for routine hypertension; reserved for hypertension WITH heart failure, kidney failure, or fluid overload.
- **K^+-sparing (spironolactone — Aldactone, amiloride, triamterene):** weak alone; added in resistant hypertension or to offset thiazide-induced K^+ loss. Watch hyperkalemia with ACE-I/ARB.

2. ACE inhibitors (enalapril — Enam, lisinopril, ramipril) and 3. ARBs (losartan — Losar, telmisartan, valsartan). As detailed in Chapter 2: block RAAS → ↓ angiotensin II → vasodilation (↓ TPR) + less aldosterone (↓ volume). Preferred in hypertension with diabetes/kidney disease (protect kidneys), heart failure, post-MI. Adverse: cough (ACE-I), hyperkalemia, first-dose hypotension, angioedema, foetal harm — contraindicated in pregnancy and bilateral renal artery stenosis.

4. Calcium channel blockers. **Amlodipine (Amlopress)** — DHP, vessel-selective: relaxes arteries → ↓ TPR; no heart-rate slowing. First-line, especially elderly; excellent with thiazides. Adverse: ankle oedema, flushing, headache, gum hypertrophy. **Verapamil/diltiazem** (non-DHP) also lower BP but slow the heart — used when rate control is also needed.

5. Beta blockers (metoprolol — Met XL, atenolol — Tenormin, propranolol — Ciplar). ↓ HR + ↓ contractility → ↓ CO; also ↓ renin release. No longer first-line for uncomplicated hypertension (less stroke protection in elderly), but first-choice with compelling indications: post-MI, heart failure, angina, AF rate control, young patients, pregnancy (labetalol/methyldopa preferred — see below). Adverse: bradycardia, fatigue, bronchospasm, masks hypoglycemia, erectile dysfunction; never stop abruptly.

6. Alpha-1 blockers — prazosin (Minipress). Blocks alpha-1 receptors on vessels → arteries AND veins relax → ↓ TPR. Useful in hypertension with prostate enlargement (BPH — improves urine flow too). Signature adverse: **first-dose phenomenon** — severe postural hypotension/syncope after the very first dose → "start low, take first dose at bedtime." Also: dizziness, nasal congestion, reflex tachycardia.

7. Central agents — clonidine (Arkamin), methyldopa (Aldomet). Act in the brainstem: stimulate central alpha-2 receptors → REDUCE sympathetic outflow → vessels relax + heart slows → ↓ BP. **Methyldopa** is the classic drug for hypertension IN PREGNANCY (long safety record). **Clonidine** used in resistant hypertension; also for opioid withdrawal and ADHD (other chapters). Critical caution: NEVER stop clonidine suddenly → rebound hypertension (sympathetic storm) — taper slowly. Adverse: dry mouth, sedation, drowsiness, postural hypotension.

8. Direct vasodilators.

- **Hydralazine:** direct arterial dilator → ↓ TPR. Used in heart failure (Chapter 2) and hypertension in pregnancy (with methyldopa). Causes reflex tachycardia + fluid retention → usually combined with a beta blocker + diuretic. Long-term high dose → lupus-like syndrome.
- **Minoxidil (Mintop):** very powerful arterial dilator (opens K^+ channels) — reserved for SEVERE resistant hypertension (excessive hair growth — hirsutism — is why it's also a hair-loss lotion!). Always combined with beta blocker + loop diuretic (reflex tachycardia + fluid retention).
- **Sodium nitroprusside (Nitropress):** IV, ultra-short-acting NO donor — dilates arteries AND veins powerfully. Drug of choice for HYPERTENSIVE EMERGENCY: titratable drip, BP falls within seconds, stops when infusion stops. Needs ICU monitoring (arterial line); prolonged use → cyanide/thiocyanate toxicity (it releases cyanide — treated with thiosulfate; another exam favourite).

Hypertensive emergency vs urgency. Emergency = very high BP WITH organ damage (stroke symptoms, chest pain/MI, acute kidney injury, eye bleeding, pulmonary oedema) → admit, IV drugs (nitroprusside, IV labetalol, nicardipine), lower BP in a CONTROLLED way (not to normal instantly — brain needs perfusion). **Urgency** = very high BP WITHOUT organ damage → oral drugs, calm management, follow-up. Mistake to avoid: aggressive IV lowering in urgency can cause stroke by under-perfusing the brain.

PART B — SHOCK

What is shock? Organs starving. Blood pressure is just a number; shock is organ starvation — cold/clammy/pale skin, fast weak pulse, rapid breathing, very low urine output, confusion. The body compensates first (fast heart, tight vessels), then decompensates (organs fail). Treatment principle: (1) restore VOLUME, (2) support PUMP, (3) tighten PIPES, (4) treat the CAUSE.

Types of shock — "Have Cold Drinks On Nice Afternoons":

1. **Hypovolemic** — fluid/blood LOSS (bleeding, severe dehydration, burns). Pipes are fine, pump is fine, but the TANK IS EMPTY. Treatment: IV fluids (crystalloids), blood transfusion for bleeding.
2. **Cardiogenic** — PUMP FAILURE (massive MI, severe heart failure). Tank full, pipes fine, pump broken. Treatment: inotropes to strengthen the pump (dobutamine, dopamine), careful fluids, treat the heart cause; vasopressors if BP very low.
3. **Distributive — septic** — infection causes MASSIVE vessel dilation + leaky capillaries; pipes go slack and fluid leaks out. Most common ICU shock. Treatment: IV fluids + antibiotics (treat cause!) + vasopressor of choice **noradrenaline**; add **vasopressin** if needed; **corticosteroids (hydrocortisone)** if shock persists despite fluids/vasopressors (relative adrenal insufficiency concept).
4. **Distributive — anaphylactic** — severe allergy: sudden massive vasodilation + airway swelling. Treatment: **adrenaline IM** immediately (tightens vessels + opens airways + strengthens heart) + fluids + antihistamines/steroids.
5. **Neurogenic** — spinal cord injury: sympathetic tone lost → vessels dilate + heart slows. Treatment: fluids + vasopressors; bradycardia may need atropine.
6. **Obstructive** — something BLOCKS blood flow (massive pulmonary embolism, cardiac tamponade, tension pneumothorax). Treatment: relieve the obstruction (the drugs are supportive only).

Drugs in shock — roles:

- **IV fluids (normal saline, Ringer's lactate):** FIRST step in almost all shock (except pure cardiogenic overload) — refill the tank.
- **Noradrenaline (norepinephrine):** FIRST-LINE vasopressor in septic shock — strong alpha (tightens vessels) + mild beta-1 (supports heart). Raises BP without much heart-rate increase.
- **Dopamine:** dose-dependent — low dose: kidney/mesenteric dilation (old "renal dose" concept, now less favoured); medium: beta-1 → stronger heart; high: alpha → vasoconstriction. Used in cardiogenic/bradycardic shock.
- **Dobutamine:** mainly beta-1 → stronger contraction with mild vasodilation — the INOTROPE of choice in cardiogenic shock with low output.
- **Adrenaline (epinephrine):** alpha + beta — the all-rounder: anaphylaxis (IM), cardiac arrest, severe shock. Raises heart rate and BP strongly.
- **Vasopressin:** non-catecholamine vasoconstrictor (V1 receptors) — added in septic shock when noradrenaline alone is insufficient; doesn't increase heart oxygen demand much.
- **Corticosteroids (hydrocortisone IV):** in septic shock unresponsive to fluids/vasopressors — replaces relative adrenal failure, restores vessel responsiveness.

PART C — STROKE

Two strokes, opposite problems. Ischemic (≈80%): clot blocks a brain artery → brain tissue starves → "time is brain" (millions of neurons die per minute). **Hemorrhagic (≈20%)**: artery ruptures → blood bursts into brain tissue → pressure + toxicity damage. Same symptom (FAST: face/arm/speech), OPPOSITE treatment — this is why a brain scan (CT) comes FIRST, before any clot drug.

Drugs in ischemic stroke:

- **Thrombolytics — alteplase (Actilyse), streptokinase (concept):** dissolve the clot (activate plasminogen → plasmin → digests fibrin). Only within a SHORT time window (a few hours from symptom onset) and only after CT excludes bleeding. Streptokinase is the affordable option widely used in India for MI; alteplase is the standard for stroke thrombolysis.
- **Antiplatelets — aspirin (Ecosprin), clopidogrel (Clopilet):** prevent new clots/platelet plugs; aspirin given early in ischemic stroke and lifelong for secondary prevention (often aspirin + clopidogrel short-term after minor stroke/TIA).
- **Anticoagulants (heparin, warfarin, NOACs):** for cardioembolic stroke (e.g., AF — clot from heart) — prevent formation, not dissolve existing clots acutely.
- **Statins (atorvastatin):** lower cholesterol + stabilize plaques + pleiotropic vessel benefits — secondary prevention after ischemic stroke/TIA.
- Supportive: BP managed cautiously (don't drop aggressively — brain needs perfusion), sugar control, swallow assessment, physiotherapy.

Drugs in hemorrhagic stroke: the OPPOSITE logic — STOP bleeding, LOWER pressure carefully, reverse anticoagulation if present, neurosurgery if needed. **Why thrombolysis is contraindicated:** a clot-buster in a bleeding brain dissolves the body's own sealing clots → catastrophic worsening of bleeding → death. This single concept is the most exam-asked point in stroke pharmacology.

Key takeaway: Hypertension = chronic pipe pressure (ABCD drugs lower CO or TPR; emergency needs IV nitroprusside; urgency does not). Shock = acute organ starvation (fluids first, then noradrenaline/dobutamine/adrenaline by type, steroids in refractory septic shock). Stroke = blocked pipe (dissolve/prevent clots, fast) vs burst pipe (stop bleeding, never give clot-busters).

4.5 Classifications

Classification of anti-hypertensive drugs:

1. **Diuretics:** thiazides (hydrochlorothiazide, chlorthalidone); loop (furosemide — for HF/renal failure); K^+-sparing (spironolactone, amiloride, triamterene).
2. **RAAS blockers:** ACE inhibitors (enalapril, lisinopril, ramipril); ARBs (losartan, telmisartan, valsartan).
3. **Calcium channel blockers:** DHP (amlodipine, nifedipine); non-DHP (verapamil, diltiazem).
4. **Beta blockers:** metoprolol, atenolol, propranolol, labetalol, esmolol (IV).
5. **Alpha-1 blockers:** prazosin, terazosin, doxazosin.
6. **Central sympatholytics:** clonidine, methyldopa.
7. **Direct vasodilators:** hydralazine, minoxidil (oral); sodium nitroprusside, fenoldopam (IV).

Classification by hemodynamic target:

- ↓ Cardiac output: diuretics, beta blockers, central agents (partly).
- ↓ TPR: ACE-I, ARBs, CCBs, alpha blockers, direct vasodilators.
- Both: central agents, nitroprusside.

Classification of shock (with cause and key drug):

1. Hypovolemic (blood/fluid loss) → IV fluids/blood.
2. Cardiogenic (pump failure) → dobutamine/dopamine.
3. Distributive–septic (infection, vasodilation) → noradrenaline + fluids + antibiotics (+ vasopressin, hydrocortisone).
4. Distributive–anaphylactic (allergy) → adrenaline IM.
5. Neurogenic (spinal injury, sympathetic loss) → fluids + vasopressors.
6. Obstructive (PE, tamponade, pneumothorax) → relieve obstruction.

Classification of stroke:

1. Ischemic (≈80%): thrombotic/embolic → thrombolytics (window), antiplatelets, anticoagulants (AF), statins.
2. Hemorrhagic (≈20%): intracerebral/subarachnoid bleed → BP control, reverse anticoagulation, surgery; NO thrombolytics/antiplatelets acutely.

4.6 Mechanisms

Thiazide mechanism: block Na^+-Cl^- cotransporter in distal convoluted tubule → ↑ Na^+/water excretion → ↓ plasma volume → ↓ CO → ↓ BP (chronic: mild vasodilation also contributes).

ACE-I/ARB mechanism: (Chapter 2 recap) ↓ angiotensin II → ↓ vasoconstriction + ↓ aldosterone → ↓ TPR and ↓ volume; ARBs block AT1 directly (no bradykinin/cough).

CCB mechanism: block L-type Ca^{2+} channels in vascular smooth muscle → relaxation → ↓ TPR (amlodipine); non-DHPs add cardiac/AV nodal slowing.

Beta blocker mechanism: β1 blockade → ↓ HR, ↓ contractility (↓ CO) + ↓ renin release from kidney (↓ RAAS).

Prazosin mechanism: selective alpha-1 blockade on vessels → arterial + venous dilation → ↓ TPR; also relaxes prostate/bladder neck smooth muscle (BPH benefit).

Clonidine/methyldopa mechanism: central alpha-2 agonism in brainstem vasomotor centre → ↓ sympathetic outflow → ↓ vessel tone + ↓ heart rate; methyldopa acts via its metabolite alpha-methyl-noradrenaline.

Hydralazine/minoxidil mechanism: direct relaxation of arterial smooth muscle (minoxidil via opening ATP-sensitive K^+ channels) → ↓ TPR; trigger baroreceptor reflex tachycardia + fluid retention (hence combination therapy).

Nitroprusside mechanism: releases NO directly in vessel wall → ↑ cGMP → dilates BOTH arteries and veins → rapid ↓ TPR and preload; ultra-short-acting (seconds–minutes), IV titration.

Noradrenaline mechanism: alpha-1 (vasoconstriction → ↑ TPR/BP) + beta-1 (mild ↑ contractility) → restores perfusion pressure in septic shock.

Dobutamine mechanism: selective beta-1 agonism → ↑ contractility (↑ CO) with mild beta-2 vasodilation → ideal for cardiogenic low-output shock.

Adrenaline mechanism: dose-dependent alpha + beta — low: beta (heart); high: alpha (vessels); in anaphylaxis IM: vasoconstriction + bronchodilation + ↑ cardiac output together.

Vasopressin mechanism: V1 receptor agonism → vasoconstriction independent of catecholamine receptors (works when receptors are downregulated in sepsis).

Hydrocortisone in septic shock: restores vascular sensitivity to catecholamines + replaces relative adrenal insufficiency.

Thrombolytic mechanism: alteplase/streptokinase activate plasminogen → plasmin → digests fibrin clot → artery reopens (only fresh clots, only ischemic stroke).

Why thrombolysis harms hemorrhagic stroke: plasmin also digests the fibrin sealing the ruptured vessel → bleeding accelerates → raised intracranial pressure → herniation/death.

4.7 Diagrams (Describe Textually So They Can Be Drawn)

Diagram 1 — BP formula with drug targets. Draw "BP = CO × TPR" large. Under CO, list "diuretics (↓volume), beta blockers (↓HR/contractility), central agents". Under TPR, list "ACE-I, ARBs, CCBs, prazosin, hydralazine, minoxidil". Caption: "Every anti-hypertensive sits under one of these two umbrellas."

Diagram 2 — Hypertensive emergency vs urgency. Two columns: EMERGENCY (organ damage: brain/heart/kidney/eye icons + "IV drugs in hospital, controlled lowering") vs URGENCY (no organ damage + "oral drugs, no panic, follow-up"). Big red cross over "rapid IV drop in urgency".

Diagram 3 — Shock types visual. Six panels: hypovolemic = half-empty tank; cardiogenic = broken pump; septic = slack leaky pipes with germs; anaphylactic = suddenly slack pipes + swollen airway; neurogenic = cut control wire to pipes; obstructive = clamp on the main pipe. Label first-line drug under each.

Diagram 4 — Vasopressor/inotrope spectrum. Horizontal line from "vessel tightener" to "heart strengthener": vasopressin/noradrenaline (left, pipes) → adrenaline (middle, both) → dopamine (dose-dependent arrow) → dobutamine (right, pump). Caption: "Match the drug to the defect: slack pipes vs weak pump."

Diagram 5 — Ischemic vs hemorrhagic stroke. Two brain panels: ischemic = artery with clot plug + starving tissue downstream ("dissolve/prevent clots — FAST"); hemorrhagic = burst artery with blood pooling ("stop bleeding — NEVER clot-busters"). CT scanner icon between them: "Scan first, then treat."

Diagram 6 — Stroke timeline. Horizontal arrow "symptom onset → minutes → hours": mark "thrombolysis window (first few hours only)" early, "antiplatelets/statins (secondary prevention, lifelong)" extending right, "rehabilitation" continuing. Caption: "Time is brain."

4.8 Flowcharts (Step-by-Step Text Flowcharts)

Flowchart 1 — Choosing an anti-hypertensive:

```
Uncomplicated hypertension → Thiazide (D) or CCB (C) or ACE-I/ARB (A)
        ↓ not controlled
Add second class (e.g., A + C or A + D)
        ↓ not controlled
Triple: A + C + D
        ↓ resistant
Add spironolactone (4th line) → investigate secondary causes
Special cases: pregnancy → methyldopa; BPH → prazosin; post-MI/HF → beta blocker + ACE-I;
   diabetes/kidney disease → ACE-I/ARB preferred
```

Flowchart 2 — Hypertensive emergency management:

```
Severe high BP + organ damage signs (neuro deficit, chest pain, kidney injury, eye bleed)
        ↓
Hospitalize, monitor; IV drug (nitroprusside / IV labetalol / nicardipine)
        ↓
Lower BP in CONTROLLED steps (not to normal at once — protect brain perfusion)
        ↓
Find and treat cause; switch to oral regimen when stable
URGENCY (no organ damage) → oral drugs + close follow-up; NO aggressive IV drop
```

Flowchart 3 — Shock resuscitation sequence:

```
Recognize shock (cold/clammy, fast weak pulse, low urine, confusion)
        ↓
1. IV FLUIDS (crystalloids) — refill the tank [all types except overload]
        ↓
2. Identify type:
   Hypovolemic → more fluids/blood, stop the bleeding
   Cardiogenic → DOBUTAMINE (strengthen pump) ± noradrenaline
   Septic → NORADRENALINE (tighten pipes) + antibiotics + source control
            → add vasopressin if refractory → hydrocortisone if still refractory
   Anaphylactic → ADRENALINE IM immediately
   Neurogenic → fluids + vasopressor
   Obstructive → RELIEVE obstruction (surgery/procedure)
        ↓
3. Monitor: BP, urine output, mental status, lactate
```

Flowchart 4 — Stroke management:

```
Sudden FAST symptoms → EMERGENCY, note time of onset
        ↓
CT/MRI brain FIRST
        ↓
    ┌── ISCHEMIC (clot) ──→ within short window: THROMBOLYSIS (alteplase)
    │                          → then aspirin ± clopidogrel, statin, AF? → anticoagulant
    │
    └── HEMORRHAGIC (bleed) ──→ NO thrombolytics/antiplatelets
                                  → careful BP control, reverse anticoagulation,
                                     neurosurgery if needed
        ↓
Rehabilitation + lifelong secondary prevention
```

4.9 Infographic Concept Box

🔴 **HYPERTENSION • SHOCK • STROKE — ONE-PAGE MAP**

HTN: "ABCD" — **A**CE-I/ARB • **B**eta blocker • **C**CB (amlodipine) • **D**iuretic (thiazide). All lower BP = CO × TPR. Special: 🤰 pregnancy → methyldopa | 🚹 BPH → prazosin (first dose at bedtime!) | 🆘 emergency → IV nitroprusside | ⚠️ clonidine — never stop suddenly (rebound!)

SHOCK: "Have Cold Drinks On Nice Afternoons" **H**ypovolemic → fluids | **C**ardiogenic → dobutamine | **D**istributive-septic → noradrenaline (+vasopressin, hydrocortisone) | **O**bstructive → relieve block | **N**eurogenic → fluids + pressor | **A**naphylactic → adrenaline IM Rule: **fluids first, then match drug to defect** (slack pipes → pressor; weak pump → inotrope).

STROKE: "FAST → SCAN → TREAT" 🧠 Ischemic (clot, ~80%): thrombolysis in hours + aspirin/clopidogrel + statin 🩸 Hemorrhagic (bleed, ~20%): NO clot-busters ever — stop bleeding, control BP ⚠️ Clot-buster in a bleed = catastrophe (dissolves the sealing clot).

4.10 Tables

Table 4.1 — Anti-hypertensive classes: full profiles

Class/drug (brand)	Mechanism	Target	Uses	Key adverse effects
Thiazides: HCTZ, chlorthalidone	↓ Na^+/water → ↓ volume	↓CO	First-line uncomplicated HTN	Hypokalemia, gout, ↑glucose
Furosemide (Lasix)	Loop diuresis	↓CO	HTN with HF/renal failure	Same as Chapter 2
Spironolactone (Aldactone)	Aldosterone block	↓CO (mild)	Resistant HTN (4th line)	Hyperkalemia, gynaecomastia
Enalapril (Enam)	ACE inhibition	↓TPR + ↓CO	HTN + diabetes/kidney/HF	Cough, hyperkalemia, foetal harm
Losartan (Losar)	AT1 block	↓TPR + ↓CO	ACE-I cough; same indications	Hyperkalemia (no cough)
Amlodipine (Amlopress)	DHP CCB → vessel dilation	↓TPR	First-line, elderly	Ankle oedema, flushing, headache
Metoprolol (Met XL)	β1 block → ↓HR/contractility/renin	↓CO	Post-MI, HF, angina, AF	Bradycardia, fatigue, bronchospasm
Prazosin (Minipress)	Alpha-1 block	↓TPR	HTN + BPH	First-dose syncope, postural hypotension
Clonidine (Arkamin)	Central alpha-2 → ↓ sympathetic	↓CO + ↓TPR	Resistant HTN	Dry mouth, sedation, rebound HTN if stopped
Methyldopa (Aldomet)	Central (via metabolite)	↓CO + ↓TPR	HTN in pregnancy	Sedation, dry mouth, liver caution, positive Coombs test
Hydralazine	Direct arterial dilator	↓TPR	HF, pregnancy HTN	Reflex tachycardia, fluid retention, lupus-like
Minoxidil (Mintop)	K^+-channel opener, arterial	↓TPR	Severe resistant HTN	Hirsutism, tachycardia, fluid retention
Nitroprusside (Nitropress)	NO donor (IV)	↓TPR	Hypertensive emergency	Cyanide toxicity (prolonged use), needs ICU

Table 4.2 — Shock: types and drugs

Type	Cause	Core problem	Key drugs
Hypovolemic	Bleeding, dehydration, burns	Empty tank	IV crystalloids, blood transfusion
Cardiogenic	Massive MI, severe HF	Broken pump	Dobutamine, dopamine; cautious fluids
Septic (distributive)	Infection	Slack + leaky pipes	Fluids + noradrenaline; vasopressin; hydrocortisone if refractory; antibiotics
Anaphylactic	Severe allergy	Sudden vasodilation + airway oedema	Adrenaline IM + fluids
Neurogenic	Spinal injury	Lost sympathetic tone	Fluids + vasopressors
Obstructive	PE, tamponade, pneumothorax	Blocked flow	Relieve obstruction; supportive drugs

Table 4.3 — Vasopressors/inotropes compared

Drug	Main action	Pipes or pump?	Key use
Noradrenaline	Alpha-1 >> beta-1	Pipes (mainly)	First-line septic shock
Vasopressin	V1 vasoconstriction	Pipes	Add-on septic shock
Dobutamine	Beta-1	Pump	Cardiogenic shock (low output)
Dopamine	Dose-dependent beta → alpha	Both	Cardiogenic/bradycardic shock
Adrenaline	Alpha + beta	Both	Anaphylaxis (IM), arrest, severe shock

Table 4.4 — Ischemic vs hemorrhagic stroke

Feature	Ischemic	Hemorrhagic
Cause	Clot blocks artery (~80%)	Artery ruptures (~20%)
Treatment goal	Reopen artery, prevent more clots	Stop bleeding, control pressure
Thrombolytics	Yes (short window, after CT)	ABSOLUTELY NO
Antiplatelets	Aspirin/clopidogrel	Avoid acutely
Anticoagulants	For AF-related (prevention)	Reverse if present
Statins	Yes (secondary prevention)	Selective
BP management	Cautious (don't drop fast)	Careful controlled lowering

4.11 Examples

1. **Thiazide first-line:** A 60-year-old with newly detected BP 150/95 and no other disease starts chlorthalidone once daily; BP settles over weeks — cheap, effective first-line.
2. **ACE-I in diabetes:** A hypertensive diabetic with protein in urine gets enalapril — BP control plus kidney protection.
3. **Prazosin first dose:** A patient takes the first prazosin tablet standing in the kitchen and faints — first-dose postural hypotension; the next doses are taken at bedtime.
4. **Methyldopa in pregnancy:** A pregnant woman with hypertension is prescribed methyldopa — the time-tested safe choice in pregnancy.
5. **Clonidine rebound:** A patient stops clonidine abruptly before travel; two days later BP surges with headache and sweating — rebound hypertension; taper, don't stop.
6. **Nitroprusside emergency:** A patient with BP 230/140 and acute pulmonary oedema receives IV nitroprusside in ICU; BP is titrated down in a controlled manner.
7. **Hypovolemic shock:** A road-traffic accident victim with bleeding gets rapid IV Ringer's lactate and blood transfusion — refill the tank first.
8. **Septic shock:** A pneumonia patient with BP 80/50 despite 2 litres of fluids is started on noradrenaline infusion plus IV antibiotics — tighten pipes + kill cause.
9. **Anaphylaxis:** After an injection, a patient develops wheezing and collapse; IM adrenaline in the thigh reverses it within minutes.
10. **Cardiogenic shock:** Post-MI patient with cold clammy skin and low output gets dobutamine infusion — strengthen the pump.
11. **Ischemic stroke:** A patient reaches hospital 2 hours after FAST symptoms; CT shows no bleed → alteplase thrombolysis → artery reopens.
12. **Hemorrhagic stroke:** CT shows brain bleed; thrombolysis is withheld, BP carefully controlled, neurosurgery consulted — opposite pathway.
13. **Secondary prevention:** After an ischemic stroke, a patient takes aspirin + atorvastatin lifelong — prevent the next clot.

4.12 Analogies

1. **Hypertension = over-pressurized pipes.** Chronically high pressure bursts joints (stroke), wears the pump (heart failure), and damages filters (kidneys) — the silent killer.
2. **Thiazides = slightly opening the drain valve.** Less water in the pipes → less pressure.
3. **Prazosin first-dose = loosening all pipe clamps at once.** Pressure crashes until the body adjusts — hence "first dose at bedtime."
4. **Clonidine = turning down the control room's alarm volume.** The brain sends fewer "tighten up!" signals; stopping suddenly = alarms blare back louder (rebound).
5. **Nitroprusside = an emergency pressure-release valve.** Instant, adjustable, but only a trained operator (ICU) should handle it.
6. **Shock = a city blackout.** Hypovolemic = the reservoir is empty; cardiogenic = the power station failed; septic = all the wires shorted and sparking; obstructive = the main cable is cut.
7. **Noradrenaline in septic shock = tightening every slack hose.** Pressure returns so water (blood) reaches the top floors (brain, kidneys).
8. **Ischemic stroke = a blocked kitchen pipe.** Dissolve the clog fast (thrombolysis) or it floods… actually starves downstream.
9. **Hemorrhagic stroke = a burst pipe flooding the house.** You would never pour drain-cleaner (clot-buster) on a burst pipe — you'd shut the water and patch the burst.
10. **"Time is brain" = a fire spreading.** Every minute of blocked brain artery burns irreplaceable tissue — hence the thrombolysis window.

4.13 Pharmacy Relevance

- Hypertension is the commonest chronic prescription in Indian pharmacies — the pharmacist must know the ABCD classes, common combinations (e.g., telmisartan + amlodipine, losartan + HCTZ), and counselling points (take daily even when feeling fine — "silent killer"; don't stop abruptly, especially beta blockers/clonidine).
- Counsel on class-specific issues: thiazide → eat potassium-rich foods/report cramps; ACE-I → report dry cough or lip swelling; amlodipine → ankle swelling is expected; prazosin → first dose at bedtime, rise slowly.
- In pregnancy hypertension, guide toward methyldopa/labetalol and AWAY from ACE-I/ARBs (foetal harm) — a critical pharmacist intervention.
- Shock drugs are ICU injectables — the pharmacist's role is correct dilution, infusion-rate calculation, compatibility, and ensuring noradrenaline/adrenaline availability in emergency trays.
- For stroke, the pharmacist reinforces FAST awareness, ensures aspirin/statin adherence for secondary prevention, and checks anticoagulant counselling (bleeding signs) in AF patients.

4.14 India Context

- Hypertension affects roughly one in four Indian adults and is often undetected — community BP screening by pharmacists (a BP410P practical skill) directly serves this need.
- The NLEM includes hydrochlorothiazide, amlodipine, enalapril, losartan, metoprolol and aspirin; Jan Aushadhi Kendras supply these at a fraction of branded cost — pharmacists should proactively offer generic substitution where appropriate.
- Streptokinase remains the workhorse affordable thrombolytic for MI in India; alteplase (costlier) is the stroke-thrombolysis standard — cost and time-window realities shape Indian stroke care, making FAST awareness and rapid hospital transfer vital.
- Rheumatic heart disease → AF → cardioembolic stroke is an Indian-relevant chain linking Chapters 1–4: rate control (digoxin/beta blocker) plus anticoagulation prevents strokes.
- Salt-heavy Indian diets, tobacco, and diabetes multiply hypertension/stroke risk — pharmacist lifestyle counselling (salt, weight, exercise, tobacco cessation) is as important as dispensing.

4.15 Key Points

1. BP = CO × TPR: diuretics/beta blockers ↓ CO; ACE-I/ARBs/CCBs/alpha blockers/vasodilators ↓ TPR.
2. ABCD first-line: ACE-I/ARB, Beta blocker, CCB, Diuretic (thiazide).
3. Thiazides: first-line uncomplicated HTN; watch K^+. Loop: only with HF/renal failure.
4. Prazosin: first-dose syncope — start low, bedtime. Clonidine: rebound HTN if stopped suddenly. Methyldopa: choice in pregnancy.
5. Nitroprusside: IV, ultra-short-acting, hypertensive emergency; cyanide toxicity with prolonged use.
6. Emergency = severe BP + organ damage (IV drugs, controlled lowering); urgency = no organ damage (oral drugs).
7. Shock = organ starvation. Types: hypovolemic, cardiogenic, septic, anaphylactic, neurogenic, obstructive.
8. Shock drugs: fluids FIRST; noradrenaline (septic), dobutamine (cardiogenic pump), adrenaline IM (anaphylaxis), vasopressin + hydrocortisone (refractory septic).
9. Stroke: ischemic (clot ~80%) vs hemorrhagic (bleed ~20%); CT first.
10. Ischemic: thrombolysis within hours + aspirin/clopidogrel + statin. Hemorrhagic: NEVER thrombolytics — they dissolve the sealing clot and worsen bleeding.

4.16 Common Confusions (with Corrections)

1. **Confusion:** Hypertensive urgency needs IV nitroprusside. **Correction:** Urgency = no organ damage → oral drugs; aggressive IV lowering risks brain under-perfusion. Emergency gets IV therapy.
2. **Confusion:** Low BP equals shock. **Correction:** Shock is poor ORGAN PERFUSION (cold/clammy, low urine, confusion); a patient can be in shock with "normal-ish" numbers early (compensated).
3. **Confusion:** Fluids are always safe in shock. **Correction:** Fluids first in most shock, but cautious in cardiogenic shock (broken pump + more fluid = pulmonary oedema).
4. **Confusion:** Aspirin helps hemorrhagic stroke. **Correction:** Antiplatelets/thrombolytics are contraindicated in hemorrhagic stroke — they worsen bleeding.
5. **Confusion:** Beta blockers are first-line for all hypertension. **Correction:** They are preferred with compelling indications (post-MI, HF, angina, AF); thiazides/CCBs/ACE-I are usual first-line in uncomplicated HTN.
6. **Confusion:** Clonidine and prazosin can be stopped abruptly like other BP drugs. **Correction:** Clonidine → rebound hypertension; prazosin → first-dose hypotension needs care at start. Both need tapering/caution, not abrupt changes.

4.17 Common Mistakes (with Corrections)

1. **Mistake:** Giving a thrombolytic without a CT scan in stroke. **Correction:** CT first — if it's hemorrhagic, thrombolysis can be fatal.
2. **Mistake:** Delaying adrenaline in anaphylaxis while arranging IV access. **Correction:** IM adrenaline in the thigh IMMEDIATELY — don't wait for IV.
3. **Mistake:** Lowering BP to normal within minutes in hypertensive emergency. **Correction:** Controlled, gradual reduction — the brain is adapted to high pressure; too-fast drops cause ischemia.
4. **Mistake:** Prescribing ACE-I/ARB to a pregnant hypertensive patient. **Correction:** Foetal harm — use methyldopa (or labetalol).
5. **Mistake:** Using thiazides as the diuretic in hypertensive heart failure with overload. **Correction:** Loop diuretics (furosemide) for HF/renal failure; thiazides for uncomplicated HTN.
6. **Mistake:** Stopping clonidine or beta blockers suddenly. **Correction:** Taper both — rebound hypertension/angina otherwise.

4.18 Mnemonics

1. **HTN classes — "ABCD":** **A**CE-I/ARB, **B**eta blocker, **C**CB, **D**iuretic → "**A** **B**ig **C**lean **D**rain for pressure".
2. **Prazosin:** "**P**razosin = **P**ostural hypotension — **P**illow (bedtime) first dose".
3. **Clonidine:** "**C**lonidine — **C**an't stop suddenly (**C**atastrophic rebound)".
4. **Shock types — "Have Cold Drinks On Nice Afternoons":** **H**ypovolemic, **C**ardiogenic, **D**istributive, **O**bstructive, **N**eurogenic, **A**naphylactic.
5. **Shock drugs:** "**F**luids **F**irst" → "**N**oradrenaline for **N**asty sepsis; **D**obutamine for **D**ead pump; **A**drenaline IM for **A**naphylaxis".
6. **Stroke:** "**FAST** — **F**ace, **A**rms, **S**peech, **T**ime" → "**S**can first, then treat"; "**I**schemic = **I**ntervene (clot-busters); **H**emorrhagic = **H**alt bleeding (no clot-busters)".
7. **Nitroprusside:** "**N**itroprusside = **N**ow (seconds), **N**osocomial-ICU only, **N**ever long (cyanide)".

4.19 Exam Summary

Hypertension (BP = CO × TPR): ABCD classes — thiazides (↓ volume; K^+ loss, gout), ACE-I/ARBs (↓ TPR; cough with ACE-I, hyperkalemia, pregnancy contraindicated), amlodipine (DHP CCB; ankle oedema), beta blockers (↓ CO; compelling indications post-MI/HF), prazosin (alpha-1 block; first-dose syncope; BPH benefit), clonidine/methyldopa (central; rebound with clonidine; methyldopa in pregnancy), hydralazine/minoxidil (direct vasodilators; reflex tachycardia), nitroprusside (IV emergency; cyanide risk). Emergency = organ damage → controlled IV lowering; urgency = oral management. Shock = organ starvation: hypovolemic (fluids), cardiogenic (dobutamine), septic (noradrenaline + fluids + antibiotics; vasopressin, hydrocortisone if refractory), anaphylactic (adrenaline IM), neurogenic (fluids + pressors), obstructive (relieve cause). Stroke: ischemic (~80%, clot → thrombolysis within hours + aspirin/clopidogrel + statin) vs hemorrhagic (~20%, bleed → no thrombolytics ever, BP control, surgery); CT before treatment; "time is brain".

4.20 One-Minute Revision

- HTN: ABCD — ACE/ARB, Beta blocker, CCB, Diuretic. BP = CO × TPR.
- Prazosin: first dose at bedtime. Clonidine: taper, rebound. Methyldopa: pregnancy.
- Emergency (organ damage) → IV nitroprusside, controlled drop. Urgency → oral.
- Shock: fluids first. Septic → noradrenaline. Cardiogenic → dobutamine. Anaphylaxis → adrenaline IM.
- Stroke: FAST → CT → ischemic = clot-busters + aspirin + statin; hemorrhagic = NEVER clot-busters.

4.21 Exam Questions

Short-answer questions:

1. Classify anti-hypertensive drugs with one example each.
2. Explain the ABCD rule with the hemodynamic target of each class.
3. Why are thiazides first-line in uncomplicated hypertension but furosemide is not?
4. What is prazosin's first-dose phenomenon and how is it managed?
5. Why is clonidine never stopped suddenly?
6. Why is methyldopa preferred in pregnancy hypertension?
7. Explain the role of sodium nitroprusside in hypertensive emergency with two cautions.
8. Differentiate hypertensive emergency from urgency with management of each.
9. Define shock and classify its types with one cause each.
10. Why are IV fluids the first step in most shocks but given cautiously in cardiogenic shock?
11. Justify: noradrenaline in septic shock, dobutamine in cardiogenic shock, adrenaline IM in anaphylaxis.
12. What is the role of corticosteroids in septic shock?
13. Differentiate ischemic from hemorrhagic stroke (any four points).
14. Why is thrombolysis contraindicated in hemorrhagic stroke?
15. List the drugs used in ischemic stroke management with their roles.

Long-answer questions:

1. Classify anti-hypertensive drugs. Explain the mechanism, uses and adverse effects of any three classes, including one emergency drug.
2. Define shock. Describe its types with pathophysiology and the drugs used in each type's management.
3. Classify stroke. Explain the drugs used in ischemic stroke and justify why thrombolytics are contraindicated in hemorrhagic stroke.

MCQs (with answer key):

1. First-line diuretic in uncomplicated hypertension:

a) Furosemide b) Hydrochlorothiazide/chlorthalidone c) Spironolactone alone d) Mannitol

2. Prazosin's signature adverse effect:

a) Dry cough b) First-dose postural hypotension/syncope c) Ankle oedema d) Bradycardia

3. Drug of choice for hypertension in pregnancy:

a) Enalapril b) Methyldopa c) Losartan d) Amlodipine

4. Abrupt clonidine withdrawal causes:

a) Rebound hypertension b) Hypoglycemia c) Bradycardia d) Nothing significant

5. IV drug of choice in hypertensive emergency:

a) Oral amlodipine b) Sodium nitroprusside c) Sublingual nifedipine d) IM furosemide

6. Prolonged nitroprusside infusion risks:

a) Hyperkalemia b) Cyanide toxicity c) QT prolongation d) Gynaecomastia

7. Hypertensive urgency is managed with:

a) Aggressive IV BP drop b) Oral drugs and follow-up c) Immediate dialysis d) No treatment

8. First step in hypovolemic shock:

a) Noradrenaline b) IV crystalloids/blood c) Dobutamine d) Adrenaline IM

9. First-line vasopressor in septic shock:

a) Dobutamine b) Noradrenaline c) Adrenaline IM d) Vasopressin alone

10. Inotrope of choice in cardiogenic shock:

a) Noradrenaline b) Dobutamine c) Vasopressin d) Hydrocortisone

11. Immediate drug in anaphylactic shock:

a) IV fluids only b) Adrenaline IM c) Noradrenaline infusion d) Antihistamine tablet

12. Corticosteroids (hydrocortisone) are added in:

a) All shock b) Septic shock refractory to fluids/vasopressors c) Hypovolemic shock d) Neurogenic shock first-line

13. Commonest stroke type:

a) Hemorrhagic b) Ischemic (~80%) c) Equal d) Subarachnoid only

14. Before thrombolysis in stroke, mandatory step:

a) Aspirin loading b) CT scan to exclude bleed c) Statin dose d) Carotid surgery

15. Thrombolysis in hemorrhagic stroke:

a) Recommended b) Absolutely contraindicated — worsens bleeding c) Optional d) Only with aspirin

16. Secondary prevention after ischemic stroke includes:

a) Aspirin/clopidogrel + statin b) Thrombolysis lifelong c) Nitroprusside d) Digoxin

Answers: 1-b, 2-b, 3-b, 4-a, 5-b, 6-b, 7-b, 8-b, 9-b, 10-b, 11-b, 12-b, 13-b, 14-b, 15-b, 16-a

Viva questions:

1. Why is aggressive BP lowering dangerous in hypertensive urgency?
2. A septic shock patient remains hypotensive despite fluids and noradrenaline — what next?
3. Why is adrenaline given IM and not IV in anaphylaxis outside ICU?
4. CT shows a brain bleed in a stroke patient on warfarin — outline immediate drug measures.
5. Why is minoxidil always combined with a beta blocker and diuretic?

Application-based questions:

1. A 58-year-old with BP 170/100, no comorbidities, starts treatment. Design a stepwise regimen per the flowchart and justify the first choice.
2. A pregnant woman (28 weeks) presents with BP 160/105. Choose the drug, justify, and name two drugs you must avoid with reasons.
3. A 70-year-old with pneumonia develops BP 78/48, cold clammy skin, and low urine output despite 2 L crystalloids. Identify the shock type and write the drug plan with rationale.
4. A 62-year-old develops sudden right-sided weakness and slurred speech 90 minutes ago. Outline the emergency steps, the key investigation before drug therapy, and the drug plan for each possible scan result.

4.22 References

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