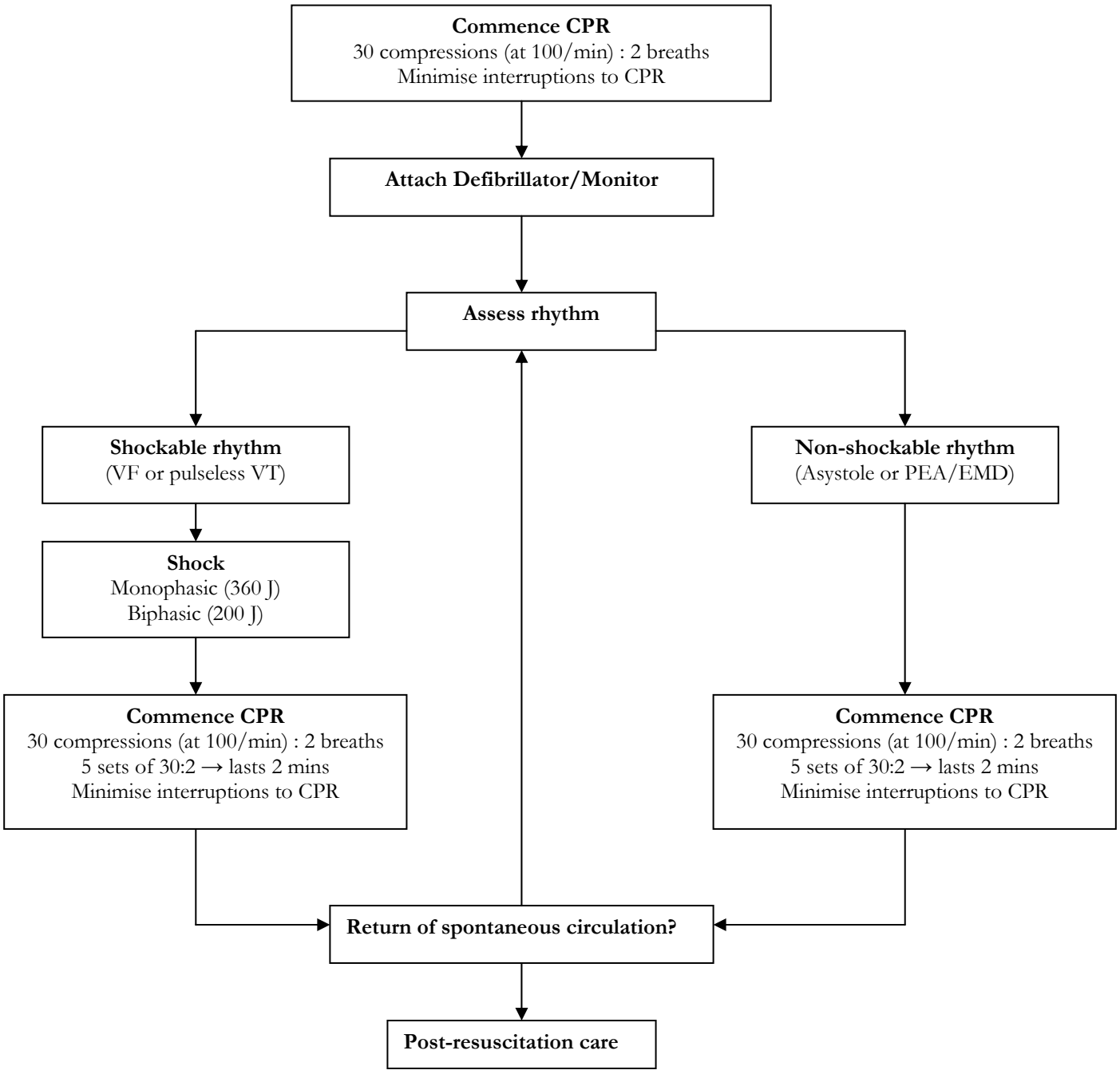
THERAPY OF CARDIAC ARREST, ISCHAEMIA AND FAILURE

(a) ***To describe the international cardiopulmonary resuscitation guidelines.***

(b) ***To describe the role of defibrillation and its potential benefits and risks during cardiac arrest.***

(c) ***To describe the pharmacology of adrenaline, vasopressin, amiodarone and lignocaine with reference to cardiopulmonary resuscitation.***

(I) International Cardiopulmonary Resuscitation Guidelines:



During CPR:
- Give 100% O_2
- Establish IV/IO access
- Secure airway (ETT/LMA) → do not interrupt CPR > 20 secs
- Obtain waveform capnography to confirm AW placement and monitor adequacy of CPR
- Give drugs:
    - Shockable rhythm
        - Vasopressor (adrenaline 1 mg) given during CPR after 2nd failed shock attempt, then during CPR every 2nd loop (every 4 mins)
        - Antiarrhythmic (amiodarone 300 mg) given during CPR after 3rd failed shock attempt
    - Non-shockable rhythm
        - Vasopressor (adrenaline 1 mg) given immediately, then during CPR every 2nd loop

Determine potential causes (4 H's and 4 T's):
- Hypoxaemia
- Hypovolaemia
- Hyper/hypokalaemia & metabolic disorders
- Hypo/hyperthermia
- Tension PTX
- Tamponade
- Toxins/drugs
- Thrombosis (PE/Coronary)

Post-resuscitation care:
- Re-evaluate ABCDE
- 12 lead ECG
- Treat precipitating causes
- Re-evaluate oxygenation and ventilation
- Temperature control (cool)

(II) <u>Role of defibrillation during cardiac arrest:</u>
- Indications for defibrillation – VF and pulseless VT
- Single shock is given:
    - Biphasic defibrillator → 200 J for all shocks
    - Monophasic defibrillator → 360 J (max energy) for all shocks
- Mechanism of action – Defibrillation shock applied through chest produces simultaneous depolarisation of a mass of myocardial cells (esp SA node) → enable resumption of organised electrical activity (as normal sinus rhythm)
- Note – ↑ success of defibrillation is a/w (i) Good CPR and (ii) Early defibrillation

(III) <u>Drugs used during cardiac arrest</u>:

Note – Route of drug administration:
- (1) IV → preferred route
    - Peripheral IVC → quick and easy to establish (but slower drug delivery and risk of tissue extravasation)
    - CVC → preferred due to more rapid drug delivery (but insertion takes time and has risks)
- (2) I/O → alternate to IV → produces similar plasma [drug]
- (3) ETT
    - Absorption is variable → plasma [drug] is ↓ cf. IV/IO (need 3-10x ↑ dose)
    - Useful for certain drugs only (adrenaline, lignocaine, atropine) → other drugs cause mucosal/alveolar damage

(1) Adrenaline:
- Class – Naturally-occurring catecholamine
- Indications:
    - (i) VF/pulseless VT (during CPR after failed 2nd shock attempt, then during CPR every 2nd loop)
    - (ii) Asystole and PEA (immediately, then during CPR every 2nd loop)
- Mechanism of action:

    - Direct-acting sympathomimetic agent with equal agonist effects on α and β receptors
    - During cardiac arrest it causes α-mediated peripheral vasoconstriction that redirects available C.O. to myocardium and brain. Also facilitates defibrillation by improving myocardial blood flow during CPR
- Dosage:
    - 1 mg (1 mL of 1:1,000 or 10 mL of 1:10,000) every 2nd loop during CPR
    - Repeated smaller doses or IVI (1-20 mcg/min) to produce adequate BP after ROSC
- Issues:
    - (i) Tachyarrhythmias and severe HTN post-resuscitation
    - (ii) Tissue necrosis if extravasation occurs → thus, requires CVC insertion

(2) Amiodarone:
- Class – Class III anti-arrhythmic agent (as a iodinated benzofurane derivative)
- Indications:
    - (i) VF/pulseless VT (during CPR when arrest refractory to 3rd shock attempt and vasopressor)
    - (ii) Prophylaxis against recurrent VF/VT
- Mechanism of action:
    - (i) Mainly a class III anti-arrhythmic effect → blocks K^+ channel
    - (ii) Also has class I (Na^+ blockade), class II (β-blockade) and class IV (CCB) effect
    - (iii) Antiadrenergic effect → non-competitive inhibition of α and β receptors
- Dosage – 300 mg bolus (+/- 150 mg bolus +/- 15 mg/kg infusion over 24 hrs)
- Issues:
    - (i) Hypotension
    - (ii) Bradycardia, heart block and even sinus arrest
    - (iii) Prolong QTc → Torsades de Pointes

(3) Lignocaine:
- Class – Class IB agent (as an amide LA agent)
- Indications – Used in situations where amiodarone cannot be used
- Mechanism of action – Inhibit fast Na^+ channels (mild potency)
- Dosage – 1 mg/kg bolus (+/- 0.5 mg/kg bolus). Infusion not recommended until ROSC
- Issues:
    - CNS toxicity
        - Excitatory symptoms initially → circumoral tingling, dizziness, tinnitus, paraesthesia, irritation/agitation, then seizures
        - Depressive symptoms later → CNS depression, confusion, apnoea, coma
    - CVS toxicity
        - Bradycardia, AV heart block and even asystole
        - Unresponsive hypotension

(4) Vasopressin:
- Class – ADH (peptide hormone)
- Indications – Alternative vasopressor to adrenaline
- Mechanism of action – At high doses → (i) V1R-mediated (Gq) peripheral vasoconstriction that redirects available C.O. to myocardium and brain, and (ii) acts synergistically with catecholamines
- Dosage – 40 units bolus
- Issues – Severe HTN post-resuscitation

(5) $NaHCO_3$:
- Class – Alkalinising solution

- Indications – Routine use for cardiac arrest not recommended (esp if early and efficient CPR and adequate ventilation instituted) → consider use with ↑ K^+, metabolic acidosis, TCA OD, protracted cardiac arrest (> 15 mins)
- Mechanism of action – HCO_3^- combines with H^+ to form H_2CO_3 → dissociates into CO_2 and H_2O
- Dosage – 1 mmol/kg (over 2-3 mins), guided as per ABG
- Issues:
    - Metabolic alkalosis (and IC acidosis due to CO_2 liberated from HCO_3^-)
    - Electrolyte imbalance – ↓ K^+ and ↑ Na^+
    - ↑ osmolality
    - Blocks IV lines → precipitates with adrenaline and Ca^{2+}

(6) Magnesium:
- Mechanism of action – Not entirely clear. It is an electrolyte vital for membrane stability (Ie. ↓ Mg^{2+} → hyperexcitable membrane causing arrhythmias)
- Indications:
    - (i) Torsades de pointes
    - (ii) Cardiac arrest a/w digoxin toxicity
    - (iii) VF/ pulseless VT (refractory to defibrillator shocks and vasopressor)
    - (iv) ↓ K^+ and/or ↓ Mg^{2+}
- Dosage – 5 mmol bolus, repeated once and then infuse 20 mmol over 4 hrs
- Issues:
    - Muscle weakness (and respiratory failure)
    - Hypotension
    - Somnolence and CNS depression

(d) ***To describe the pharmacology of drugs used to manage myocardial ischaemia/infarction with particular reference to nitrates, beta blockers, calcium antagonists, anti-platelet agents, anti-coagulants and fibrinolytic agents.***

Myocardial ischaemia → occurs when there is inadequate myocardial O_2 supply to meet myocardial O_2 demand → thus, the aim of treatment is to:

- (i) ↑ O_2 myocardial supply by ↑ coronary blood flow (as heart already has ↑ extraction ratio) → either (i) ↑ coronary perfusion pressure (≈ ↑ aortic diastolic pressure) and/or (ii) ↑ diastolic perfusion time of coronary arteries (Ie. ↓ HR)
- (ii) ↓ O_2 myocardial demand → either (i) ↓ HR and/or (ii) ↓ myocardial contractility

Drugs used to treat myocardial ischaemia/infarction:

(1) Nitrates
- Class: Organic nitrate
- Mechanism of action:
  - NO liberated from GTN via a thiol-dependent pathway (nitrate reductase – 1°ly in liver, but also in vascular SM cells)
  - NO → activates guanylyl cyclase in VSMC 1°ly in veins (> arterioles) → ↑ IC [cGMP] → cGMP activates protein kinases → cause ↓ IC [Ca^{2+}] (by ↓ Ca^{2+} influx and ↑ Ca^{2+} sequestration in SER) → relaxes venous VSMC (> arteriolar VSMC) → 1°ly veno-dilation (> arteriolar vasodilation)
- Effect on myocardial O_2 supply/demand:
  - ↑ O_2 supply – ↑ blood flow to subendocardial tissue (2° to large coronary artery vasodilation), without a coronary steal effect
  - ↓ O_2 demand – ↓ wall tension due to (i) ↓ preload/LVEDP (2° to venodilation) and (ii) ↓ afterload (2° to arteriolar vasodilation)
- Issues:
  - Headaches
  - Facial flushing
  - Hypotension with reflex tachycardia
  - Tolerance (esp with > 24 hrs of continuous treatment

(2) Beta-blockers
- Class: β1 selective agents (Eg. metoprolol, atenolol, esmolol)
- Mechanism of action:
  - Bind selectively and competitively to cardiac β1-adrenergic receptors (GPCR – Gs) → inhibit catecholamines or other sympathomimetics from provoking a response → thus, ↓ activation of adenylyl cyclase → ↓ cAMP and PKA activation
  - Causes – (i) ↓ myocardial contractility, and (ii) ↓ SAN/AVN activity
- Effect on myocardial O_2 supply/demand:
  - ↑ O_2 supply – ↑ diastolic perfusion time of coronary arteries due to ↓ HR
  - ↓ O_2 demand – ↓ HR and ↓ myocardial contractility
- Issues:
  - Acute HF/cardiogenic shock
  - Severe bradycardia and bradyarrhythmias
  - Hypotension
  - CNS effects (depression, nightmare, lethargy)
  - Masks symptoms of ↓ BGL
  - Loss of β1 selectivity at high doses → unwanted β2 effects (↓ BGL, bronchospasms, peripheral vasoconstriction, GI effects)
  - Withdrawal syndrome if ceased abruptly with chronic use (rebound HTN, tachycardia, arrhythmias, myocardial ischaemia)

(3) Calcium antagonists
- Class: Verapamil (class I – phenylalkylamine) or Diltiazem (class III – benzothiazepine)

- Mechanism of action:
    - Inhibit L-type Ca^{2+} channels (binds to cytoplasmic aspect of channel (esp when in opened state during depolarisation) and maintains it in a close/inactivated state) → ↓ Ca^{2+} influx → ↓ IC [Ca^{2+}]
    - Causes – (i) ↓ myocardial contractility, (ii) relaxation of arteriolar SM cells, and (iii) ↓ SAN/AVN activity
- Effect on myocardial O_2 supply/demand:
    - ↑ O_2 supply – (i) ↑ diastolic filling time due to ↓ HR, and (ii) Coronary artery vasodilation
    - ↓ O_2 demand – (i) ↓ contractility, (ii) ↓ HR, and (iii) ↓ afterload (2° to arteriolar vasodilation)
- Issues:
    - Headaches
    - Flushing
    - Peripheral oedema
    - Hypotension
    - Bradycardia and bradyarrhythmias
    - N/V

Note:
- Clinical effects and potential for adverse effects are SYNERGISTIC with each of these agents listed above
- Above agents can worsen myocardial ischaemia due to either (i) hypotension (↓ coronary perfusion pressure → ↓ O_2 supply), and/or (ii) tachycardia (↓ diastolic perfusion time → ↓ O_2 supply; also ↑ O_2 demand)

(4) Anti-platelet agents (See "Drugs and coagulation")

(5) Anti-coagulants (See "Drugs and coagulation")

(6) Fibrinolytic agents (See "Drugs and coagulation")

(e) ***To describe the pharmacology of drugs used to manage acute or chronic cardiac failure with particular reference to sympathomimetics, phosphodiesterase inhibitors, digoxin, diuretics, ACE inhibitors, nitrates and beta blockers.***

(I) Inotropes:

> Inotrope → drug that alters the force of contraction of cardiac muscle without changing the preload or afterload
>
> Nb. +ve inotrope ↑ cardiac contractility; -ve inotrope ↓ cardiac contractility

(1) Sympathomimetics (see "Pharmacology of autonomic nervous system"):
- Includes:
  - (i) Catecholamines (natural – Adr, NAd, DA; synthetic – Isoprenaline, dobutamine, dopexamine)
  - (ii) Synthetic noncatecholamines (Ephedrine, metaraminol)
- Mechanism of action – Directly and/or indirect exert agonist activity at cardiac β1 receptor → via Gs mechanism (↑ IC cAMP) → ↑ IC [Ca^{2+}] → +ve inotropy

(2) Phosphodiesterase inhibitors (PDEi):
- (a) Selective PDEi
  - Types:
    - (i) Bipyridine derivatives (Amrinone, Milrinone)
    - (ii) Imidazole derivatives (Enoximone)
  - Clinical uses – Short-term management of acute LVF (esp those who are refractory to catecholamines or β-blocked):
    - ↑ C.O. due to "inodilator" effect → +ve inotropy (↑ myocardial contractility) and vasodilation (↓ afterload)
    - Acts synergistically with catecholamines independently of β-adrenoceptor effect (as these agents also ↑ IC [cAMP])
  - Mechanism of action – Competitive inhibition of PDE III → ↓ hydrolysis of cAMP and cGMP → ↑ IC [ ] cAMP and cGMP → activates protein kinases
    - Within myocardium → PDE III inhibition results in ↑ slow-inward Ca^{2+} current → ↑ Ca^{2+} for contractile element activation AND ↑ diastolic relaxation (enhance Ca^{2+} removal from myoplasm) → +ve inotropy
    - Within vascular SM → PDE III inhibition results in ↓ slow-inward Ca^{2+} current → vasodilation
  - Pharmacokinetics:

	Amrinone	Milrinone	Enoximone
Absorption	IV (bolus, then infusion) or PO	IV (bolus, then infusion) or PO	IV only (due to significant hepatic first-pass metabolism)
Metabolism and elimination	Renal excretion (40%) → elimination t ½ 6 hrs	Renal excretion (80%) → elimination t ½ 3 hrs	Hepatic metabolism to an active metabolite (10% activity but longer t ½ of 8 hrs → renally excreted) Elimination t ½ 5 hrs

  - CVS effects – All agents have the following effects:
    - ↑ C.O. due to ↑ SV (↑ contractility) → ↓ LV EDP
    - ↑ HR
    - ↓ SBP (due to vasodilator effect)
    - Lack anti- or pro-arrhythmic effects
    - Cardiac MRO_2 extraction ratio unchanged (due to ↓ ventricular wall tension and ↑ coronary perfusion 2° to coronary vasodilation)

- Issues:
  - All have ↑ therapeutic indices cf. cardiac glycosides (100:1 vs 1.2:1) → side-effects include hypotension (due to vasodilation), thrombocytopaenia (with chronic therapy) and hepatic dysfunction (with chronic therapy)
  - Chronic oral milrinone for severe CHF is a/w ↑ morbidity/mortality
  - Severe renal dysfunction warrants dose reduction (due to renal clearance)

- (b) Non-selective PDEi (Eg. Aminophylline)
  - A methylxanthine derivative → comprises of a complex of 80% theophylline and 20% ethylenediamine (used to ↑ solubility of theophylline)
  - Clinical uses:
    - (i) Treat bronchospasm a/w acute asthma exacerbation refractory to β2-agonists and steroids (Nb. acts synergistically with β2 agonists)
    - (ii) Treat LVF (rarely)
  - Mechanism of action:
    - (i) Non-selective inhibition of all PDE isoenzymes (I-V) → ↓ hydrolysis of cAMP and cGMP → ↑ IC [ ] of cAMP and cGMP → this causes:
      - ↑ Ca^{2+} entry into myocardium → +ve inotropy
      - ↓ Ca^{2+} entry into smooth muscle → vasodilation and bronchodilation
    - (ii) Directly releases NAd from SNS neurons to act on adrenoceptors (of which it acts synergistically with as they both ↑ IC [cAMP])
    - (iii) Competitive inhibition of adenosine receptors
  - Pharmacokinetics:

Absorption	PO (good GIT absorption with > 90% bioavailability) and IV
Metabolism and elimination	- Hepatic CYP450 metabolism (90%) and renal excretion (10%) → Elimination t ½ 9 hrs - Clearance ↑ with smoking and CYP450 induction (phenytoin, carbamazepine, rifampicin, barbiturates) - Clearance ↓ with CYP450 inhibition (cimetidine, erythromycin, OCP)

  - Pharmacodynamic effects:

CVS	- Mild +ve ino- and chronotropy - Coronary and peripheral vasodilation
Respiratory	- Bronchodilation - ↑ respiratory centre sensitivity to CO_2
CNS	CNS stimulant
Renal	Weak diuretic due to natriuretic effect (inhibits tubular Na^+ reabsorption)
Issues and side-effects	- Narrow therapeutic index → therapeutic plasma [ ] ~ 10-20 ug/mL, while toxic plasma [ ] > 35 ug/mL (as CYP450 is saturated and metabolism transforms from 1st to zero-order kinetics) - Toxicity: - CVS toxicity – Tachyarrhythmias, such as VF (esp with halothane) - CNS toxicity – Tremor, insomnia and seizures - Rhabdomyolysis - N/V - Gastro-oesophageal reflux (relaxes LOS) - Can cross placenta to cause toxicity - Thus requires frequent plasma [ ] monitoring due to variations in its clearance (see above)

(3) Digoxin (see "Anti-arrhythmic drugs")
- Cardiac glycoside extracted from the leaves of foxglove plant → steroid cyclopentenophenanthrene nucleus with a:

    - (i) Glycone portion (pharmacologically inactive) → a sugar (often glucose) that fixes drug to cardiac muscle
    - (ii) Aglycone portion (pharmacologically active) → exerts drug activity
- Clinical uses:
    - (i) Treat chronic low-output HF → weak +ve inotrope that improves symptoms and LV performance (↑ C.O.)
    - (ii) Treat acute ↓ LVF → rarely used b/c ↑ death from sudden cardiac death due to arrhythmias (despite ↓ mortality from HF), and other more potent and less toxic agents available
    - (iii) Ideal rate control agent for AF in pts with HF → ↓ HR 2° to slowed AVN conduction improves diastolic coronary perfusion and ventricular filling
- Mechanism of action:
    - (1) Direct effects on heart
        - Reversible inhibition of Na^+/K^+ ATPase in sarcolemma of cardiac cell membrane → binds extracellular α-subunit → induces conformational change that interferes with outward Na^+ and inward K^+ transport → results in ↑ $[Na^+]_{IC}$ and ↓ $[K^+]_{IC}$
        - ↑ $[Na^+]_{IC}$ causes ↓ Ca^{2+} extrusion across a Na^+/Ca^{2+} exchanger → ↑ $[Ca^{2+}]_{IC}$ → results in +ve inotropy and ↑ force of contraction
        - ↓ $[K^+]_{IC}$ causes – (i) ↑ effective refractory period of AVN → slowed conduction rate through AVN → ↓ HR, and (ii) ↑ automaticity (excitability)
    - (2) Alters ANS activity
        - Digoxin activates vagal nuclei centrally and sensitises arterial baroreceptor → ↑ PNS activity (↑ ACh effect on cardiac mAChR)
        - Causes – (i) ↓ SAN activity, and (ii) prolongs effective refractory period of AVN and slow conduction through it → both causes ↓ HR
- Pharmacodynamics:
    - CVS effects:
        - Dose-dependent ↑ myocardial contractility → ↑ SV → ↑ C.O.
        - Blunts excess SNS a/w compensatory response to HF → ↓ SVR → ↓ afterload → ↑ C.O.
        - Vagotonic effect, ↓ SAN discharge, ↓ AVN conduction → ↓ HR
    - Renal effects
        - ↑ RBF/GFR due to ↑ C.O. → ↑ diuresis

Important to note → ECG features of digoxin:
- Prolonged PR interval (delayed conduction through AVN)
- Shortened QTc interval (more rapid ventricular repolarisation)
- Scaphoid ST segment depression (decreased slope of phase 3)
- Flattening or inversion of T-waves

Nb. They do NOT suggest toxicity → they disappear 3 weeks after digoxin is ceased

- Digoxin toxicity → digoxin has a very narrow therapeutic index → toxicity occurs in 20% of patients:
    - GI symptoms – Anorexia, N/V, diarrhoea, abdominal pain
    - CNS symptoms – Visual disturbances (deranged red-green colour perception), headaches, confusion, drowsiness, muscle weakness
    - CVS symptoms – Any arrhythmia can occur, although atrial tachycardia with block is more common, while death is usually a/w VF
        - ↑ automaticity – PVBs, atrial and ventricular tachycardias, bigemini, Etc.
        - Delayed AVN conduction – Junctional rhythm and AV heart block
        - Sinus arrest (at high doses) due to SAN block by vagal tone

- Others: Skin rash and gynaecomastia are rare

> Note – Plasma digoxin levels usually 0.5-2.5 ng/mL → toxic if > 3 ng/mL (BUT symptoms can occur below this toxic levels, esp when risk factors are present)

(4) Myofilament calcium sensitizers (Eg. levosimendan):
- Mechanism of +ve inotropy – ↑ myocardial contractility due to enhanced myofilament contractile response (Ie. prolonged actin-myosin interaction) to Ca^{2+}, INDEPENDENT of IC [ ] of Ca^{2+} or cAMP

(5) Glucagon:
- Overview – Polypeptide hormone secreted from pancreatic α-cells
- Clinical use – Limited role in treating LVF. Mainly used to ↑ HR/contractility in setting of β-blocker overdose. Only given IV (as it is a peptide)
- Mechanism of action:
  - (i) Acts on glucagon receptors (GPCR; Gs) → ↑ AC and IC cAMP → ↑ Ca^{2+}
  - (ii) Also evokes release of catecholamines
- CVS effect:
  - ↑ C.O. (due to ↑ SV and HR)
  - ↑ MAP (due to ↑ C.O.)
  - SVR unchanged or ↓
  - ↑ automaticity of SAN/AVN
- Side-effects – ↑ BGL, ↓ K^+, systemic HT (due to catecholamine release), N/V

(6) Calcium (as 10% CaCl or Ca gluconate)
- Clinical use – Treat circulatory collapse due to CCB overdose, ↑ K^+ or ↓ Ca^{2+}
- Mechanism of action – ↑ IC [Ca^{2+}]
- IV Ca^{2+} produces intense +ve inotropy and ↑ BP for short period of time (10-20 mins):
  - ↑ C.O. (due to ↑ SV a/w ↑ contractility) → ↓ LV EDP
  - ↑ BP (due to ↑ C.O.)
  - ↓ HR and SVR
- Issues – Cardiac arrhythmias (esp in those on digoxin and ↓ K^+)

(7) T3/T4:
- +ve ino- and chrono-tropic effects due to IC mechanisms

(II) <u>Other drugs used to treat heart failure</u>:

(1) Diuretics (see "Diuretics"):

Class	MOA	Use in heart failure	Issues and notable points
Thiazide (HCT, indapamide)	Inhibits Na^+/Cl^- cotransporter in early DCT and cortical portion of TAL of LoH → ↓ Na^+ (and H_2O) reabsorption	All diuretics cause ↓ ECFV (and intravascular	- Requires good renal function - Metabolic alkalosis - ↑ BGL, TAG, cholesterol and urate - ↓ BP 2° hypovolaemia - ↓ Na^+, Cl^-, K^+, Mg^{2+}, Ca^{2+} → arrhythmias
Loop diuretics (Frusemide)	Inhibit NKCCT co-transporter in medullary portion of TAL of LOH → ↓ Na^+, K^+ and Cl^- reabsorption → ↓ medullary hypertonicity		- Potent diuretic ideal to treat APO - Similar side-effects as thiazides → but also nephro- and oto-toxicity

	→ impairs CCM → ↓ H_2O reabsorbed in CD	volume) → ↓ preload	
Aldosterone antagonists (Spironolactone)	Binds to cytoplasmic mineralocorticoid receptor at principal cell of CD/DCT → competitive antagonist to aldosterone → ↓ Na^+ (and H_2O) reabsorption		- Used in severe LVF → improves LV remodelling (esp post-MI) → ↓ mortality - Issue with ↑ K^+

(2) ACE inhibitors (see "Anti-hypertensive drugs"):
- Types:
  - Group 1 (Captopril) – Active drug that is metabolised into active metabolites
  - Group 2 (Enalopril, Rampiril) – Prodrug that increases oral bioavailability prior to activation by hepatic metabolism to a diacid moiety
  - Group 3 (Lisinopril) – Active drug that is not metabolised and excreted unchanged in urine
- Mechanism of action:
  - Competitive inhibitor of ACE in pulmonary endothelium causes ↓ conversion of AI to AII → ↓ activation of AII receptor (AT_1 subtype – Gq mechanism)
  - Results in – ↓ vasoconstriction, ↓ aldosterone release (from adrenal cortex), ↓ Na^+/H_2O retention, ↓ SNS activation, and ↓ thirst
- Use in heart failure:
  - (i) ↓ afterload (due to ↓ SVR)
  - (ii) ↓ preload (due to ↓ intravascular volume)
  - (iii) Remodelling myocardium in LVF (esp a/w MI) → causes LVH to regress → improves LV function and survival
- Issues – Angiooedema and dry cough (due to bradykinin), ARF, ↑ K^+, and hypotension

(3) Nitrates (see "Anti-hypertensive drugs"):
- Mechanism of action:
  - NO is liberated from GTN via a thiol-dependent pathway involving nitrate reductase → occurs 1°ly in the liver, but also in vascular SM cells
  - NO then activates guanylyl cyclase in VSMC 1°ly in veins (> arterioles) → ↑ IC [cGMP] by converting GTP to cGMP → cGMP activates various protein kinases that cause ↓ IC [Ca^{2+}] by ↓ Ca^{2+} influx into VSMC and ↑ sequestration of Ca^{2+} in SER → results in relaxation of VSMC → 1°ly veno-dilation (> arteriolar vasodilation)
- Use in heart failure – ↓ preload (due to venodilation)
- Issues:
  - (i) Tolerance if used > 24-48 hrs (due to depletion of thiol/sulphydryl groups within vascular SM cells)
  - (ii) Side-effects – Headache, facial flushing, postural hypotension (a/w reflex tachycardia and syncope), and rarely methaemoglobinaemia

(4) Beta blockers (see "Adrenoceptor blocking agents"):
- Type – Cardioselective (β1-selective) β-blockers (Eg. metoprolol, carvedilol, atenolol)
- Mechanism of action – Bind selectively to β1-adrenergic receptors → competitively inhibit catecholamines or other sympathomimetics from provoking a β1 response → thus, inhibits Gs response (↓ AC activation → ↓ IC cAMP)
- Use in heart failure
  - (i) Favours myocardial O_2 supply > demand → ↑ O_2 supply (due to ↑ diastolic perfusion time of coronary arteries due to ↓ HR) and ↓ O_2 demand (due to ↓ -ve ino- and chronotropic effects) → ↓ myocardial ischaemia/infarction
  - (ii) ↓ renin release from JGA → ↓ AII and aldosterone production → ↓ myocardial remodelling → ↑ LVEF and survival

    - (iii) ↓ catecholamine-induced arrhythmias a/w sudden cardiac death
- Issues:
    - (i) Dose-dependent loss of β1 selectivity → unwanted β2 antagonist effects
    - (ii) –ve inotropy (can ppt LVF) and –ve chronotropy (severe bradycardia)
    - (iii) CNS symptoms (depression, lethargy, nightmares)
    - (iv) Abrupt cessation of chronic therapy → rebound HTN, myocardial ischaemia and arrhythmias