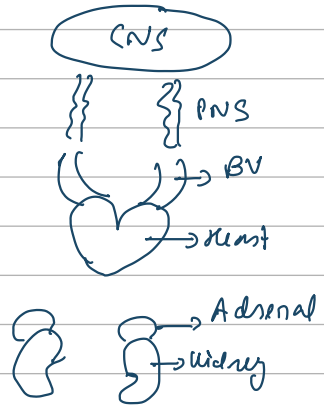
Cardiovascular system

1) DRUGS ACTING ON RAAS

↓BP, ↓BV, ↑ NaCl loss → ↓ renal perfusion → ↑ Renin → AT-I ↑ → AT-II ↑

Angiotensin - II : Achieves

↓BP, BV ↓, NaCl loss ↑ — Renin inhibitors, ARB, ACE



Opposite of these actions → Captopril

i) BV → VC ⟹ ↑ BP

ii) Heart → ↑ OC ↑, rate ↑, HR, BP ↑ — CO ↓ → ↑ vessel wall intimal thickening ← hypertrophy & hyperplasia

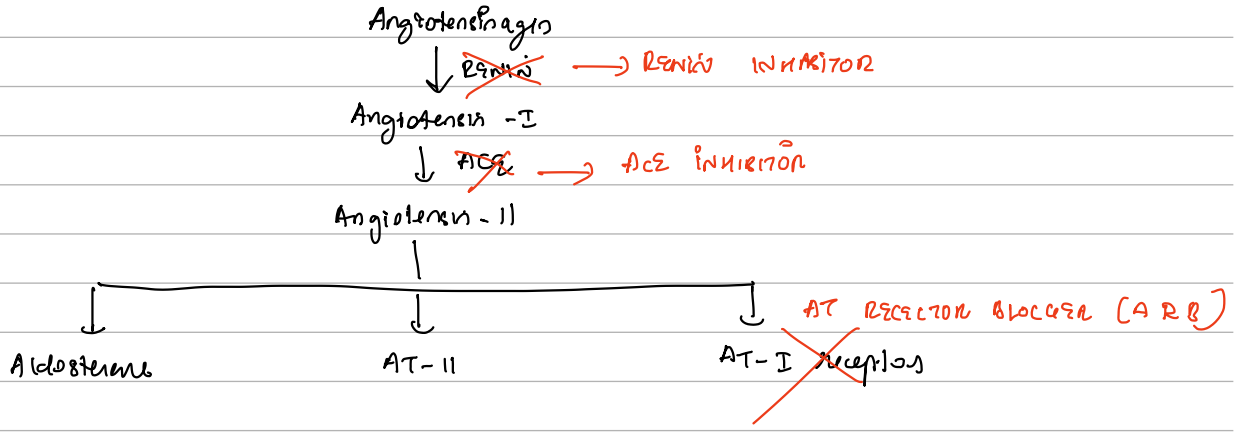
iii) Kidney → Na & H_2O retention ∴ BV ↑ (Direct effect) ← Aldosterone ↑ (Indirect effect)

iv) Adrenal cortex → Na & H_2O retention ← Aldosterone ↑

v) CNS & thirst ↑ → water ↑ → volume ↑

vi) PNS : Sympathetic stimulation → ↑BP

Inhibition of RAAS

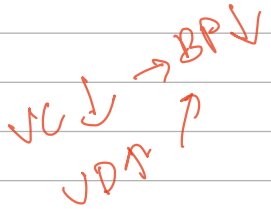


- Inhibition of ACE

Captopril (C)	Enalapril (E)	Lisinopril (L)	Perindopril (P)	Ramipril (R)	Fosinopril (F)
Sulfhydryl	Carboxy	Carboxy	Carboxy	Carboxy	Sulfhydryl
Active	Prodrug	Active	Prodrug	Prodrug	Prodrug
BA max		BA min			
Renal	Renal	Renal	Renal	Renal	Renal

CAPTOPRIL

- Ang-I ⟶ Ang-II
- MOA → ACE ↓ → Ang-II ↓ → VC ↓ VDT → BP ↓



* Postural hypotension is not a problem
* 1st dose hypotension may occur → for 1 week ½ dose
  then → 1 dose

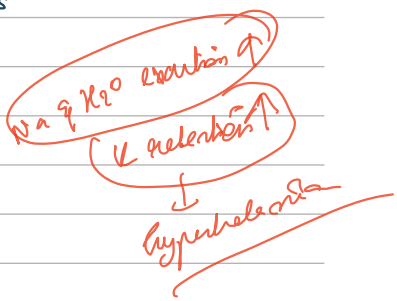
PK

- Orally – BA max → food interferes

USES

H M Paraplegia Cap definitely stop

- H → Hypertension → 1st line drug
- M → MI
- Paraplegia → Prophylaxis in high CVS risk
- Cap → CHF
- definitely → diabetic nephropathy
- stop → Scleroderma crisis



ADR: C A P T O P R I L

- Cough
- Angioneurotic edema
- Proteinuria
- Taste disturbances
- Others (fatigue, nausea)
- Potassium ↑
- Renal impairment
- Itch
- Low BP

CI: P A R K

- Pregnancy
- Allergy
- Renal artery stenosis
- K ↑ – hyperkalemia

Angiotensin receptor blockers (ARB) - sartans

LOSARTAN

- Selectively AT_1 blocker
- VC, sympathetic stimulation, Aldosterone release, H_2O & Na retention, Renin growth promoting action of heart & BV → all blocked

all blocked
renin action

PK

- not affected by food
- Carboxylated in liver to active metabolite
- t/2 : 2 hr

USE

HT, CHF, MI, DN

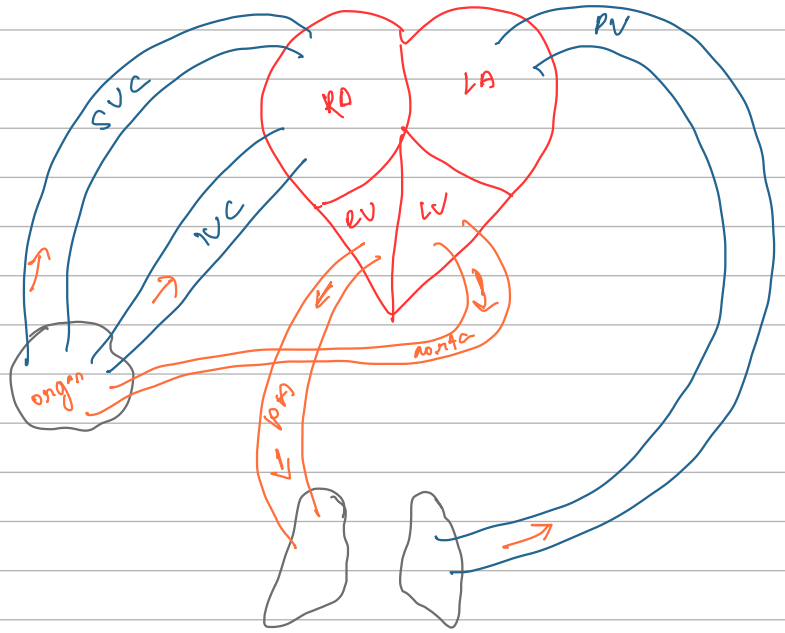
ADR

Hypotension, hyperkalemia, free of cough, Angioedema, Headache, dizziness, weakness

H^3ADW

2) HEART FAILURE DRUGS

BAVRID



Preload ∝ venous return (blood comes from SVC & IVC) → depends on veins

Afterload ∝ blood going to aorta (∴ VC/VD of aorta - depends on afterload)

Rt HF → edema of all organs

Lt HF → Pulmonary edema

BAVRID

BAVI DR

Drugs for CHF → goal : BV & BP ↓

- (↑ contractility) Ionotropic drugs
  - Cardiac glycosides: Digoxin, Ouabain
  - Sympathomimetics: Dobutamine, Dopamine
  - PDE-3 inhibitors (↓BP & ↓BV)
- Diuretics (↓BV)
  - High ceiling: Furosemide
  - Thiazide like
- RAAS inhibitors
  - ACE inhibitors (Cpril)
  - AR B inhibitors (Sartan)
- Vasodilators (↓AL & ↓PL)
  - Venodilators: GTN
  - Arteriodilators
  - Vaso-arteriodilators
- (↓BV) Aldosterone antagonists: Spironolactone
- β-blockers (inhibit renin ∴ ↓BV): Carvedilol, Nebivolol

PDE3 inhibitors :

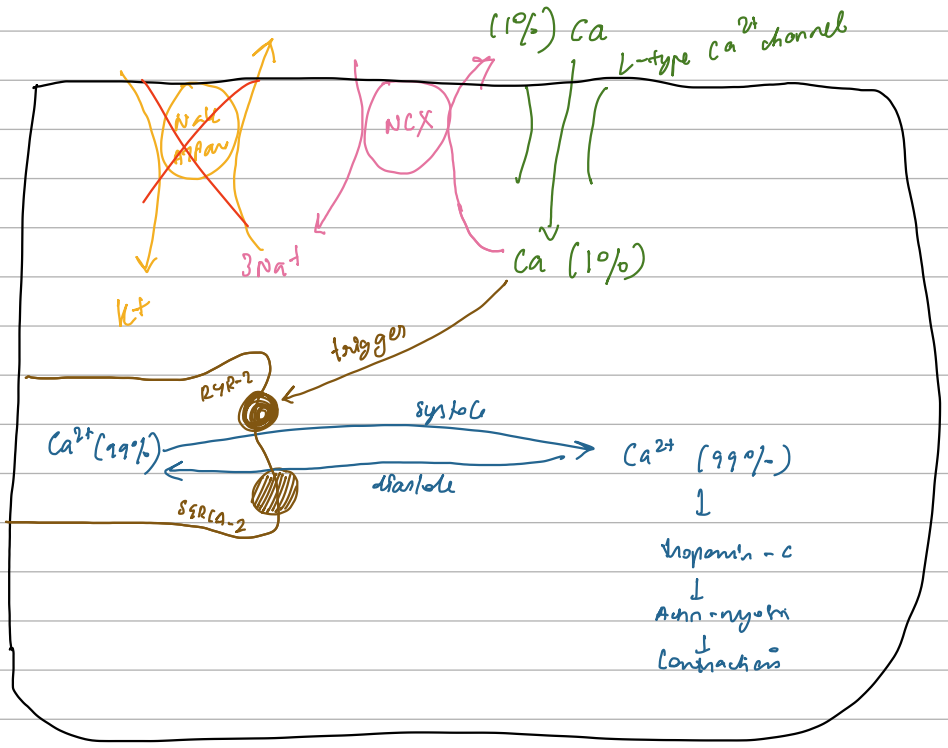
Normally, cAMP – activates protein kinase A → phosphorylates L-type Ca channels – ↑Ca influx ↑ cardiac contractility ↑

PDE3 degrades cAMP normally, but due to the inhibitor ↑cAMP ↑ ∴ phosphorylation ↑

Digoxin

- Cardiac ionotropic drugs
- ↑ output & contractility in a hypodynamic heart
- Digoxin, digitoxin, Ouabain

MoA



Digitalis binds to Na+-K+-ATPase of myocardial fibres

↓

Inhibits the transporter

↓

Accumulation of Na+ intracellularly ↑

↓

∴ More Na+ not req in cell

↓

∴ Ca^{2+} is not extruded out (NCX)

↓

↑ Ca^{2+} intracellularly — triggers

↓

further ↑ in Ca release from SR (RYR 2)

↓

Ca binds to troponin

↓

Actin - myosin

↓

Contraction

Delayed action of digitalis : Binding to Na-K-ATPase is slow & Ca^{2+} rises gradually only

* Hypokalemia causes digitalis toxicity
* Hypercalemia causes " "

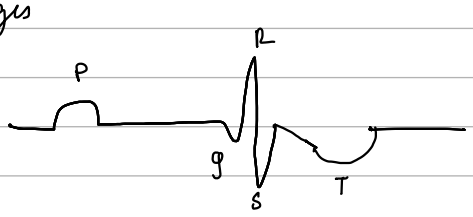
PHARMACOLOGICAL ACTIONS :

i) Heart
- ↑ FOC ✓
- ↑ excitability ✓
- ↓ HR (Bradycardia) ✓

HR ↓

Digitalis
↓
Stimulation of vagal centre & direct depressant action on SA & AV nodi
↓
↓ AV conduction
↓
Bradycardia

- ECG changes



PR interval ↑
QT interval ↓
ST segment depression
T wave inversion

ii) Blood vessels
- Weak direct VC effect

iii) Kidney
- Diuretic → ↑ urine output

iv) CNS
- Nausea & vomiting

PK
- IV/ oral
- Renal excretion

USES
- CHF
- Arrythmias (due to bradycardia)

ADR

- Digitalis toxicity
- extracardiac ⇒ Anorexia, vomiting, nausea, abdominal pain, headache, fatigue, confusion, restlessness, disorientation
- cardiac ⇒ Arrythmia
  - tachyarrythmia
  - ventricular arrythmia
  - supraventricular arrythmias
  - AV block & bradycardia

CI ⇒ Contraindicated in weak heart

Contra - cardiac

Indicated - ↑ Ca

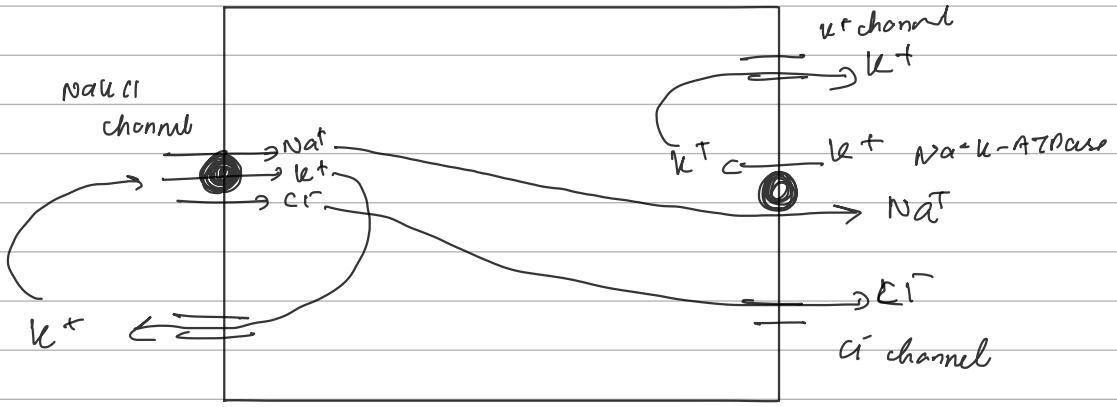
Weak - WPW syndrome

H - Hypokalemia

E - elderly

A - AV block

R - Renal failure



Diuretics (BV ↓)

High ceiling (Na+ K+ 2Cl- inhibitor)
→ furosemide

Medium efficacy (Na+ Cl- inhibitor)
- Thiazide
- Thiazide like

weak diuretic
- carbonic anhydrase inhibitor
- K-sparing diuretics
- Osmotic diuretic

Rationale for using nitrates

Preload ↓ >> ↓ O_2 demand → useful in stable angina
Afterload ↓ or predictable angina

coronary VD → ↑ O_2 supply → variant angina

Platelet inhibition → unstable angina

Cyanide poisoning

Hb
↓ Na nitrate
Methaemoglobin
↓ cyanide
Cyanomet Hb
↓ Sodium thiosulphate
Met Hb + Sodium thiocyanate
excreted

Ca - channel Blocker

Ca^{2+} channels
✳
Ca^{2+}
↓ calmodulin
Ca calmodulin
↓
MLCK ⟶ active MLCK
↓
MLC ⟶ MLCPOH
↓
contraction

Ca^{2+} channels block
DHP | Phenylalkylamine | Benzothiazepine

Rational

↓ HR & ↓ contractility
↓ Ca workload
↓ afterload
} ↓ O_2 demand → stable angina

coronary VD → ↑ O_2 supply → variant angina

Antihypertensive

D
R
S
C
V

Antiepileptics

Classification

i) Barbiturate → Phenobarbitone

ii) Dibenzylbarbiturate → Primidone

iii) Hydantoin → Phenytoin, Fosphenytoin

iv) Iminostilbene - Carbamazepine & Oxcarbamazepine

v) Succinimide - Ethosuximide

vi) Aliphatic carboxylic acid - Valproic acid

vii) Benzodiazepines - Diazepam, Lorazepam

viii) GABA analogues - Gabapentin, Pregabalin

ix) New drugs - Topiramate, Vigabatrin

x) Phenyltriazine - Lamotrigine

Classification based on MOA

1) Inhibition of voltage-gated Na channels
- Blocks Na channel that cause repetitive neuronal firing
(Na) (drugs) - prolong the duration of inactivated phase & delays its reversion to resting phase
eg. Phenytoin, Valproic acid, Lamotrigine, Carbamazepine, Topiramate

2) Enhancement of GABA-ergic action
- some AEDs activate GABA-A receptors, to facilitate GABA mediated Cl channel opening & Benzodiazepines

- GABA transmission (metabolic enzyme) inhibition → Vigabatrin
- GABA uptake transporter inhibition - Valproate, Tiagabine

3) Blockade of NMDA / AMPA receptors.
   - Blocker of glutamate receptors.
   - NMDA blockers.
   - AMPA blockers
   - Inhibition glutamate synthesis - Valproate

4) Blockade of VGCs - N type Ca channels
   - Reduce glutamate release

5) Blockade of T-type Ca channels.
   - Resp. for absence seizure
   - Valproate

6) Selective binding to synaptic vesicular protein (SV2A)
   - Reduce synaptic release of glutamate
   - ↑ synaptic release of GABA

7) Blockade of Kcnq-2
   - imp for release of epileptogenic factors.