PC
Pharmacology Concepts
By Rajesh Choudhary

Drugs Used in CVS Disorders

Pharmacology 2

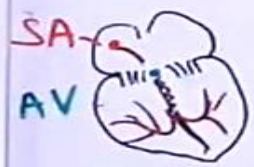
CVS : General Introduction

Cardio → Heart | Vascular - Blood Vessels

HEART - [Contractile muscles
Conductive cells - SA, AV, Fibres

1. **Rythmicity** :- 60-80 Beats/min (HR) 0.8 Sec/beat
Ventricle - Systol = 0.3 sec & Diastol = 0.5 Sec.
Atrium = Systol = 0.1 sec & Diastol = 0.7 Sec

2. **Automataciity** :- Intrinsic property of Card. muscle to generate Impulse by SA-node and Conduct through AV node to whole Heart.



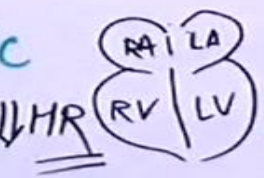
SA node → Atria → AV node → Bundle of His (AVB) (R&L) → Purkinje Fibre ← Muscle

3. **Excitability & contractility** = Respond to stimulys & contract

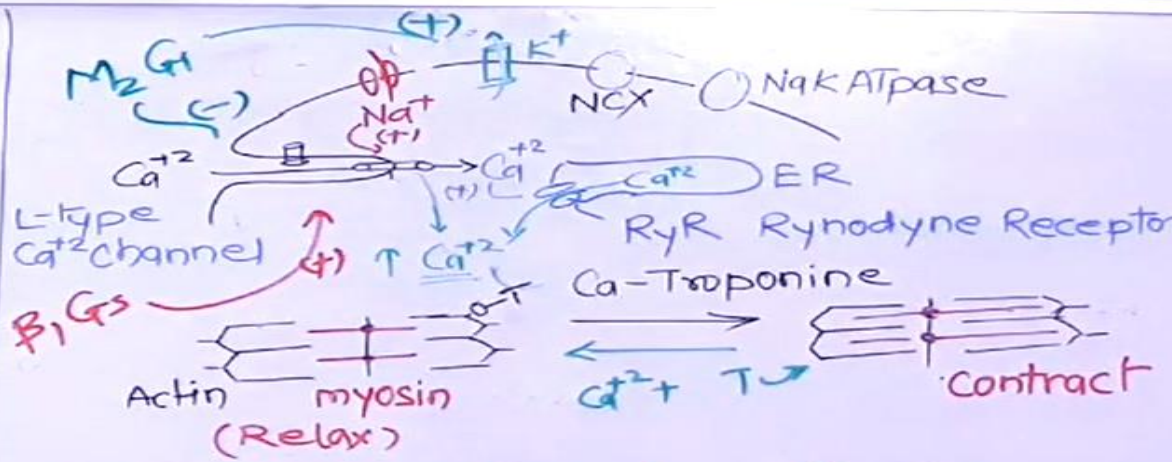
4. **Tonicity** = have some tone, not fully relaxed

NEUROGENIC CONTROL = "Autonomic Neurones"

Parasympathetic
Ach → M_2 (GiPCR)
↓HR

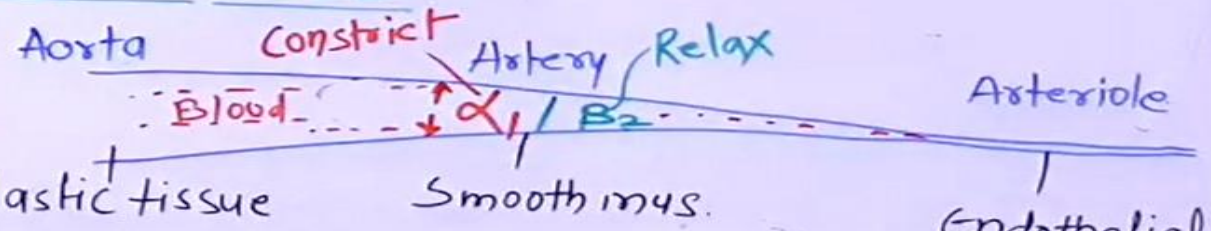


Sympathetic Neur.
N-Ad/Ad
↑HR ... B_1 (GsPCR)



DISORDERS = CHF, Arrythmia

BLOOD VESSELS :-



Sympathetic Neuron only → N-Ad/Ad → α_1 (GqPCR)
→ B_2 (GsPCR)..

Role = Transportation of O_2 / Neutrients / molecules through Blood to all body tissues

Disorder = Peripheral Artery disease
↳ Hypertension
- Coronary A.D. → Myocardial Infarction
Angina

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CARDIO-VASCULAR DISORDERS

HEART :→ MI, CHF, Arrhythmia, Valvular disease

Vessels → Hypertension, Atherosclerosis, Coronary artery disease

- → Genetic
- → Unhealthy Life Style
- → Kidney Problem
- → Neurogenic defect
- → Hyperlipidemia
- → Diabetes
- → Adrenal tumour
- → Hyper Thyroidism
- → Aging
- → Steroids
- → Races

→ (+) Sympathetic
→ (+) RAAS
→ (+) ROS
→ (+) Vascular Damage

(+) HR, (+) TPR
(Vasoconstriction)

BP = CO × TPR
CO = HR × SV

HYPERTENSION

↑ Aortic Pressure
↑ Required force on LV wall
↑ Cardia work load
Weakness
↓ SV
↓ CO

ATHEROSCLEROSIS
↑ Atheroma Deposition
↑ Vas. Endothelial Damage
- Inflammation
- Hyperlipids
- Diabetes
- HTN
- Genetic
- Unhealthy L.S.

Myocardial Ischemia
ANGINA / M. INFRACTION
Ischemia
- Coronary Artery Dis
- Hyperlipids
- Atheroma
- HTN
- Diabetes
- Unhealthy L.S.

Myocyte damage (Weakness)
↓ Contract° force
↓ SV
CHF
↓ CO

Ischemia
- Ischemic Heart Dis. (IHD) - Angina/MI
- Coronary artery Dis (CAD)
- Hypertension
- Cardiomyopathy
- Valvular disease

End Organ Damage
- → Kidney
- → Brain
- → Eye

+ RAAS
↑ HR
ARRHYTHMIA

Odema
Cardiovascular Complecation

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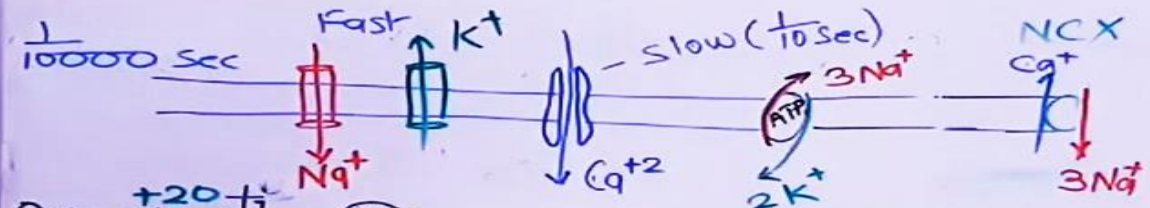
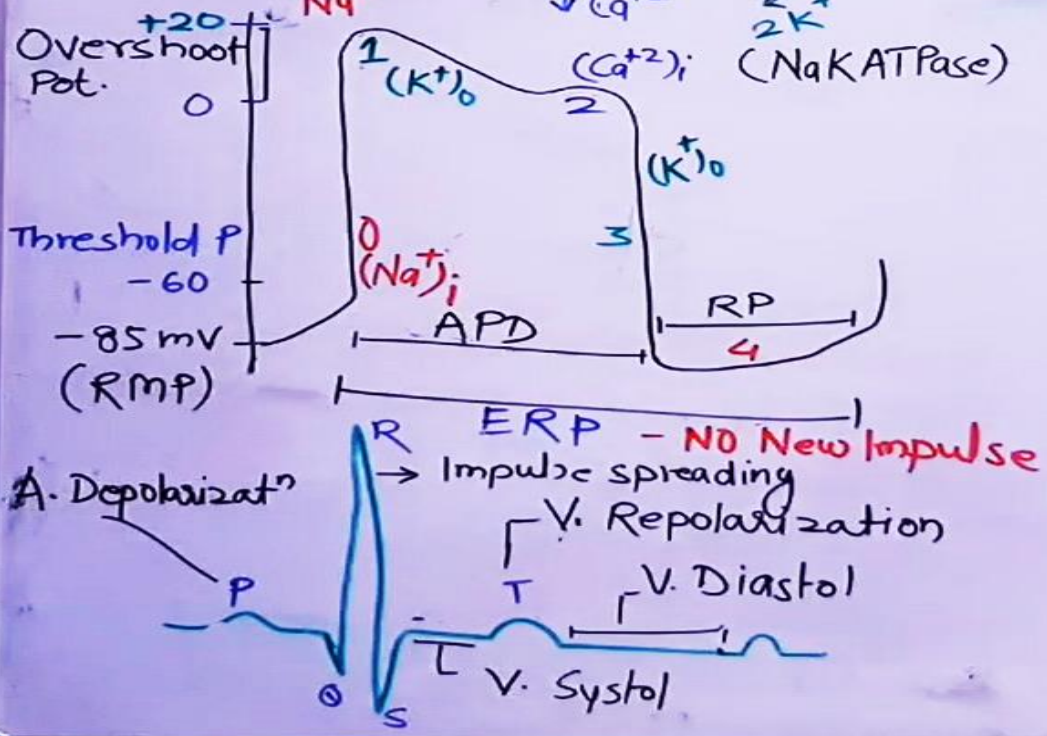
ELECTROPHYSIOLOGY & ACTION POTENTIAL IN CVS

RESTING POTENTIAL = Potential energy at cell mem at resting state.

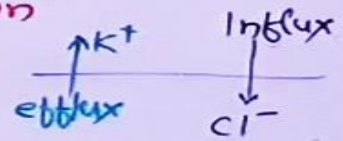
A/V muscle → −85 to −90 mV
Purkinje fibre → −90 to −100 mV
SA node → −50 to −60 mV



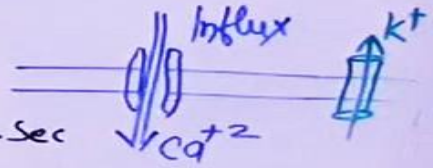


Phase-0: - "Fast Depolarization"
↳ Influx of Na^+, (opening - $\frac{1}{10000}$ sec)
↳ −85 mV → −60 mV ⟶ +20 mV,
↳ at +20 mV = Channel closed
↳ $(Ca^{+2})_i$ by S. Reticulam, Initiate Contraction

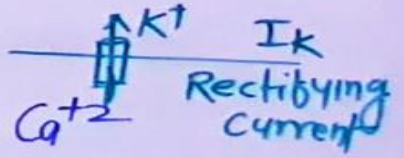
Phase 1 = "Partial Repolarization"
→ opening of K^+ & Cl^- channel



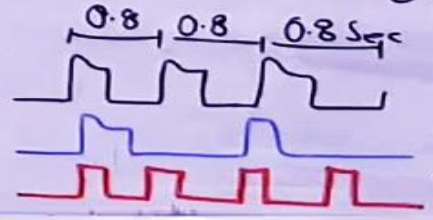
Phase 2 = "Plateau Phase"
→ opening of L-type Ca^{+2} ch. /
→ mus. Contraction



Phase-3 = Repolarization
→ Efflux of K^+ & Sequestration of Ca^{+2}



Phase-4 = "Restoration" "Resting Phase"
* Pacemaker pot. gradually Depolarised due to
↑ Inward Current (Na^+) – If
↳ X Ivabaradine



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CHF: CONGESTIVE HEART FAILURE

Congestive :- Congestion of Fluid / Volume Overload

Heart failure :- Cardiac Dysfunction

HEART - FAILURE (HF)

$CO_{sup} < CO_{demand}$

* Function of Heart ⇒ Blood Circulation → CO
* In HF ⇒ Heart unable to maintain CO

$CO = SV \times HR = 70 \times 72 \approx 5\ L/min$

* HF = ↓CO = ↓SV (pump) × HR $< 3\ L/min$
  - ↳ Heart unable to pump enough amount of Blood
  - ↳ Due to either Systolic or Diastolic Failure

* **SYSTOLIC FAILURE** - Left Ventricles unable to produce adaquate wall pressure to overcome the *Afterload or Aortic Pressure
* **Afterload** :- load or pressure required on LV wall to eject blood from Heart

Proper Ejectn = Pressure Generated by LV wall > Aortic pressure

* Systolic failure occurs due to → ✓HTN, ↑HD, Cardiomyopathy

Ejection Fraction = Stroke Volume (SV) / End Diastol Volume (EDV)

$= \frac{70\ ml}{110\ ml} = 0.64$, o/oE = 64%

In SHF → ↓SV, $EF = \frac{44}{110} = 0.40$ ⟹ o/oE = 40% (50-70%)

* HF refers when o/o Ejection < 40%

* **Preload** = load/Pressure on LV wall after EDV/ED
  - Preload ↑ due to ↑↑ Venous Return and Venoconstrictn
  - In CHF → ↑Afterload & Preload both are Increased

DIASTOLIC FAILURE :- Reduction on filling or ↓EDV

DHF occurs due to chronic HTN, Cardiomyopath, Congenital Heart Disease, Ventricular Hyperthophy

DHF = ↓↓EDV → ↓SV → ↓CO
= ✓EF

$0.64 = \frac{SV}{70}$

$SV = 0.64 \times 70 \approx 45\ ml$

$CO = 45 \times 72 = 3.2\ L/min$

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PATHOPHYSIOLOGY OF CHF

PATHOGENESIS:- ↓ ATP Production

① HTN → ↑ Aortic Pressure (Afterload) → Harder to Pump (↑ Req. Pressure) → Hypertrophy → ↑ O_2/Engery Demand → weaker Contraction → ↓FC* → ↓SV → ↓CO → CHF

Systolic Failure

② IHD → ↓ O_2 Supply → Myocardial Damage → Cardiomyopathy → ↓LV Space → ↓EDV → ↓SV → ↓CO → CHF

Diastolic Failure

③ ↑ Venous Return → ↑ Filling → ↑ EDV → Dialated Cardiomyopathy → Weak contraction → ↓FC* → ↓SV → ↓CO → CHF

Systolic H.F.

PATHOPHYSIOLOGY

CHF (Weak Heart) ↓CO

(+) Sympathetic System (CO = SV x HR) → Nor-Ad/Ad → HR↑, ↑FC, α_1 Vasoconstriction → ↑Afterload → ↑↑CHF

(+) RAAS → ① Edema ② ↑Afterload ③ CVS Remodelling → ↑↑CHF

(+) Hypertrophy → ↓FC → ↑EDV → Dialated Cardiomyopathy → Hypertrophy

HR↑ → Tachycardia → O_2 demand → ↑Weakness → ↑↑CHF

① ↓CO/SV/FC
② Tachycardia
③ Edema
④ Shortness of breathing
⑤ weakness in exercise

CLASSIFICATION OF ANTI CHF DRUGS

Therapeutic Goal : →

1. Improve Cardiac Performance (↑FC)
2. To Reduce HR & O_2 demand
3. To Reduce Volume Overload
4. To Reduce Afterload & Preload

ANTI CHF DRUGS :-

I. (+) Inotropic Drugs ⇒ ↑FC
- a) Cardiac Glycosides - Digitoxin, Digoxin
- b) B_1- Agonist → Dobutamine & Dopamine
- c) PDE Inhibitors – Amrinone & Milrinone

II Diuretics – ↓ Volume overload
- a) Loop diuretic - Furosemide
- b) Thiazides - Hydrochlorthiazide
- c) K^+ sparing - Spironolactone, Amiloride

III Vasodilators → ↓ Preload / Afterload
- a) Arteriodilators (Resistance vesseles)
  - ↳ Direct :- Hydralazine
  - ↳ K^+ ch. opener - Minoxidil, Pinacidil
  - ↳ CCB → Nifedipine, Amlodipine
  - ↳ ↓ Afterload
- b) Venodilators (Capicitance Vesseles)
  - ↳ Nitrates → ↓ Preload

IV Others :-
- ⓐ ACEIs – Enalapril → ↓ Volume Overload & ↓ After & Preload
- ⓑ ARBs → Losartan – 〃 – 〃 –
- ⓒ α, blocker – Prazosin → ↓ Afterload / Preload
- d) B- blocker – Carvedelol, Atenolol – ↓ O_2 demand, ↓ Afterload

STAGE OF HF

Stage I → At risk → HTN, Diabetes, Atherosclerosis
↳ Drugs → ACEIs & ARBs

Stage II → At Enhanced risk → Previous MI, LV Remodeling, Valvular Disease → ACEIs/ARBs Or B-blocker → Implantable deFibrillator

Stage III – Clinicaly Evident HF ⇒ HR↑, Shortness of breath, ↓ Exercise tolerance, Structural Heart Disease → Digitalis, Diuretics, ARB, B-blocker, Hydralazine, Difibrillator

Stage IV – End Stage → Heart Transplantat" / chronic Inotropes / Mechanical Support

DIGITALIS → CARDIAC GLYCOSIDE

Digitoxin :→ Digitoxigenin (Aglycane)
Digitoxose (Glycane)

Digoxin :- Digoxigenin (AGlycane) → Additional −OH group
Digitoxose

MOA → Inhibition Na^+K^+ ATPase Pump

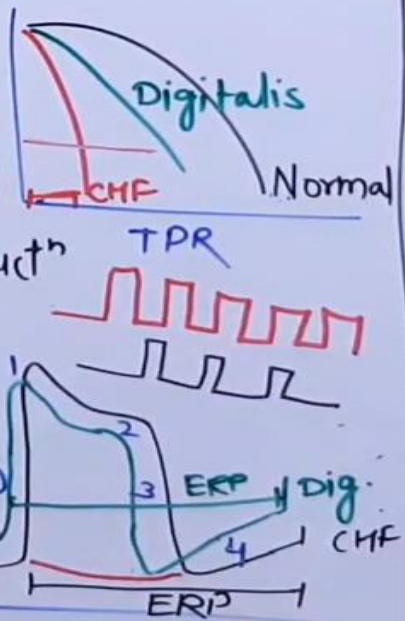
↑↑ $(Ca^{+2})i$ → +INOTROPIC

↓↓ K^+ → (−) CHRONOTROPIC

+ Vegal Action

PHARMACOLOGY :-

Heart :→ (+)Inotropic → ↑FC
(−) chronotropic → ↓HR
Vegomimetic Action (Ach)
Extravegal - ↓ SA/AV Conduct^n



Electrophysiology :-

AP ⇒ ↓ 0, 1, 2, 3 phase
↑ 4 phase

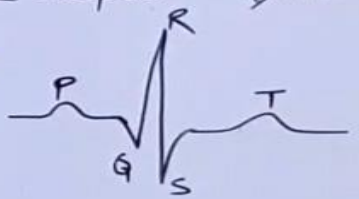
↓AV conduction Δ ↑ 4 phase → Ectopic Automaticity ↑

ERP ⇒ ↑ ERP = AV & Bundle of His
→ ↑ERP (Direct) = Atrium ↓
↓ERP (Vegal action) Ventricle ↓
→ ERP Abreviated

Excitability :- ↑ excitbitily at low dose
↓ ← at high dose

Conduction - ↓ Rate of Ophase depd. → ↓ AV Conduct

ECG → ↓ inversion of T-wave
↑ P-R Interval (↓AV)
shorting QT interval



BLOOD VESSELS :- mild Vasoconstrictor in Normal.
In CHF Patients → Digitalis improve circulat^n & Venous tone So net ↓ TPR (↑ SBP & ↓ DBP), but not affect much. So Not contraindicated in HTN

Kidney :→ Diuretic Action & Improve circulation & Renal Perfusion → ↑ Na^+/water excret^n,
helpful in CHF Patient.
Not effective in Edema Only

CNS :- ⊕ CT2 (high dose)
⊕ Central Sympathetic
− Visual Disturbance

DIGITALIS → CARDIAC GLYCOSIDE

Digitoxin :→ Digitoxigenin (Aglycane)
Digitoxose (Glycane)

Digoxin :- Digoxigenin (AGlycane) → Additional −OH group
Digitoxose

P'KINETICS :-	Digitoxin	Digoxin
Solubility :-	lipid soluble	Water Soluble
PB	95 %	25 %
Onset of actn	½ - 2 h	15 - 30 min
$t_{½}$	5 - 7 day	40 h
Duration	2 - 3 Weeks	2 - 6 days
Pc (Therap.)	15 - 30 ng/ml	0.5 - 1.5 ng/ml
Pc (Toxic)	> 35 ng/ml	> 2 ng/ml
Eliminatn	Hepatic	Kidney

Therapeutic use →
- CHF
- Atrial Fibrillation
- Proximal Supraventricular Tachycardia

ADR :-
↳ Cardiac Arrhythmia - Extrasystole
↳ Hypokalemia
↳ Gynaecomastia
↳ Visual Disturbance, Fatigue

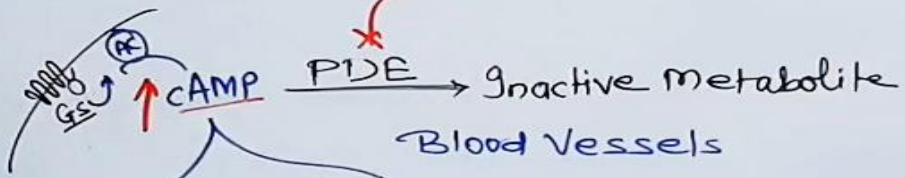
Treatment Against Digitalis toxicity
(A) V. Arrhythmia — Lidocain, Phenytoin
(B) S.V. Tachycardia — Propranolol
(C) AV-Block — Atropine
(D) Universal Antidote - Digibind (D. Antibody)

CONTRAINDICATION =
(1) Ischemic Heart Disease - MI
(2) Thyrotoxicosis — ↓ Responsiveness for Digitalis
(3) Myxoedema — ↓ eliminatn
(4) Wolff Parkinson White Syndrome (Arrhythmia)

INTERACTION —
Digitalis + CCB/β-blocker — Cardiac arrest
Digitalis + Diuretic — ↑ Hypokalemia
+ Quinidine — ↓ Eliminatn of digitalis

PDE Inhibitors

PDE-III Inhibitors – Amrinone, Milrinone



"Ino-Dilator"

① ↑ Force of Contraction – ↑ Cardiac Performance
② Vasodilation → ↓ Afterload & Preload

Amrinone – Bipyridine derivative
↳ Selective PDE-III Inhibitor
↳ Heart, B.V, Broncho smooth mus. cell
↳ ↑ LV Ejection Fraction, ↓ TPR, ↓ EDV
↳ Onset → 2-3 h, $t_{1/2}$ = 2-5 h

ADR – Thrombocytopenia
Hepatotoxic
Fever
Arrhythmia

Milrinone = Similar action as Amrinone but –
– more selective to PDE-III
→ 10 times more potent
– Shorter Acting $t_{1/2}$ = 40-80 min
– No Significant Thrombocytopenia Side Effect
– Better in short term use

Use of PDE III Inhibitor :- Short-term i.v. use in Sever & Refractory CHF

CLASSES OF PHOSPHODIESTERASE

Non Selective PDE Is – Theophylline
PDE-I ⟶ Vinopectine
PDE-II ⟶ Oxindole
PDE III ⟶ Amrinone → Heart, BV
PDE IV ⟶ Rolipram, Roflumilast – use in COPD
↳ Bronchomus., Immune cell, Inflammatory cell
PDE V & VI ⟶ Sildenafil → used in ED
↳ ↑ cGMP → Pulmonary HTN
PDE VII ⟶ Quinazoline – Anti inflammatory
Neuroprotective
PDE X ⟶ Papaverin – ↑ cAMP & cGMP
↳ Antipsychotic

HYPERTENSION (HTN)

HTN:- Consistant Elevation of BP/Arterial Pressure Above the normal (120/80 mmHg)

Class of HTN, According to BP:-

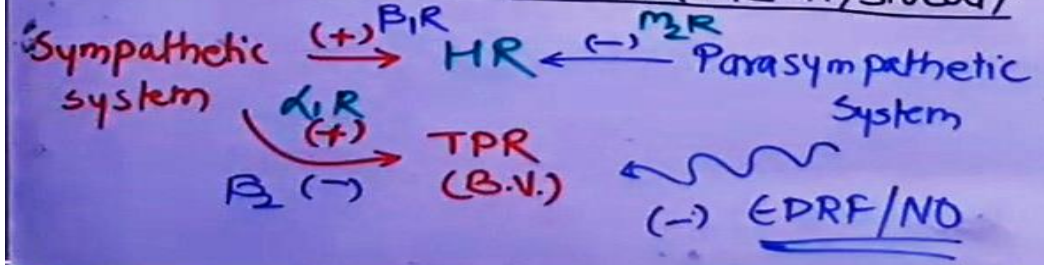
JNC - Joint National Committee

	SBP	DBP
1. Normal -	90-119	60-79
2. Pre HTN -	120-139	80-89
3. Stage I (Mild)	140-159	90-99
4. II, (Moderate)	160-179	100-109
5. III, (Sever)	>180	>109
6. Isolated Systolic HTN =	≥140	<90

$BP = CO \times TPR$ | $CO = HR \times SV$

$PP = SBP - DBP$ | $MAP = DBP \times \frac{1}{3} PP$

AUTONOMIC CONTROL IN NORMAL PHYSIOLOGY



HTN (DISEASE) = ↑↑ BP, ↑↑ TPR, ↑ HR

↑ ∈ ↑ TARGETS

CLASSIFICATION BASED ON OCCURANCE

I. P°/ESSENTIAL/IDIOPATHIC HTN =

↳ 90% Cases are P°HTN

↳ Etiology is unclear & unclear Pathophysiology

↳ Possible Pathophysiology → "Genetically"

- ↳ Volume Overload
- ↳ Salt/Water Retaintion ← Abnormal kidney Funct° & RAS
- ↳ Over Sympathetic Stimulation
- ↳ Abnormal Diet/Life Style

II. SECONDARY HTN: → Only 10% Cases.

* Due to - "Renal Artery Stenosis" → ⊕RAS → Hyper Aldosteronism & Pheochromocytoma

Treatment = Angioplasty, α_1 blocker, ACEIs/ARBs

III MALIGNANT HTN: →

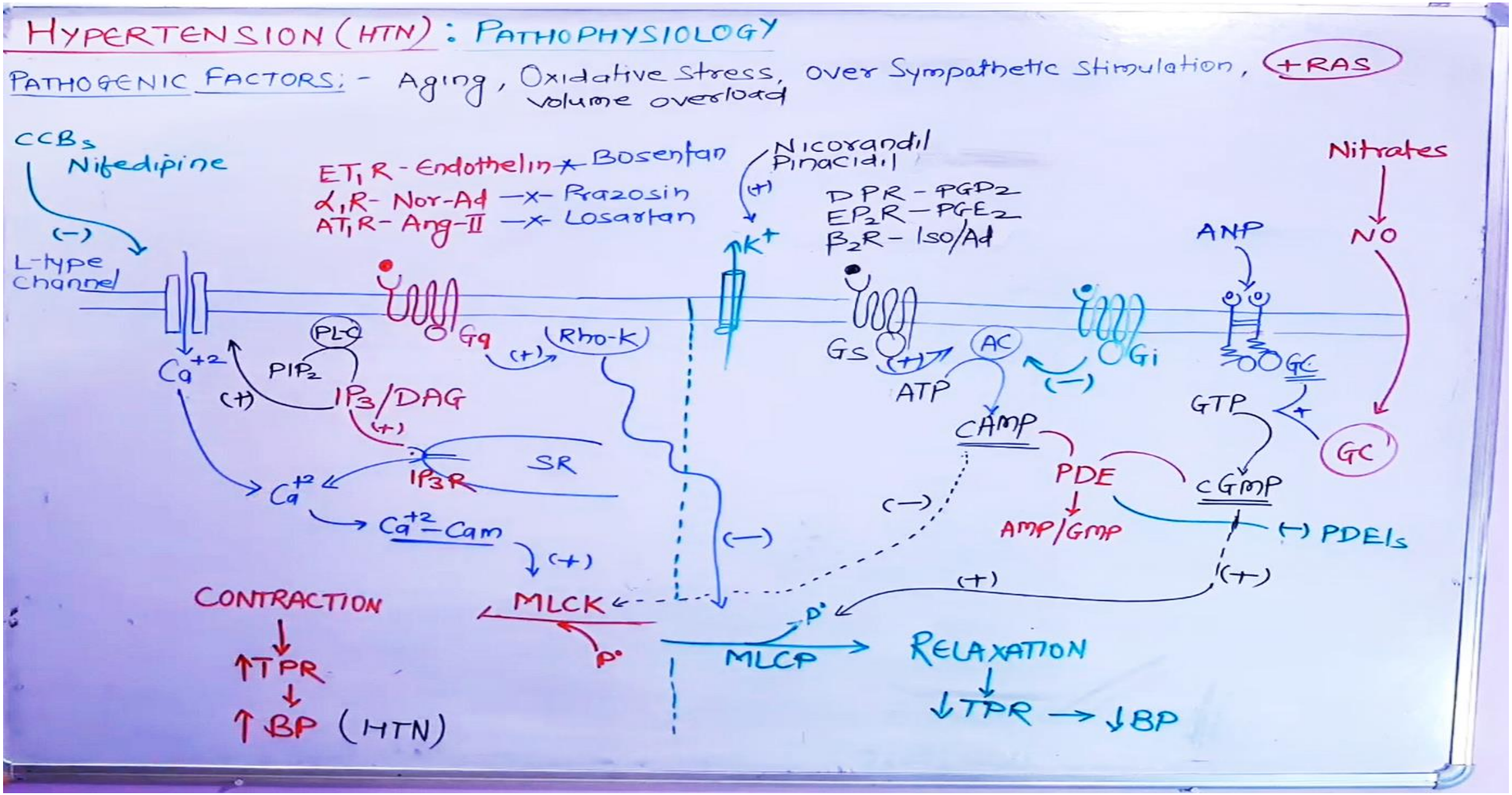
= Sudden dramatic ↑ in BP > 140 mmHg

= Emergency of Treatment Required ⇒ Vasodilators

MANIFESTATION OF HTN ⇒

Vascular hypertrophy, Coronary Artery Diseases, Heart failure, Arrythmia, Renal failure, Edema, Retinal Damage, etc

HYPERTENSION (HTN): PATHOPHYSIOLOGY



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ANTI-HYPERTENSIVE DRUGS

I. SYMPATHETIC MODULATORS → [↓TPR / ↓HR]

A) α_1-blockers – Prazosin, Terazosin
Phentolamine, Phenoxybenzene

B) β-blockers → Propranolol (B_1+B_2)
Atenolol, Metoprolol, Acebutalol (B_1)

C) α+β blockers – Lebetalol, Carvedilol

D) α_2- Agonist → Methyldopa, Clonidine

II RAAS MODULATORS [↓TPR ↓vol. overload]

A) Renin Inhibitor → Aliskiren

B) ACEIs → Captopril, Enalopril
Ramipril, Linsopril ["Pril"]

C) ARBs → Losartan, Olmesartan,
Candesartan, Telmisartan "Sartan"

III. VASODILATORS – [↓TPR]

A) Arteriodilators

i) Direct → Hydralazine – Renal Selective
↓ IP_3 Sig.

ii) Calcium Channel Blockers (CCBs)
Dihydropyridines – Nifedipine, Amlodipine (BV)
Phenyl Alkylamine – Verapamil] Heart > BV
Benzothiazepine – Diltiazem]

iii) K^+ channel opener → Nicorandil, Pinacidil
Minoxydil

B. VenoDilators – "Nitrates" — NO

Glyceryl Trinitrate (GTN), Isosorbid dinitrates
(A+V) = Nitroprusside

IV. DIURETICS → ↓ Volume Overload

A) Thiazide – HydrochlorThiazid, Benzthiazide

B) Loop Diuretic – Furosemide, Bumetanide

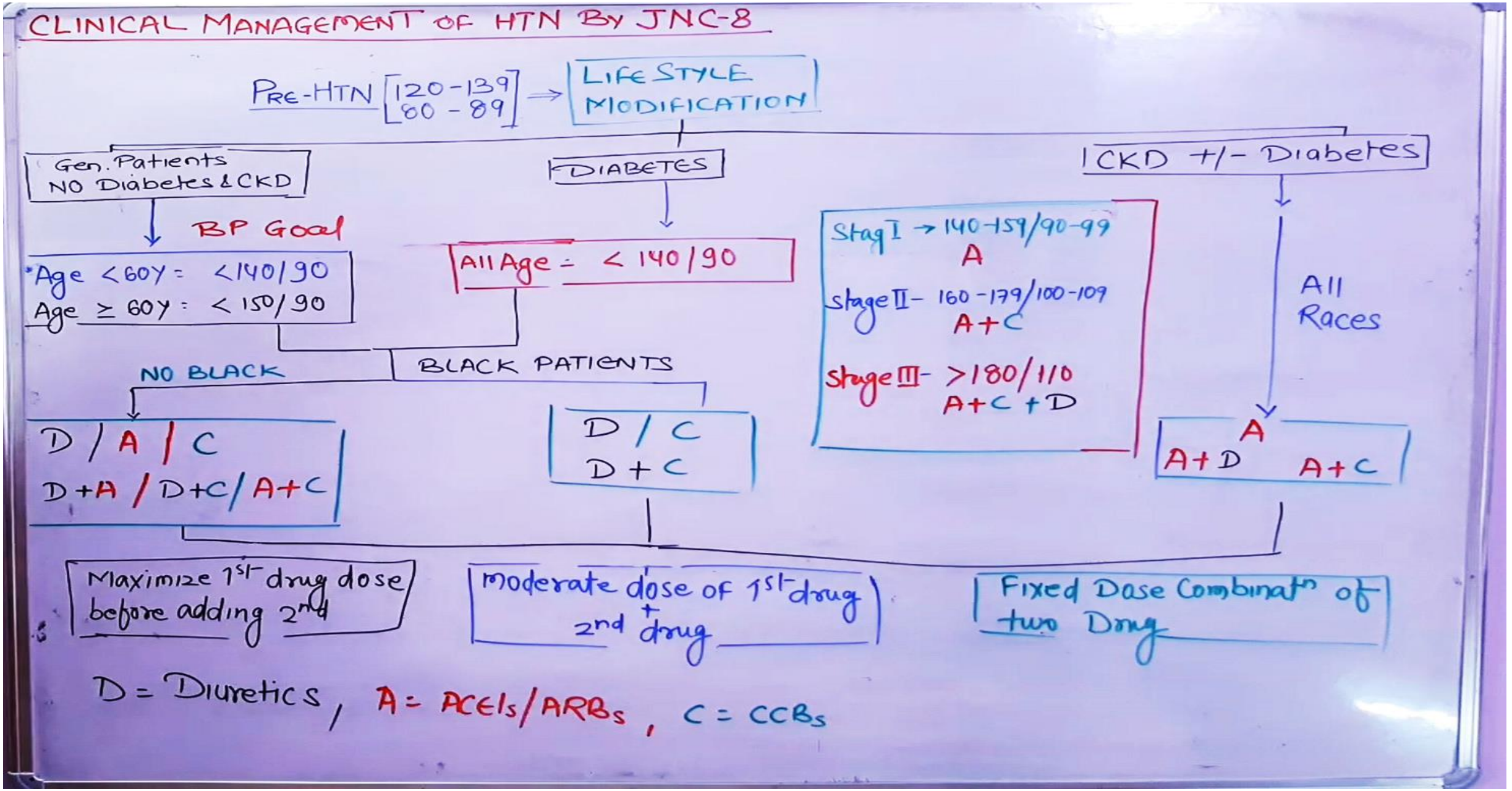
C) K^+ Sparing – Spiranolactone, Amiloride,
Triamterine

V. OTHERS

A) Antioxidants – Flavonoids, Multivitamins

B) Adrenergic Neurotransmission modulators ↓

→ Guanethidine
→ Reserpine



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FUTURE APPROACH FOR HTN

Recent Trends → Drug-based Therapy
→ Newer Approaches - Gene Therapy & Vaccine Therapy
→ Device Based Therapy.

A. NEW TARGETS & DRUGS -

① RAS modulators -
↳ Renin Inhibitor → Aliskiren
↳ (P)RR blockers - Handle Region Peptide (HRP)
↳ Prevents cardiac Remodeling
↳ Ang(1-7)/ Mass receptor/ACE-2 Act. (DIZE)
↳ AT_2R Agonist

2) Vasopeptidase Inhibitor
↓
Neprilysin → ↑ metabolism of NPs (ANP)
↳# ↑ degradatn of Ang-II & Endothelin

Neprilysin Inhibitor = LCZ696 < ↑ ANP, x-AT_1R
Valsartan + Sacubitril
1:1

3) ANP (Atrial Natriuretic Peptide)
↳ Natriuresis
↳ Vasodilatn
↳ ↓ RAAS
PL-3994 (+)
ANP-receptor

4) ET_1R blocker → Bosentan, Ambrisentan

5) Endothelin Converting Enz Inhibitor
- Daglutril < ↓Endothelin, Neprilysin Inhibitor

6) Aldosterone R blocker - Spironolactone, Eplerenone, Finerenone = MR blocker
* Nimodipine - CCB + MR blocker

7) Aldosterone Synthase Inhibitor
→ LCI699, Fadrozole

B. GENE BASED THERAPY -

Target = ACE-II & AT_2R expression Enhanced
= Adino viral Vector → Gene → ↑eNOS/NO
- Antisense Gene For- ACE & AT_1R

C. VACCINE → PMO 3117 - Against Ang II
CYTO06 → Against Ang II

D. Device BASED Therapy -
* Renal Sympathetic Denervation
* Baroreflex Activatn therapy
* Arterio venous fistula

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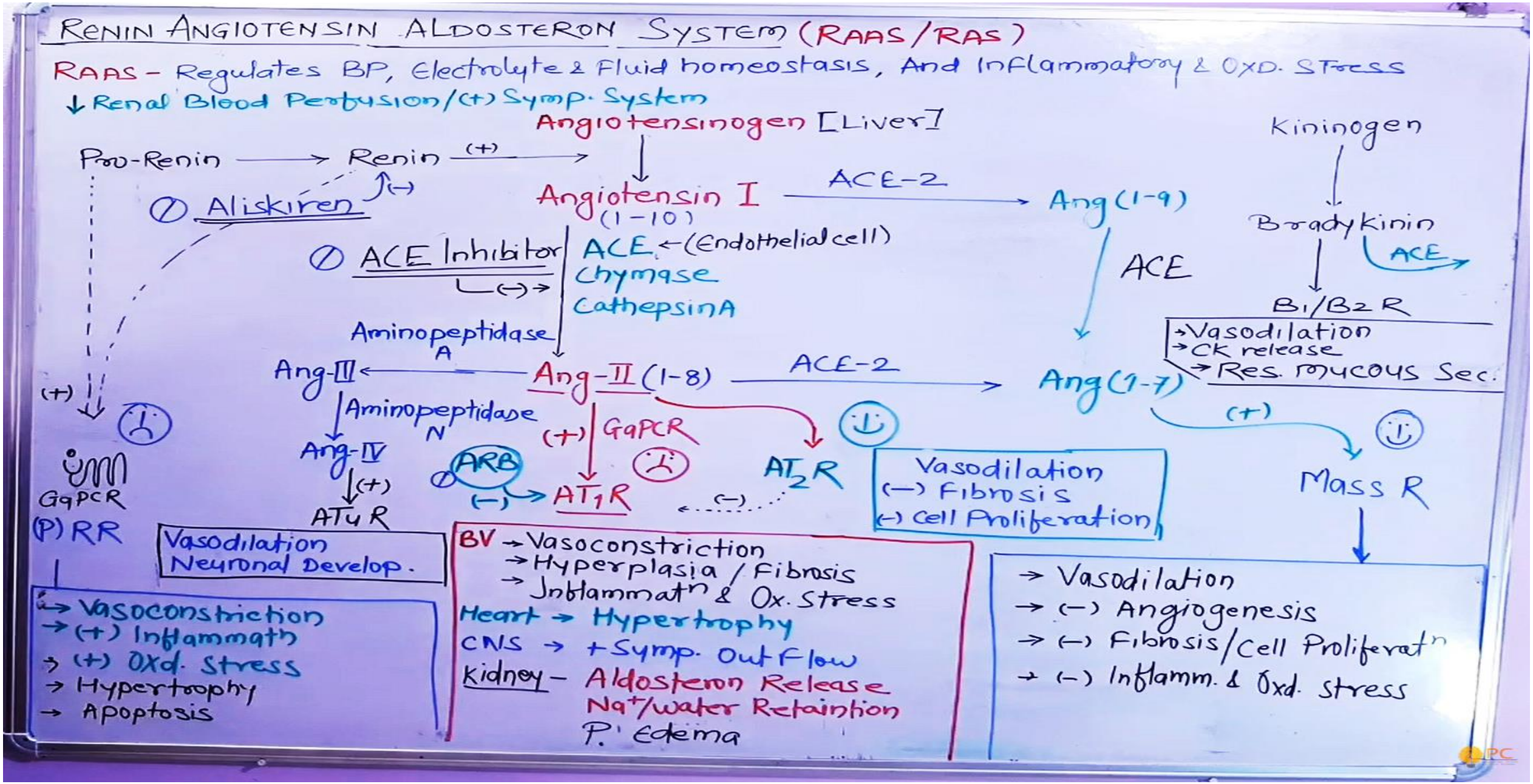
Renin Angiotensin Aldosteron System (RAAS/RAS)

RAAS - Regulates BP, Electrolyte & Fluid homeostasis, And Inflammatory & Oxd. Stress

↓ Renal Blood Perfusion / (+) Symp. System



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P'COLOGY OF ACEIs

ACEIs → "Teprotide", Captopril, Enalapril, Ramipril, Quinapril, Perindopril, etc

MOA :→ Ang-I —ACE→ Ang II ↓ --- ↓Response ①#

② ↑ Bradykinin → ↑ Vasodilatn ; Bradykinin → Inactivatn (ACEIs, Kinase I)

Ang(1-7)/MasR → Vasodilatn ③

↳ Short term :→ Antihypertensive actn by Sudden ↓ in productn of Ang II and ↑ Bradykinin. So initial dose of ACEIs should Be low

L, Long Term - Antihypertensive Actn by ↓Ang II and ↑ productn of Ang(1-7). In later Ang II is formed by an Alternate pathways or Enzyme Chymase and Cathepsin-B. So in long term ACEIs can be effective with Diuretics or low Na^+ diet.

CVS Action :- ↓TRP → ↓SBP/DBP

* It has no major effect on - CO, CVS Reflexes, & Sympathetic action
* No affect Renal Blood Flow

P'kinetic :→

→ 70% drug absorbed orally, + Food ↓ BA
→ Partialy metabolised & partialy excrete unchanged
→ $t_{1/2}$ = 2h & duration = 6-12h
→ Renal Impairement → ↓ Renal clearance

Uses :- ① HTN ② Left Ventricle Systolic Dysfunction ③ Acute MI ④ Chronic Renal Failure ⑤ Diabetes Nephropathy

ADR :- ① Hypotension ② Persistant/Dry Cough - due to kinin, PGs, Sub-p ③ Angiodema ④ Hyperkalemia - ↑ with K-sparing diuretics & R failure ⑤ Dysgesia (Taste Alteratn) ⑤ Foetopathic

* Enalapril maleate (60% BA) → Enalaprilate - IV only ##
* Ester prodrug has greater BA but 100-1000 times less potent.
* ACEIs - ↑ Renin → ↑ PRA (plasma Renin Activity) render patients (Heart failure, Salt dependant) hyperresponsive to ACEIs and produce Hypotension.

Sulfahydryl → Captopril
Phosphorus → Fosinopril
Dicarboxyl - Enalapril, Lisinopril, Ramipril, Quinapril, Benazepril.

P'COLOGY OF ARBs "SARTANS"

ARB = Ang-II Type-I (AT_1R) Blocker

Drugs - Losartan, Olmesartan, Telmisartan, Candesartan, Irbesartan

MOA :- Ang-II ⟶ AT_1R —X— ARBs

Vasoconstrict^n Na^+/water Retaint^n (+)Sympathetic Sys.

Differ From ACEIs :-

1) Complete block the Ang II/AT_1R mediated HTN
2) Not interfere with the Kinins level unlike ACEIs So ↓ Cough Format^n
3) Indirect activate the AT_2R (Protective Effects)
4) Little ↑ the Ang(1-7) production

P'cological Action :—

1) ↓ TPR ⟶ ↓ SBP/DBP
2) Not interfere with HR & Cardiac Reflexes
3) No Significant action on Lipid profile, Carbohydrate metabolism & Insulin Sensetivity

P'KINETIC (Losartan)

↳ 33% B.A. (High first pass metabolism)
Irbesartan - ∓70% BA
↳ Metabolite → 10-30 time more potent & Non-Competitive blocker of AT_1R
↳ $t_{\frac{1}{2}}$ = 2h, Durat^n = 24h, PB = 98%

→ Dose should be reduce in Hepatic dysfunction Not in Renal Failure

ADR :- Hypotension, Hyperkalemia, Foetopathic

Uses :- HTN, MI, CHF, Nephropathy

CONTRA-INDICATION — Pregnancy & Renal Artery Stenosis

AT_1R Binding Order/Affinity —

Candesartan = Olmesartan > Irbesartan = Eprosartan > Telmisartan = Valsartan > Losartan

Binding of ARB to AT_1R is compititive, But inhibition is insurmountable.

\# The max response of Ang II can not be restored in the presence of ARB

α AND β-BLOCKERS AS ANTIHYPERTENSIVE DRUGS

BETA (β) - BLOCKER :- Propranolol, Atenolol

MODE of ACTION → Block the β_1 Receptor (GsPCR) in Heart. → ↓HR, ↓FC, ↓CO, ↓Myocardial O_2 demand. Improve cardiac vitality

⇒ ↓ BP in long term use

⇒ used as a mild Antihypertensive

* Selective β_1 blocker — ↓↓ Cardiac Activity (↓↓HR/CO)
* Non Sel. β blocker → ↓↓ HR/CO, § TPR
* β blocker with ISA ⇒ ↓ HR/CO § TPR
* Non-Sel. β-blocker = ↓ Renal Blood Flow & ↓ GFR

CONTRAINDICATION :- Cardiac, Pulmonary & Peripheral Vascular disease. Diabetes*

Propranolol –x- not used in "Asthma" & "Hyperlipid"

ADR of Propranolol ⇒ Fatigue, loss of libido, nightmares. Rebound Hypertension

* β-blockers are not preffered in Old age Patients
* Better Effective in Angina & MI Patients

⇒ Atenolol (25, 50, 100 mg/day)

ALFA (α_1) - BLOCKERS - Prazosin

MOA = Block α_1R (GqPCR) in B.V. & causes - Vasodilation [↓↓BP]

$BP = CO \times TPR$

$CO = HR \times SV$

Artery = Resistance Vessels

Veins = Capicitance Vessels

Effects = ↓↓TPR with little ↓ in Venous Return Unlike Vasodilators.

ADR ⇒

⇒ Reflux Cardiac Stimulat^n (↑HR) & Renin Release

⇒ Reflux Tachycardia doesn't compansate BP because α_2R is not blocked

⇒ Postural Hypotension by "First Dose Effect" so always start with low dose (0.5 mg)

⇒ Fluid Retaintion — (so not used in CHF)

So it is not used as first choice

DOSE of Prazosin - 0.5, 1, 2, 2.5, 5 mg (2-6 mg/day)

also used in comb. with ⇒ Diuretics or β-blocker

PHARMACOLOGY OF α-BLOCKERS

I α_1-Blocking Action:- (Phenoxy benzene)

1. CVS ⇒ ↓TPR (Total Peripheral Resistance)
   ↓↓ BP & ↑↑HR (Tachycardia)*

   $BP = CO \times TPR \mid CO = HR \times SV$

* Vasomotor Reversible action of Dale:-
  α_1-blocking causes fall in BP by abolish the action of Ad. on α_1 receptors, & dominant action on β_2 receptor

2. Kidney → marked Hypotension causes ↓ in GFR resulted in Na^+/water retain ion*
   by RAS activation [β_1 activation by Ad] (↑)

3. Other Effects:-
   - Eyes → Miosis* (pupil constriction)
   - Nassal → Stiffness*
   - GIT → ↑ GI motility (diarrhoea)*
   - Bladder tone → Relax (↑ urination)
     ↳ ↓ Prostate Resistance to urination
   - Vas-deference → ↓ Semen Ejaculation**

ADR/Side Effects

- → Reflux Tachycardia
- → Peripheral Edema
- → disturbe in far vesion
- ⇒ Postural Hypotension
- → Diarrhoea
- → Sexual dysfunction
- → Nassal stiffness

Clinical uses -

- ↳ Hypertensive Emergency = "Zosins"
- ↳ Benign Prostate Hypertrophy (BPH) - Alfuzosin, Silodosin, Tamsulosin

- ↳ Pheochromocytoma
- ↳ Secondary Shock
- → migrane → Ergot Alk. = Ergotoxin & Ergotamine

II α_2-Blocking Action

→ Vasoconstriction, ↑ NA release, ↑ Insulin release

Ergot Alk → (A) Amino Acid Alk = Ergotamine & Ergotoxin
(B) Amine Alk = Ergometrine
↳ No α_1 activity

α_1 blocking Action → DH Ergotamine > DH Ergotoxin

Vasoconstrict → Ergotoxin > Ergotamine

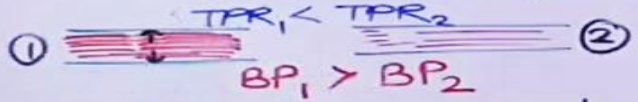
* DH Ergotamine ⇒ Cognitive Enhancer

PHARMACOLOGY OF B-BLOCKERS / PROPRANOLOL

A. Heart:- ↓HR (−chronotropic), ↓FC (−Inotropic) (−β_1R) ↓CO, ⇓Cardiac workload & O_2 demand #

B. B. Vessels → ↓coronary blood flow & ↑TPR (−β_2R) in acute treatment [↑BP]

* During prolong therapy, ↓BP# is reduced by
↳ Vascular Adaptation



BP = ⇓CO × TPR↑
CO = ↓HR × SV↓

↳ ↓ NA Δ Renin Secretion by β_1R blockade

C. Respiratory Tract : Bronchoconstriction *
(−β_2R) ↳ Asthmatic precipitation

D. Metabolism – ↓ lipolysis → ↑ Fatty A, TG, LDL
(−β_2) ↓ Gluconeogenesis Δ ↓ Glycogenolysis *
↳ ↓ Carbohydrate Tolerance

E. Sk. Mus – ↓ muscular tone, ↓ Tremor#, *
(−β_2) ↓ Exercise Capecity → ⇓ BloodFlow
↓ Glycogenolysis

F. Eye – ↓ IOP, Aq. Secretion #
(−β_2)

G Uterus – Contraction *
(−β_2)

H. - CNS – Anxiolytic effect by its Peripheral Action

I. Local Anaesthic effect, but not useful due to irritation.

P'kinetic – First Pass metabolism – ↓BA P : oral 40 : 1
Cross BBB, 90% PB,
Excrete through Glucoronic conjugation

* ADR = Bradycardia, Bronchocostriction, metabolic Disorder, Fatigue Sexual Impairment

C.I. – Asthma, Hyperlipidemic Patient

* Clinical uses → HTN, Angina, MI, Arrhythmia
↳ Anxiety Δ Tremor
↳ Migrane – Block catecholamine induce cerebral Vasodilation effect
↳ Glaucoma – Timilol (topically)

Drug Interactions :–
+ Digitalis → Cardiac Arrest
+ Verapamil → —|—
+ Oral Hypoglycemics → ↑↑ Hyperglycemia effect
+ α_1 Agonist ⇒ ↑↑ BP (Hypertension)

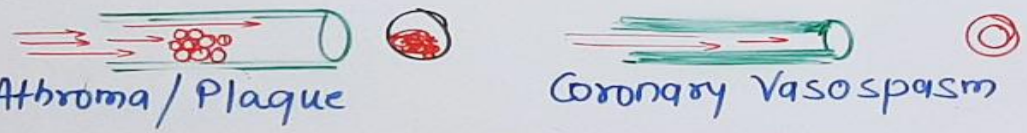
ANGINA PECTORIS

"Angina Pectoris (Chest pain) is caused by Myocardial Ischemia that lead to the imbalance b/w Myocardial O_2 demand & O_2 Supply

In Normal – O_2 demand = O_2 Supply
In Angina – O_2 demand >> O_2 Supply

"Ischemia" → ↓↓ Blood Supply ⇒ Hypoxia → ↓↓ O_2 Supply

#



Alternate Vessel → "Collateral Vessels"
↳ Developed in old-Age = ↓ Chance of Heart Attack

Symptoms:- chest pain, Pressure & burning Sensat", shortness of breath, Fatigue, Dizziness

TYPES OF ANGINA PECTORIS :–

(A) Classical / External / Stable Angina ⇒

↳ Pain occurs due to ↑ Work load on Heart caused by "Excercise", Emotion, Stress, & Cold
↳ "Predictable" & Symptoms may remain Stable for no. of years.
"Atherosclerosis" - is the main reseon
Treatments:- Antiplatelates, Thrombolytics

(B) Unstable Angina –

↳ Attack during Rest condition "Pre-Infract"
↳ Extensive Coronary Artery blockade due to either "Atheroma" and/or "Vasospasm"
↳ Treatment ⇒ Vasodilators & Antiplatelates

(C) Prinz Metal / Variant / Vasospastic Angina

↳ "Unpredictable" & Attack during "Rest & Sleep"
↳ Coronary Vasospasm due to Stress, Cold, Bad life Style, Smoking
↳ Associated with CAD but may result from chronic over Sympathetic Activity

(D) Silent Angina :– "Ischemia without Symptoms"

Diagnosis – Holter monitoring & Exc. stress testing

Rational Treatment :–

Non-Pharm. Therapy → Life Style monitoring

Pharmacotherapy →
↳ ↑ Coronary Flow → Vasodilators – Nitrates, CCB
↳ ↓ Atheroma → Antiplatelates, Thrombolytics
↳ ↓ Cardiac Workload → β-blockers

Surgery – Coronary Angioplasty
Coronary artery Bypass Grafting

ANTI-ANGINAL DRUG

Myocardial Ischemid
↑ Myocardial O_2 demand
Coronary Vasospasm ◯ → O
Atherosclarosis / Atheroma 

Therapeutic Goal :→
↳ "To improve Coronary blood flow"

CLASSIFICATION :—

I. Org. Nitrates :— ⊕ cGMP
- (A) Short Acting — Glyceryl Tri Nitrate (GTN)
- (B) Long Acting → Isosorbiddinitrate
  Isosorbidmononitrate
  Ethyl tetranitrate

II β-blockers → ↓ Cardiac Work load & O_2 demand
- ↳ Propranolol, Metaprolol, Afenolol

III Calcium Channel Blockers — ⟷ L-type Ca^{+2} channel
- ↳ Verapamil
- ↳ Diltiazem
- ↳ DHPs — Nifedipin, Amlodipine

IV K^+ channel Opener
→ Nicorandil, Pinnacidil, Minoxidil

V Anti-Platelate Drugs — "Anti-Atheroma"

(A) Platelate Aggregatⁿ Inhibitors
- → Aspirin (75-150mg) — COX-I Inhibitor
- → ADP-R ($P_2Y_{12}R$) blockers — Clopidogrel
  Ticlopidine, Prasugrel, Ticagrelor

(B) GP IIb/IIIa (Glycoprotein Receptor blockers) →
Abciximab, Tirofiban, Eptifibatide

(C) Protease Activated Receptor-1 (PAR-1) blocker —
— Vorapaxar

VI OTHERS — Trimetazidine, Dipyridamol
Ronazoline, Ivabradine

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VASODILATORS : NITRATES

NITRATES/NITRITES - "NITROVASODILATORS"

- Org Nitrates → Polyester of Nitric acid [-C-O-NO_2]
- Org. Nitrites → Polyester of Nitrous a [-C-O-NOT]

ORG. NITRATES :- GTN (Nitroglycerine)
- Isosorbide dinitrate
- Isosorbide mononitrate

-C- NO_2

GTN - PHARMACOLOGY

MOA ⇒ ~ NO ⟶ (+) Soluble Guanylyl cyclase (sGC)

GTP → ↑ cGMP → (+) PK-G

① (+) MLCP

② (-) PDE (2,3,5)

(-) Ca^{+2} Signaling

" VASODILATORY EFFECTS"

CVS ACTION -

① Haemodynamic → Venodilator → ↓EDV & Pressure
- ↓ Preload
- ↓↑ TPR

✓ No change in HR

✓ ↓CO & Pulmonary Vascular Resistance

✓ ## GTN does not alter Systemic Arterial Pressure

Arteriolar dilation in Face, Neck - Flush and in meningeal artery — headach

High dose of GTN :- Arteriodilation → ↓ BP & CO → (+) Sympathetic

↑↑ Venous Pooling ← Restore Systemic Resistance ← ↑HR, ↑TPR

② Coronary blood Flow → Nitrates restore the coronary blood flow by vasodilatn in ischemic condition.

③ Myocardial O_2 demand - ↑ O_2 Supply and ↓ O_2 demand by ↑ coronary blood Flow.

Major actn → # ↓ cardiac workload by ↓ After and Preload
↓ O_2 damand # ↑ Coronary Flow

P'kinetic :- Sublingual GTN - P_C max reach within 4 min
$t_{1/2}$: 1-3min

ADR - Flush, Headach, Postural Hypotension, Weakness, Dizziness,
✓ Sublingual GTN - Bradycardia & Hypotension by Bezold - Jarisch Reflex

Uses - MI, CHF (Relief Pulmonary Congestion)
Angina - Unstable and Varient-

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P'COLOGY OF CCBs → VASODILATOR

A) Dihydropyridines (DHPs) - Nifedipine, Amlodipine, Felodipine, Nicardipine
B) Phenylalkylamine - Verapamil
C) Benzothiazepine - Diltiazem
D) Diaryl amino propyl amine → Bepridil

MOA:- Block the L-type Ca^{+2} channel

* DHPs - Vasoselective, BV >> Heart → HTN
* Verapamil & Diltiazem - Heart >> BV → SVT

	Nifedipine	Verapamil	Diltiazem
Potency -	+++	++	+
HR →	↑ + Sym. Reflex	↓↓ - chrono tropic	↓↓
FC →	↑	↓↓ - Inotropic	↓
CO →	↑	↓	↓
TPR	↓↓↓	↓↓	↓

DHPs -

Amlodipine → less Reflex Tachycardia than Nifedipine due to longer $t_{1/2}$ (35-50h)

Felodipine → has greater vaso spacificity

* Isradipine → ↓ SA Node, No Tachycardia

ADR:-
① Palpitat^n ② Flushing ③ Hypotension ④ drawsiness
* ↑ O_2 demand, worsned MI in Angioplasty patients

Use - ① HTN, Isolated Systolic HTN
② Varient Angina

VERAPAMIL:- (−) Ino, (−) chrono, (−) dromotropic
↳ ↓ TRP → ↓ BP but No Reflex Tachycardia Effects
* ↳ Not useful in CHF due to ↓ in Cardiac performance
↳ ↓ Myocardial O_2 demand - preferred in Angina

ADR → Bradycardia, HF,
+ Digitalis/β-blocker → Cardia Arrest

DILTIAZEM - IV. administrat^n initially marked ↓ in TPR/BP that can lead to reflux Tachycardia (↑HR & ↑CO) & then HR & CO fall below to initial level due to direct (−) chrono & (−) inotropic effect

BEPRIDIL - Similar action as Verapamil
↳ ↓ Slow Inward Ca^{+2} & Fast inward Na^+
↳ ↓ HR & ↓ AV Conduction
ADR - prolonge QT Interval - "Torsades de-points"

VASODILATORS : K^+ CHANNEL OPENER & HYDRALAZINE

HYDRALAZINE :- Direct Arteriodilator

↳ It was discovered while Scientist at CIBA looking for an antimaleria drug. Patented at 1949.

↳ It is on WHO list of Essential Medicine.

MOA :- ↓ intracellular Ca^{+2} #

ACTION — ① ↓TPR → ↓BP → ② Reflex Tachycardia

③ + Renin Activity → Fluid Retention

Coronary, Cerebral & Renal Vasculature (↓BP)

P'KINETIC :- Well oral Absorbed, Metabolished by N-Acetylation, $t_{1/2}$ = 1h & Cl = 50ml/Kg/min

ADR = Hypotension, Tachycardia & Palpitation, Dizziness,

↳ ↑Cardiac O_2 demand → Angina

"Lupus Syndrome" - Immunological Reaction → Haemolytic Anemia, Vasculitis, Glomerulonephritis

USES ⇒ HTN - Emergencies is pregnant lady especially in "Pre eclampsia"

CHF - Combinat^n with Nitrates

K^+ CHANNEL OPENERS - Nicorandil, Pinacidil Minoxidil, Diazoxide

Diazoxide $\xrightarrow{(+)}$ K^+ $\xleftarrow{(-)}$ Sulphonyl urea

Nicorandil $\xrightarrow{(+)}$ K_{ATP} $\xleftarrow{(-)}$ Glibenclamide

MINOXIDIL → # Minoxidil N-O Sulphate

MOA : ⊕ K^+_{ATP} channel → Hyperpolarization → "ARTERIODILATION"

* ↑ blood flow in - Skin, Skeletal Mus., GI, Heart
* Reflex myocardial Contractility & CO - ↑
* CO increased 3-4 Fold due to enhance Venous Return
* Renal → Dialet Renal Artery but Systemic hypotension produced by drug — can ↓ Renal blood flow → (+) Renin
* Used in Renal dysfunctn associated with HTN

ADR ⇒ Cardiovascular Effects - ↓BP, ↑HR

Na^+/water Retention

Hypertrichosis → Abnormal Hair Growth

USES :- HTN in Emergency

→ Topically - in Alopecia

Myocardial Infarction

MI :- Irriversible myocardial damages, death or injury that caused by "Chronic Ischemia" and leads to "Heart Attack"

Reseon :- Oclusion of coronary Vesseles due to lipid deposition-"Atherosclerosis" & Chronic Vasospasm.

Coronary Artery :

(A) Left CA :→

↳ Left Anterior Descending :- Anterior L.V. wall

↳ Circumflex Branches :- L.A. & Posterior & lateral Wall of L.V.

B) Right C.A. → Right Atrium & Ventricle

* 50% Cases → Left Anterior Descending artery

Types of MI :-

① Transmular → thickness of V. wall

② Subendocardial → ⅓ - ½ inner wall

Manifestation :-

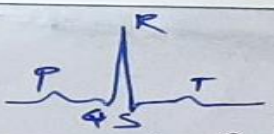
↳ Chest pain & Discomfort

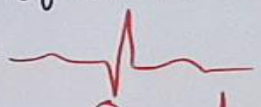
↳ Irriversible Cell injury after 20-30 min of Ischemia

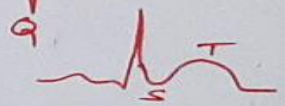
↳ Release myoc. Creatine phosphokinase (CPK)

↳ ECG :- Inversion of T-Wave, elevatⁿ of ST & pronoused Q-wave

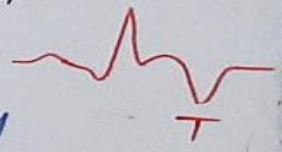
↳ Inflammatory & Oxd. stress







Complication :- Thromboembolism, Cardiogenic Shock, Pericarditis, CHF



Compansatory mech. Activatⁿ :- CA release, (+) RAAS, V. Hypertrophy

Therapy :-

A) Anti-Atherosclerotic drugs
↳ Anti-Platelet drugs

(B) Coguants / clot-disolving Agents - Streptokinase

(C) Tissue Plasmogen Activators - ↑ blood Flow

(D) Anti-hyperlipidemic drugs - "Statins"

ANTI-PLATELET DRUGS

Aspirin :- Irriversible inhibit the COX-I in platelet & ↓ TXA_2-mediated Platelet Aggregation. → "↓ TXA_2 & Platelet Activat^n"

↳ ↑ bleeding or ↑ blood Cloting time

USES: → At low Dose (150-375mg) → Angina, MI, Atherosclerosis & ↓ Incidence of Colon Cancer. At high dose (1g) → Antiinflammatory, Analgesic, Antipyratic ["NSAID"]

ADR - GI bleeding, Raye's Syndrome & Tinitis

CLOPIDOGRES :- Block the ADP-mediated Platelet Aggregation by Antagonising P_2Y_{12}-Receptor and further ↓ GpIIb/IIIa expression

USES: → Thrombotic stroke, Unstable Angina, MI, Acute Coronary Syndrome, Atherosclerosis

ADR(Ticlopidine) → Neutropenia, Thrombocytopenia

ABCIXIMAB :- Antagonise the GpIIb/IIIa Receptor on activated Platelet & prevent platelet aggregation.

USE - Acute Coronary Syndrome

ADR - Bleeding, Thrombocytopenia

PDE-III Inhibitors - Dipyridamol, Cilostazol

↳ ↓ Phosphodiesterase III → ↑ cAMP → ↓ Platelet Aggregation

USE - Angina, Prevent Stroke

ADR - GI upsate, Palpitation, Facial Flussing, Hypotension

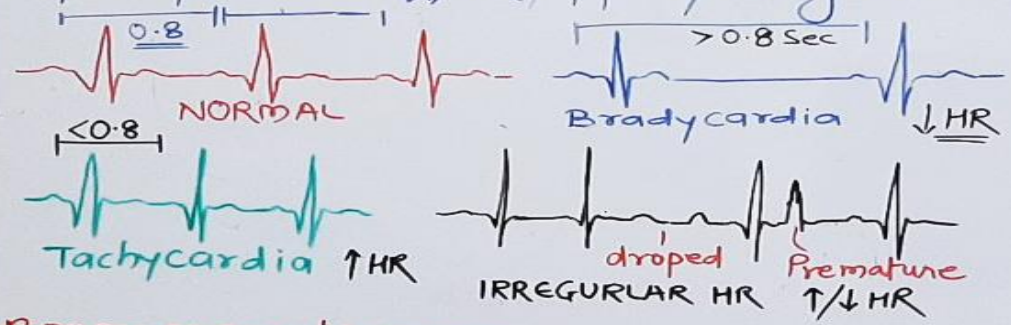
ARRHYTHMIA

→ Disturbance in cardiac rhyth due to improper impulse generatn and/or impulse conduction.

Normal Rhythm (HR) = 60 – 100 beats/min

Cardiac Cycle 1 beat ⇒ 0.8 Sec. (Systol + Diastol)

Dysrhythmia ⇒ ↓↓ HR / ↑↑ HR / Irregular HR



BRADY-CARDIA/ARRHYTHMIA = HR ≪ 60 bpm

↳ During Sleep & Common in "Athlets"

↳ "Carotid Sinus Syndrome" → Oversensetivity of carotid artery for BP through "Baroreceptor"

CO = HR × SV

BP = CO × TPR

Type- 1) Sinus Brady Cardia – ↓ Pacemaker Activity

2) Heart Block – Conduction Block (I, II, III degree)

3) Sick Sinus Syndrome = Improper Impulse generatn
↳ Bradycardia, Tachycard., Brady-Tachy Syndrome

TACHYCARDIA/TACHY ARRHYTHMIA – HR ≫ 100 bpm

↳ Body temp > 105 F – ↑HR (↑ 10 beats with 1 F Temp)

↳ (+) Sympathetic Activity

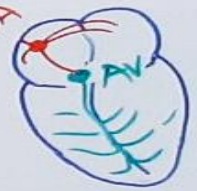
↳ Hyperthyroidism

↳ Myocardia Weakness

Tachy Arrhythmia :–

I Narrow QRS

Ⓐ Regular HR → Sinus Tachycardia
- Atrial Flutter (Fixed AV conductn)
- Atrial Tachycardia (Paroxymal / Non Paroximal)
→ Wolf Parkinson White Syndrome (WPW-Syndrome)
- AV nodal reentrant Tachycardia (AVNRT)



Ⓑ Irregular HR → Atrial Fibrillation
→ Atrial Flutter (Variable AV Conductn)
→ A. Tachycardia (Variable AV block)

II Wide QRS –

Ⓐ Regular – Ventricular Tachycardia
↳ SVT, ↳ AVNRT, ↳ WPW-Syndrome
↳ Atrial Tachycardia ↳ Sinus Tachycardia
↳ Atrial Flutter

Ⓑ Irregular – Atrial Fibrillatn, Torsades de points

Reason Behind Arrhythmia

① Ectopic foci
② After Depolarizatn
③ Re-entry
④ Conductn Block

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PC Pharmacology Concepts By Rajesh Choudhary

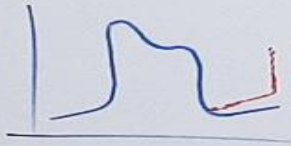
ARRHYTHMIA

↳ Disturbance in cardiac-rhythm

Reseons of Arrhythmia :—

I] Ectopic Foci / Enhance Pacemaker Activity –

⇒ During cardiac ischemia or cardiac arrest Impulses are generated from other than SA-node for Safty mechanism.

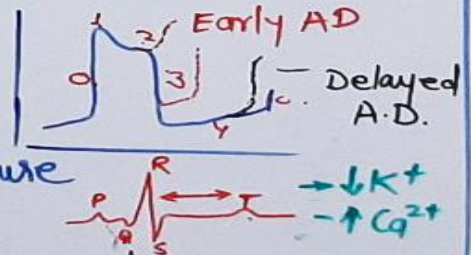


→ (+) Sympathetic – β,
→ Hypokalemia
→ Myocardial Stretch

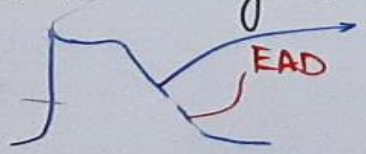
* Increase rate of depolarizatn during Phase IV is also called Spontaneous Distolic depolarizatn on the SA, AV, PF, Δ Cardiac-musde

II After Depolarization :–

This produce 2° depolarizatn and lead to normal and Premature Action Potential.

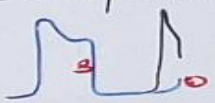


Early-AD. → Extra impulse is generated during Ph. III
It is associated with long QT interval due to slow repolarizatn



They result from depression of delayed rectifier K+ current

Delayed AD → DADs begin during phase 4, after repolarizatn is completed but before another normal AP would occur.

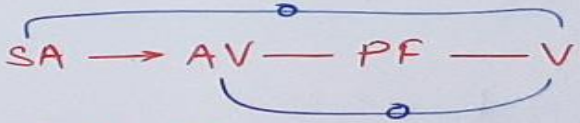


→ This occurs due to ↑ cystolic Ca^{2+} – Initial Premature AP,

P.AP ↳ Ca^{+2} overload [Digitalis, ↳ HF ↳ M. stretch
↳ Adrenergic stress – Catacholaminergic polymorphic Ven. Tachycardia (CPVT)

↳ Couple of beats ↳ Torsades De-Point

III] REENTRY – Due to abnormility of Conduction, an impulse can recirculate Δ cause repetitive activatn ↓ HR

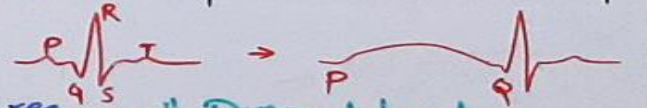


– Acessory Electrical Pathway (Fast Responsive)
↳ In Wolf Parkinson White Syndrom

IV] Conduction Block :–

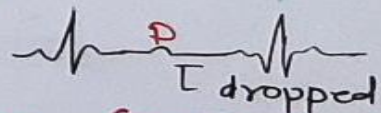
→ Due to Ischemia or Calcified tissue

① 1st degree → Incomplete Heart block, prolong PQ/PR interval



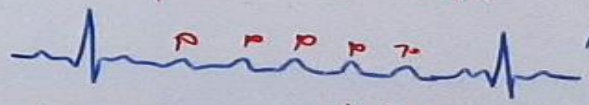
– ↓HR

② 2nd degree → " Droped beat



Atria beat is faster than Vent.
A : V = 2:1, 3:1

③ 3rd degree – Complete Heart block



Atrial Rate >100
Ventricle rate <40

Ventricle escape → Stokes Adams Syndrome

Anti-Arrhythmic Drugs

"Vaughan Williams & Singh" – Classified in to 4 class & further DC Harrison proposed a modified Subgrouping of Class-I agents.

Class-I :– Membrane Stabilizer (Na^+ channel blockers)

Ia :→ Moderate blocker, Prolonged APD & $\downarrow \frac{dv}{dt}$ of 0phase
↳ Quinidine, Procainamide, Disopyramide, & Moricizine → They block channel in Open state

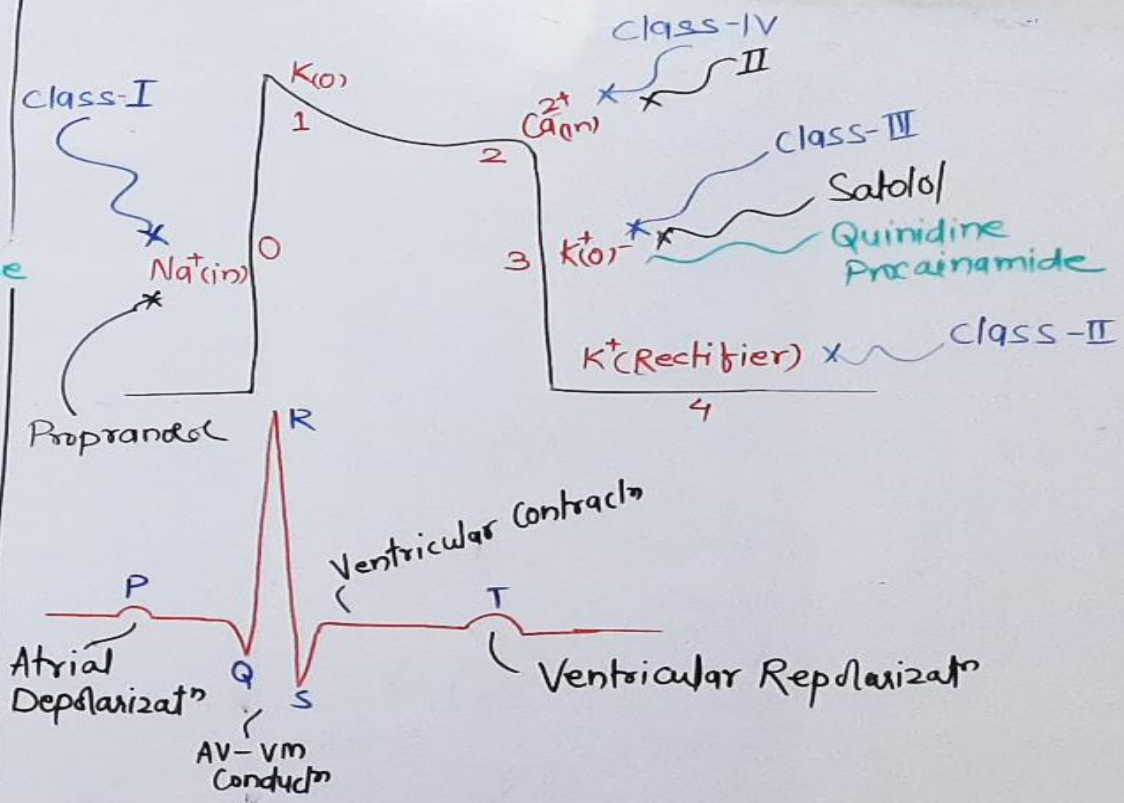
Ib :– Mild blockers, shorten APD, $\downarrow \frac{dv}{dt}$ of 0phase
↳ Lidocain, Phenytoin, Tocainide & Mexiletine
↳ They block the Na^+ channel in both State

Ic :→ Marked blockers, No effect on APD
↳ Encainide, Flecainide, Indecainide, Propaferone
↳ They block in open state & prolong Recovery time

Class-II :– "β-Blockers" – Slowdown Phase-4
↳ Propranolol, Metaprolol, Sotalol

Class-III – "K^+ channel Opener" – ↓ phase-3
Amioderone, Bretylium tosylate

Class-IV – "Ca^{+2} channel Blockers" – ↓ phase 2
- Verapamil, Diltiazem, Nifedipine



Cardiac Cycle → 0.8 Sec./beat
Ventricles – Systol – 0.3 Sec. / Diastol – 0.5 Sec
Atria – Systol – 0.1 Sec. / Diastol – 0.7 Sec.

QUINIDINE :- CLASS Ia ANTI-ARRHYTHMIC DRUG

↳ Quinine Alkaloid ⇒
↳ (+)-Anti-Arrhythmic / (−)-Anti-malerial drug

MOA :→ Open State Na^+ Channel Blocker, & moderately delay the channel recovery (1-10 Sec)

EFFECTS = # ↑ threshold potential to excitation
Block the AV-Conduction, Prolong ADP (due to k^+ channel blocker), Prolong Refraction - ERP/APD >1
↑ PR & QT intervals tends to Broaden QRS Complex
Abolish Re-entry & ↓ Ectopic pace-maker activity, ↓ Premature AP
Anti vegal Action → Prolong Atrial ERP

Other Effects :-
↳ CVS ⇒ ↓ BP (due to α_1-blockade & direct Cardiac depression)
↳ At high dose - L-type Ca^{+2} channel blocker
↳ ↓ skeletal muscle contraction
↳ ↑ Uterine Contraction
↳ Neurological Effects - Vertigo, Ringing in Ear, Visual disturbance ##
- "CINCHONISM EFFECTS"

ADR - ① Cardiac-Arrest - Sudden death
② Cinchonism
③ Idosyncrasy & Hypersensetivity (Allergy)

Uses :- ① Atrial & Ventricular Arrhythmia
② Prevention of Proxymal recurrent Atrial Fibrillation (Triggered by vegal overactivity)

Interactn :-
+ Digitalis → ↑ Palsma Digitalis - toxicity
+ Vasodilator → Hypotension
+ Diuretics → Hypokalemia → Torsades de point
+ β-blocker, CCB → ↑↑ Cardiac Depression

Most of Anti-Arrhythmic may precipitate Arrhythmia, They called "Pro-Arrhythmic Drug" except β-blocker & CCB

* Ia - Procainamide → N-acety Proc. ⇒ K^+ ch. blocker
* ↳ ADR → Torsades-De-points

Ib :- Lidocain → block Na^+ ch. in both state but dont delay the recovery, "No Supress AV Conductn" "↓ Card. Contractility" "↓ Ectopic Automataculty"
use → V. Arrhythmia, # Digitalis toxicity"

Ic - Propofenone - block in open state, long recovery time
- Depress Impulse transmission & has profound effect on HIS-Purkinje & Accessory Pathway Conductn
- Used in PSVT

ATHEROSCLEROSIS / LIPIDS

Arterial Diseases: – "Atherosclerosis, Aneurysm, Embolism, Vasospastic,

ATH. ⇒ It is caused by deposition of "Lipid" plaques in the "Artery wall"

⇒ It can lead to "IHD" = Angina & MI

LIPIDS / LPs: – Dietary lipids & cholesterol are insoluble in blood plasma. And they are transported as a complex → "Lipoproteins"

D.Fats → Intestine → Blood → Liver

chylomicrone

VLDL

Tissues ← LDL ← Blood

HDL

① Chylomicrone – 90% TG, 3% CH.
- ↳ lowest Density, ↳ Formed in Gut-wall
- ↳ Transported Dietary TG from intestine into blood.

② **VLDL:** – Very Low Density LPs –
- ↳ 55% TG & 20% CH. ↳ Syn. in liver
- → VLDL → ILDL in blood

③ ILDL = Equal amount of TG, Phospholipids & CH.

④ LDL = Low Density LPs – "Bad Cholesterol"
- ↳ 50% CH. & 10% TG ↳ (+) LDL Receptor
- ↳ Carrier of cholesterol from liver to Tissue

⑤ HDL = High Density LPs "Good Cholesterol"
- ↳ 5% TG & 20% CH.

"Atherosclerotic Index = $\frac{LDL}{HDL}$ >

	Normal (mg/dL)	Risk / Hyperlipidemia
TG →	50 to 150	> 500 ↑
T.C. →	150 to 200	> 240 ↑
LDL →	80 to 150	> 160 ↑
HDL →	35 to 60	< 35 ↓

Risk Factors :→ Hyperlipidemia, HTN, Alcohol, Smoking, β-blockers

Manisfastation ⇒ P.A.D. / C.A.D. / I.H.D.
- ↳ Aneurysm, Embolism, Hemorrhage

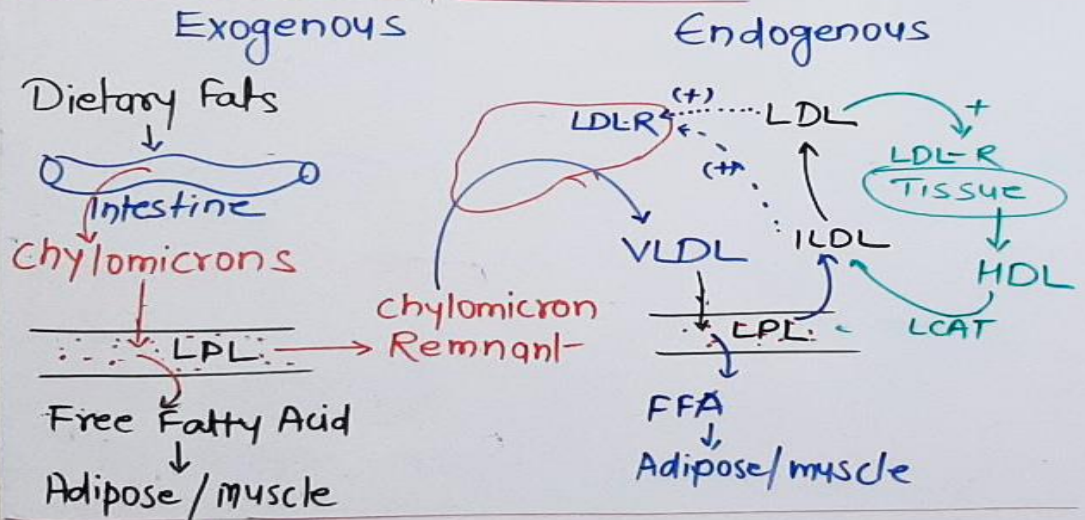
THERAPY – ① Antihyperlipidemics
② Anti-Coagulants – Warfarin
(3) Anti-Platelets – Aspirin
(4) Thrombolytics – Streptokinase

ANTI-HYPERLIPIDEMIC DRUGS

HYPERLIPIDEMIA :- Increased blood lipids

CH =	150 - 200 mg/dL	> 240 mg/dL
TG =	50 - 150 mg/dL	> 200 " "
LDL =	80 - 150 mg/dL	> 160 " "
HDL =	35 - 60 mg/dL	< 30 " "

Lipid Transports / Metabolism



Hyperlipidemias :-

1. Primary → Genetic / Monogenic
2. Secondary → Associated with Diabetes, Myxodema, Alcoholism
3. Polygenic → Multifactorial

Types of Primary Hyperlipidemia

	Elevated LPs	Lipids
I. Familial LPL deficiency	Chylomicrons	↑↑CH & ↑↑↑TG
IIa Fam. Hypercholesterolamia	LDL	↑↑CH.
IIb Polygenic "	LDL	↑↑CH.
III Fam. Dysbetalipoproteinemia	IDL & Chy. Rem.	↑CH & ↑TG
IV Hypertriglyceridaemia	VLDL	↑↑TG
V Fam. Comb. Hyperlipidemia	VLDL & LDL	↑CH & ↑TG

ANTI HYPERLIPIDEMICS -

1. HMG-Co-Reductase Inhibitors - "Statins"
   - Lovastatin, Simvastatin, Atorvastatin
2. Bile Acid Sequestrants - Cholestyramine, Colistipol, Colesevelam
3. LPL-Activator (PPARα-Agonist) = "Fibrates"
   - Gemfebrozil, Fenofibrate, Bezafibrate
4. Lipolysis & TG Syn. Inhibitors - Nicotinic acid
5. Sterol Abs. Inhibitor - Ezetimbe

Pharmacology of "Statins"

HMG (3-hydroxy-3-methyl glutaryl)-Co-A Reductase Inhibitors → "Lovastatin" (1980s), Atorvastatin, Simvastatin

MOA:- HMG-CoA —(HMG CoA-Reductase / "Statins")→ Mevalonate → Cholesterol

Statins ↓ LDL-CH Synthesis (20 to 50%)

Lovastatin (40mg) → ↓ 30-35%
Atorvastatin (10mg) → ↓ 30-35%
Simvastatin (80mg) → ↓ 40-50%

(+) feedback mechanism

↑ LDL Receptor Expression on liver cell
↓
↑ Receptor-mediated uptake & catabolism of IDL/LDL

HMGCoA Reductase Enz. activity maximal at midnight so all "Statins" should given at bed time.

All statin produce peak LDL-CH lowering effect after 1-2 weeks of therapy.

They also ↓ T.G level (10-30%) & ↑ HDL (5-15%)

USES: 1) First choice for Pº hyperlipidemia with raised LDL-CH. Type- IIa, IIb, V

II) Secondary Hypercholesterolemia

III) Atherosclerotic CVS-disorders – Angina & MI → Acute Coronary Syndrome, Thrombic Stroke, PAD

ADR: –# GI-Complication, Headache → Common
Sleep disturbance, Rashes
↑ Serum Transaminase – but Liver Damage is rare – So keep in monitoring
Muscle aches,
↑ Serum CPK – Myopathy (rare)

Hepatic injury & myopathy can occurs when Statins are given alongwith – Niacin/Gemfibrozil/or Enz. Inhibitors – Ketoconazole, Erythromycine etc

"Fibrates – interfere with the Hepatic uptake of Statin by Org. Anion Transporter (OAT-P2) & Should not given with them.

Contraindicated in – Pregnancy & Diabetes

P'Kinetic – Lovastatin –
→ Lipophilic in nature & given orally in precursor "Lactone"
→ Metabolites are mainly excreted by bile
→ $t_{1/2}$ = 2-4 h

FIBRATES

LPL-Activators – Gemfibrozil, Bezafibrate, Fenofibrate
(Iso Butyric ā derv.)

MOA – ⊕ PPAR$_\alpha$ → ↑ LPL Synthesis & Fatty ā Oxidation

LPL – is a key Enz in degradatⁿ of VLDL, resulting in lowering of blood TG level.

Activatⁿ of PPAR$_\alpha$ also enhance LDL-Receptor expression in liver (Bezafibrate, Fenofibrate)

Fibrates also ↓ hepatic TG Synthesis

Major Effects – ↓ TG (20-50 %)
↓ LDL-CH (10-15 %)
↑ HDL (10-15 %)

Gemfibrozil – fibric ā derivative

↳ ↓ Plasma TG level by enhancing breakdown & Supressing hepatic Synthesis of T.G.

↳ # In "Helsinki Heart Study", men without known CAD treated with Gemfibrozil had a 34 % reduction in fatal & nonfatal MI

Effective against High TG & low HDL patient

P'Kinetic – orally abs, metabolized by Glucuronic Conj. Excreted through urine, $t_{1/2}$ = 1-2 h

ADR –
↳ Epigastric distress, loose motion
↳ Body pain, Rashes, Eosinophelia,
↳ Impotence, Blurred Vision,
↳ Myopathy & Hepatitis – Uncommon but increased risk with "Statins"

Contraindication – Pregnancy

Uses – Gemfibrozil – 600 mg – B.D

↳ Anti-Hyperlipidemia – patient raised with T.G.
↳ Most Effective in Type III – Hyperlipoproteinaemia
↳ Also Effective in Type IV & V
↳ Also suitable for Type II-Diabetes
↳ ↓ Atherosclerotic CVS-diseases

2nd Generation – Bezafibrate
→ Alternative to Gemfibrozil for Type III IV V P°Hyper——
→ has greater LDL-CH lowering effects
→ ↓ Coronary Events
→ ADR & CI – Similar as Gemfibrozil
→ Dose should be reduced in older & Renal insufficiency patients

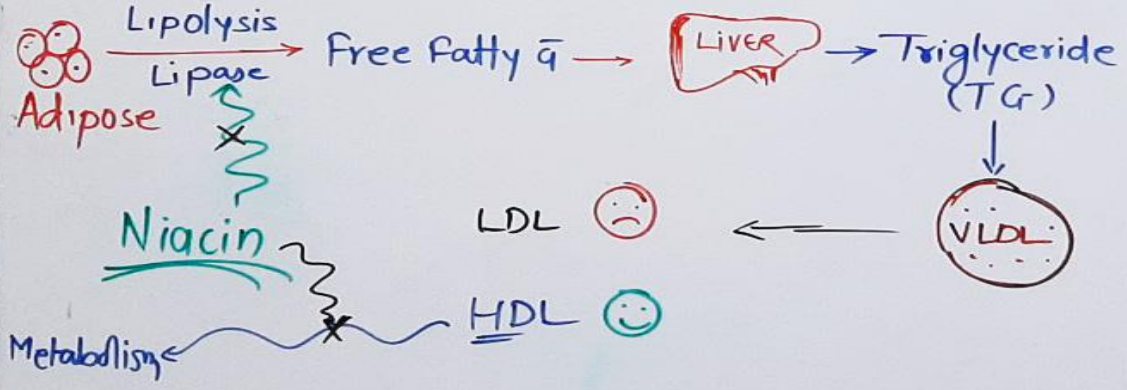
Fenofibrate – has Greater HDL raising & LDL-CH lowering Effects than other.

NIACIN / NICOTINIC ACID / VIT. B_3

MOA – Inhibits the Lipolysis & T.G. Synthesis

Effects – ↓ TGs and VLDL level rapidly, followed by modest fall ↓ in LDL-CH & T.C.

→ ↓ Plasma TG – 20-50%
→ ↓ Plasma CH. – 15-20%
→ ↑ HDL-CH – 20-35%



Niacin (+) → Niacin Receptor (GiPCR) at Adipocyte and Cause decrease in hormone stimulated intracellular cAMP formation & ↓ Lipolysis

USES/BENEFITS – Type III, IV, V Hyperlipidemia

(1) Dyslipidemia → to ↓ Plasm TG, LDL & ↑ HDL
(2) ↓ Atherosclerotic CVS events – MI, Angina,
(3)# To control pancreatitis associated with Hypertriglyceridemia (Type IV & V disorder)

Contra-Indication :-

The NICE guideline (2014) do not recommend use of Niacin ± Statin For 1° and 2° preventn of CVD
Also donot use in Diabetes patient to prophylaxis of CVD

ADR :– (I)* Flushing, Heat, itching due to Cutaneous Vasodilatn (↑ PGD_2) → * Aspirin (325mg) before Niacin or use Sustained release Tablet or "Lorapiprant" ↳ PGD_2 Antag.

* ER Tab - 1g Niacin + 20mg Lorapiprant

(II) Dyspepsia, Vomiting, diarrhoea
(III)# Hepatic damage – imp risk
(IV)# Dryness & Hyperpigmentatn of skin
(V)# Hyperglycemia – Not used in Diabetes
(VI)# Hyperuricaemia – —"— gout

"SHOCK"

↳ It is the state of insufficient blood perfusion & Oxygenation of the cells as a result of problem with the CVS. ⇒ Tissue Ischemia/Hypoxia

↳ It can lead to Multi-Organ Dysfunctn Syndrome (MODS)

Heart/CVS unable to produce adaquate "CO"

"BP = CO · TPR" & "CO = HR x SV"

Symptoms :- Weakness, Palpitatn, Hypotension, Confusion, Thirst, Anxiety, ↑ Respiration

Types & Reason :-

I] **Hypo-Volemic** ⇒ "low Circulating blood Volume"

→ Hemorrhagic :- Internal & External bleeding - Blood loss

→ Non-Hemorrhage :- "Fluid loss" - Vomiting, Diarrhoea, Burns, Pancreatitis

II] **Cardeogenic** :- "Failure of Heart to pump enough"

↳ M. Ischemia/infraction, M. weakness, Arrhythmia, Myopathy, CHF, Valvular dysfunctn

III] **Obstructive Shock** = It is associated with physical obstruction of great vessels of Systemic & pulmonary circulatn

→ Pulmonary Embolism - due to thrombosis

→ Aortic stenosis

IV. **Distributive Shock** -

↳ low BP due dilation of blood vessels

(A) **Septic shock** - Systemic infection leads to Hypotension. Bac. → E.coli, K. pneumoniae, Streptococci

↳ They have endotoxins which produces harmfull biochemical, immunological & neurological effects

(B) **Anaphylactic Shock** → "Allergic Response"

Anaphylaxis - Hypersensitivity - IgE mediated - "Ag-Ab"

Anaphylactoid Reactn :- Do not Require Sensetizing exposure → Non-IgE mediated

(C) **Neurogenic Shock** - "loss of Sympathetic tone"

↳ Spinal Cord injury, Above T_1 injury leads to entire sympathetic disturbance

Hemodynamic Feature

	TPR	Preload	CO	others
Hypovolemic -	↑	↓	↓	30-40% blood loss
Cardiogenic -	↑	↑	↓↓	EF < 50% SBP < 90 mm Hg
Anaphylactic -	↓	—	↓	↓BP - Allergy
Hypodynamic Septic Shock	↓	↓	↓	↓BP - Infection

Drugs Used in Shock

I. Hypovolemic Shock ⇒ "low Blood Volume"

↳ Fluid Replacement Therapy – I.V. Fluids

"Crystalloids"

→ Nacl, Lactated Ringers, electrolyte

→ colloidal Plasma Expander – "Dextron"

Dextron – Isolated from beet Roots

→ Whole blood

II Cardiogenic Shock – "Heart Failure"

Ⓐ Inotropic Drugs – Adrenaline, Dobutamine, Dopamine (preffered in Oligouric Condition), PDE Is – (Amrinone, Milrinone)

III Obstructive Shock – "Obstruction in/out of Heart)

↳ Antiplatelets drugs,

↳ Thrombolytic Agents

↳ Angioplasty

IV. Septic Shock – "Infection + ⇓ SVR/BP"

↳ Antibiotics

↳ Pressor Agents – "Nor-Adrenaline
Phenylphrine
Vasopressin

↳ Isoprinaline – ↑ Tissue Perfusion

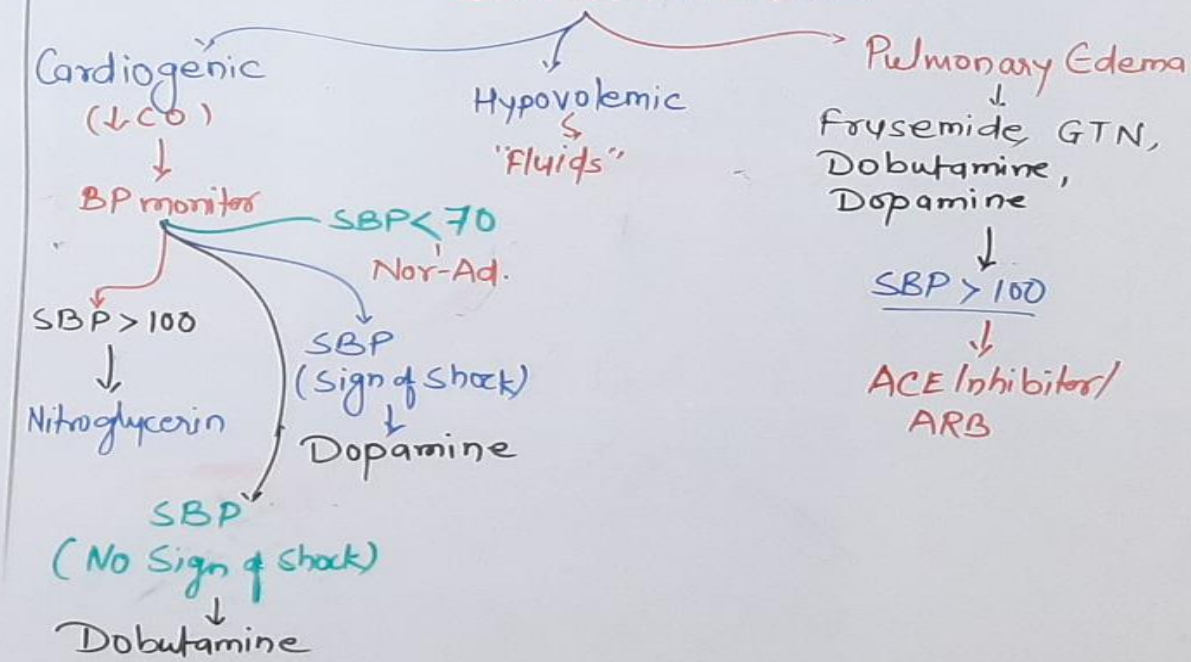
V Anaphylactic Shock – "Allergy" & ⇓ SVR/BP

↳ Anti-Allergic – Antihistaminics (H1-Antagonist)
– Steroids

↳ Adrenaline & Non Adrenaline

↳ Inhaled Oxygen

CLINICAL APPROACH



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