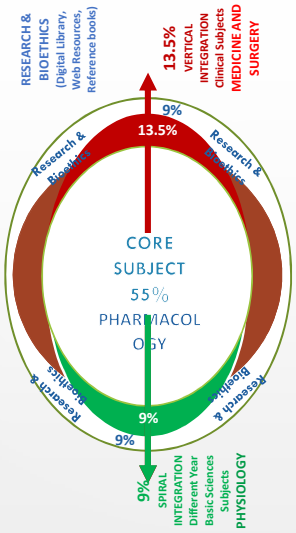
MOTTO AND VISION

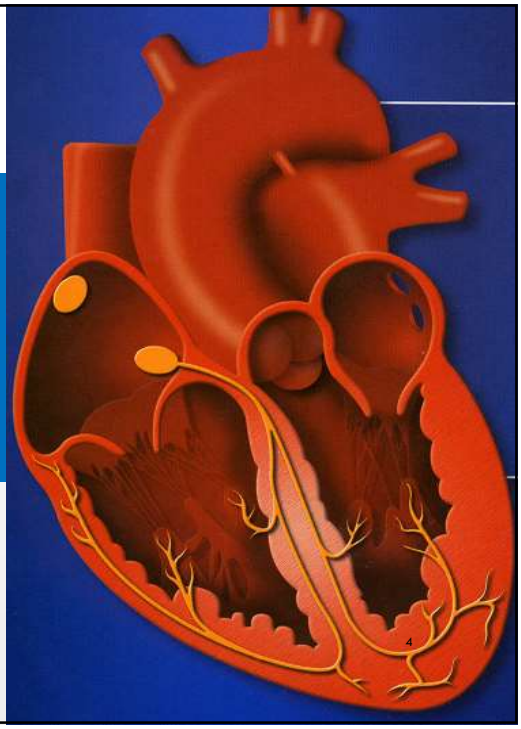
- TO IMPART EVIDENCE BASED RESEARCH ORIENTED MEDICAL EDUCATION
- TO PROVIDE BEST POSSIBLE PATIENT CARE
- TO INCULCATE THE VALUES OF MUTUAL RESPECT AND ETHICAL PRACTICE OF MEDICINE

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



Model 3rd Year Pharmacology LGIS (slides)	
Core Subject – 70%	
Horizontal Integration – 10%	
Vertical integration (Clinical Subjects)	• Medicine (10 %)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	
Research & Bioethics 5%	

DRUGS USED IN HEART FAILURE



➢ **VERTICLE INTEGRATION MEDICINE/ SURGERY**

CARDIAC FAILURE

- Heart failure (HF)/Congestive Heart Failure (CHF)Congestive Cardiac Failure (CCF)
- Progressive disease
  - when cardiac output is inadequate to fulfil oxygen requirement of the organs according to their needs
- Is a syndrome with many causes, may involve one or both ventricles

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HORIZONTAL INTEGRATION – PATHOLOGY

Compensatory Physiological Responses In CCF

- NEUROHUMORAL (EXTRINSIC) COMPENSATION
- INTRINSIC COMPENSATORY MECHANISM

NEUROHUMORAL (EXTRINSIC) COMPENSATION

- **Sympathetic nervous system stimulation**
- **Renin-angiotensin system activation**

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Natriuretic Peptides, Endothelin & Vasopressin

- Hormones released in HF
  - **Natriuretic peptide (ANP & BNP)**
  - **Endothelin**
  - **Vasopressin**
- ANP & BNP released in response to increase in atrial & ventricular volume/pressure
- ANP & BNP suppress renin & aldosterone production, promoting vasodilation & natriuresis
- BNP(A biomarker of HF)

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Intrinsic Compensatory Mechanisms

MYOCARDIAL HYPERTROPHY

- Important intrinsic compensatory mechanism increase in muscle mass, helps to maintain cardiac performance initially in volume overload
- Long term hypertrophy lead to **CARDIAC REMODELING**

CARDIAC REMODELING

- Cardiac dilation with slow structural changes
- Interstitial fibrosis
- Ventricular wall stiffness
- Formation of abnormal myocardial cells

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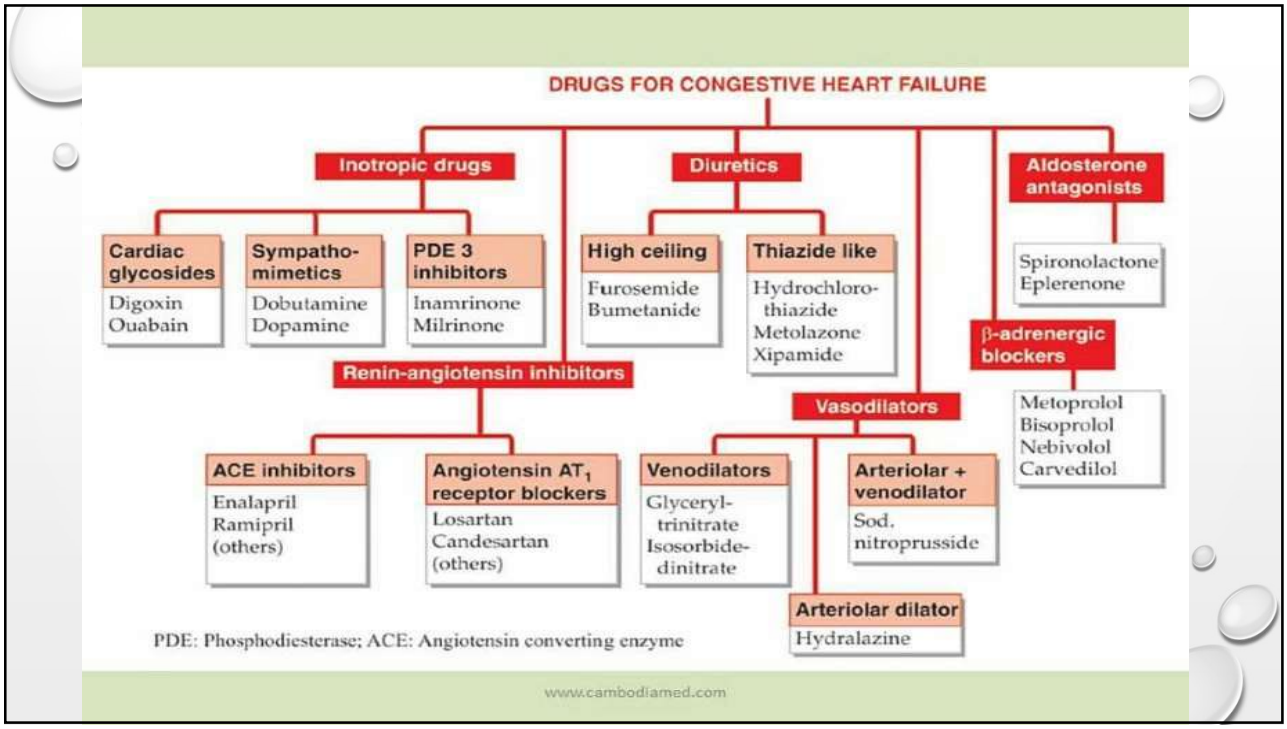
CORE SUBJECT – PHARMACOLOGY



Renin–angiotensin–aldosterone Axis Antagonists/Angiotensin-converting Enzyme Inhibitors

ACE Inhibitors --- CAPTOPRIL, ENALAPRIL, LISINOPRIL

- Drug of choice in pts with CHF
- ACE inhibitor used with diuretics in chronic HF

- **DECREASE AFTERLOAD**

- **DECREASE PRELOAD DECREASE SYMPATHETIC ACTIVITY**

- **DECREASE REMODELING OF HEART & VESSELS**

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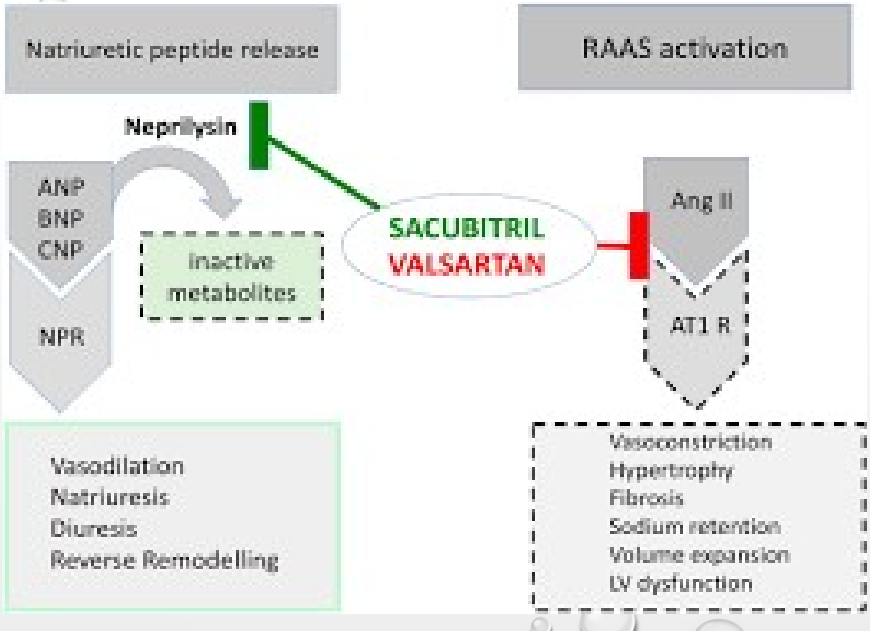

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BETA BLOCKERS

CARVEDILOL, BISOPROLOL, METOPROLOL & NEBIVOLOL

- β blockers are helpful by preventing changes that occur b/c of chronic activation of sympathetic nervous system
- ↓HR & ↓ renin release
- Decreasing remodeling, hypertrophy, & cell death
- Reduce morbidity & mortality associated with HF
- Very low starting dose, titrated gradually to effective doses in chronic HF
- ONLY TO STABLE PATIENTS

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DIURETICS

- Diuretics, are drugs of choice in heart failure
- Reduce pulmonary congestion & peripheral edema by causing diuresis→ reduce extracellular fluid volume → reduction in preload→ decreases cardiac workload & oxygen demand
- **Reduces afterload**
- **No direct effect on cardiac contractility**

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VASODILATORS

- Fixed combination of Hydralazine & Isosorbide dinitrate available for pts with chronic HF

ISOSORBIDE DINITRATE

- Preferentially dilates large blood vessels, venous capacitance & arterial blood vessels
- Main effect (low dose) is "venous Pooling" & reduction of preload
- Dilatation of arteries (high dose) → decreases afterload

HYDRALAZINE: direct arteriolar vasodilator

- Dilation of arteries→ decrease afterload
- Both drugs also prevent remodeling of heart

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VASODILATORS

NESIRITIDE:

- Recombinant synthetic form of endogenous peptide brain natriuretic peptide (BNP)
- Use in acute (not chronic) cardiac failure
- Increases cGMP in smooth muscle cells & reduces venous & arteriolar tone
- Also causes diuresis
- Has a short half-life: 18 minutes
- Given as a bolus IV dose followed by continuous infusion
- A/E: Excessive hypotension

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BETA-ADRENOCEPTOR AGONISTS

DOPAMINE & DOBUTAMINE
+ve ionotropic agents used in acute decompensated heart failure with reduced CO

DOBUTAMINE
- Principal hemodynamic effect of dobutamine is ↑in stroke volume from positive inotropy, & a small decrease in systemic vascular resistance & therefore, afterload
- Half life 2 min so must be given by I.V

A/E: Tachycardia & ventricular arrhythmias

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DOPAMINE

Mechanism of action:

- Dose related action on D_1,β_1 & α_1

Pharmacological action:

- Low dose→ activate D_1→

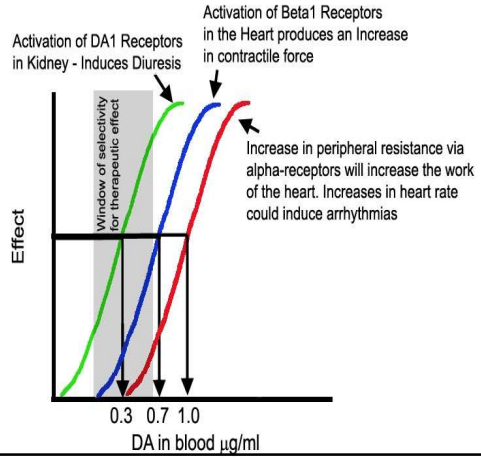
causes increase in RBF

- Intermediate dose→ activate β_1→

cause increase FOC, HR, CO

ROA: Given by IV infusion

Adverse effects: Cardiac arrhythmias



CARDIAC GLYCOSIDES

SOURCES

DIGITALIS PURPUREA LEAVES (Foxglove)
DIGITOXIN, GITOXIN, GITALIN
DIGITALIS LANATA LEAVES (White flowers)
DIGOXIN, DIGITOXIN, GITOXIN

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PHARMACOKINETICS

- Route of administration: Oral as well as parenteral
- Large volume of distribution, distributed to tissues, including CNS, principal tissue reservoir is skeletal muscle
- Half-life: 36–40 hrs.
- Has small hepatic metabolism
- Excreted unchanged by kidneys
- **Narrow therapeutic index**

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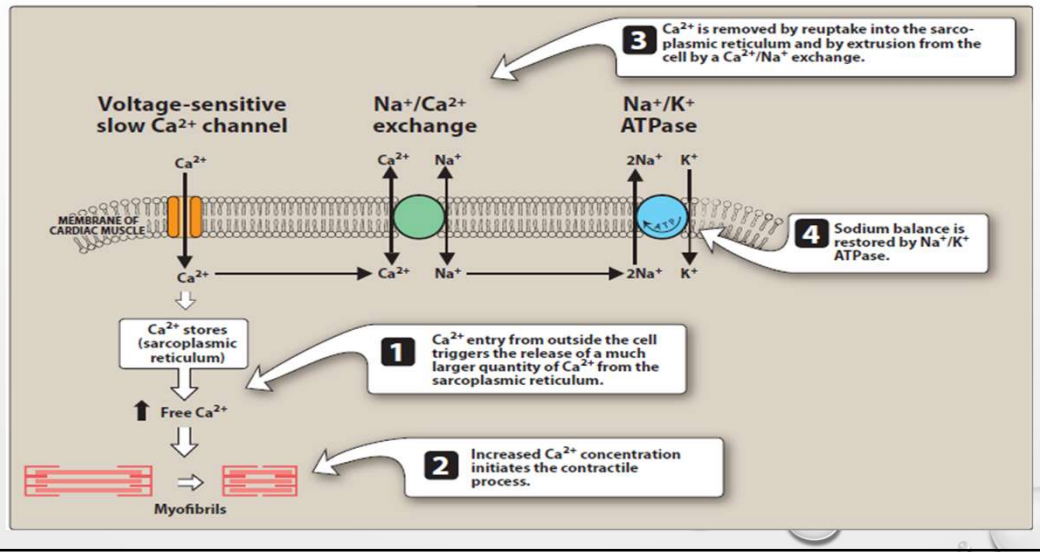
PHYSIOLOGY OF MYOCARDIAL CONTRACTION



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MECHANICAL EFFECTS/MOA

DIGOXIN/DIGITOXIN ADMINISTRATION

↓

BINDING TO ALPHA SUBUNIT OF CARDIOMYOCYTE MEMBRANE NA^{+}/K^{+}ATPASE ELECTROGENIC PUMP

↓

INHIBITION OF NA^{+}/K^{+}ATPASE

↓

↓ NA^{+} EFFLUX

↓

↓ NA^{+}-CA^{2+} EXCHANGER ACTIVITY

↓

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CONTD….

↑↑ CA^{2+} AVAILABLE FOR INTERACTION WITH CARDIAC MYOCYTE CELL CONTRACTILE PROTEINS

↓

↑ FORCE OF MYOCARDIAL CONTRACTION
(+VE INOTROPIC EFFECT)

↓

↑ CARDIAC OUTPUT

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KIDNEY- Diuresis occurs due to improvement in renal perfusion

Electrical Effects On Cardiac Tissues

Tissue	Effect at Therapeutic dosage	Effect at toxic dosage
SA NODE	↓ Rate	Sinus bradycardia
AV NODE	↓ Conduction velocity ↑ Refractory period	AV nodal block Heart block
ATRIAL MUSCLE	↓ Refractory period	Atrial flutter-fibrillation
PURKINJE SYSTEM, VENTRICULAR MUSCLE	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation

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A

CLINICAL USES

i. **Congestive heart failure (LV systolic dysfuction)**

i. **Atrial arrhythmias including Atrial flutter and fibrillation**

i. **Paroxysmal Atrial & Atrioventricular nodal tachycardia**

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ADVERSE EFFECTS

Cardiac glycosides have an extremely narrow therapeutic index

CARDIAC:

- Extreme bradycardia, Atrial fibrillation, Atrioventricular block
- Overloading of intracellular Ca^{2+} stores produce depolarizing afterpotentials (**DELAYED AFTERDEPOLARIZATIONS**)
- After depolarization on reaching threshold, produces **ECTOPIC BEATS**
- Further intoxication → ventricular fibrillation
- Almost every type of arrhythmia can be produced by digitalis

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ADVERSE EFFECTS

NON CARDIAC ADVERSE EFFECTS:

- **GIT-** anorexia, diarrhea, nausea, vomiting & abdominal pain (may be initial indicators of toxicity)
- Spastic contraction of mesenteric artery can rarely lead to severe diarrhea & life-threatening necrosis of intestine

CNS effect- disorientation, hallucination

- Visual disturbance & aberrations of color perception (green yellow halos around bright objects)

Gynecomastia

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DIGOXIN TOXICITY

Stop the drug immediately

- Slow **I/V K^+ supplementation** for correction of hypokalemia
- **Cholestyramine** binds unabsorbed digoxin & increases its elimination
- **Atropine** heart block……if not effective…. Cardiac pacing
- **Lidocaine or phenytoin**, for digoxin induced Ventricular arrhythmias
- Digitalis antibodies, **digoxin immune fab (Digibind)**
- It binds to digoxin forming a complex which can be excreted through kidneys

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Interactions With Potassium, Calcium, And Magnesium

POTASSIUM:

- Digoxin competes for K^+ binding at Na^+/K^+ATPase
- Hypokalemia: increases toxicity
- Hyperkalemia: decreases toxicity

MAGNESIUM:

- Hypomagnesemia : increases toxicity

CALCIUM:

- Hypercalcemia: increases toxicity……. abnormal automaticity……. Arrhythmias

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BIPYRIDINES

MILRINONE & INAMRINONE

- Selective **phosphodiesterase (PDE3) inhibitors**
- Inhibition of PDE prevents cAMP breakdown → ↑ intracellular conc. of cAMP in cardiac myocytes → ↑ cardiac contractility
- Dilate resistance & capacitance vessels (vasodilation decreases preload & afterload
- Improves CO by +ve Ionotropic effect & by reducing preload & afterload
- Suitable only for acute CHF

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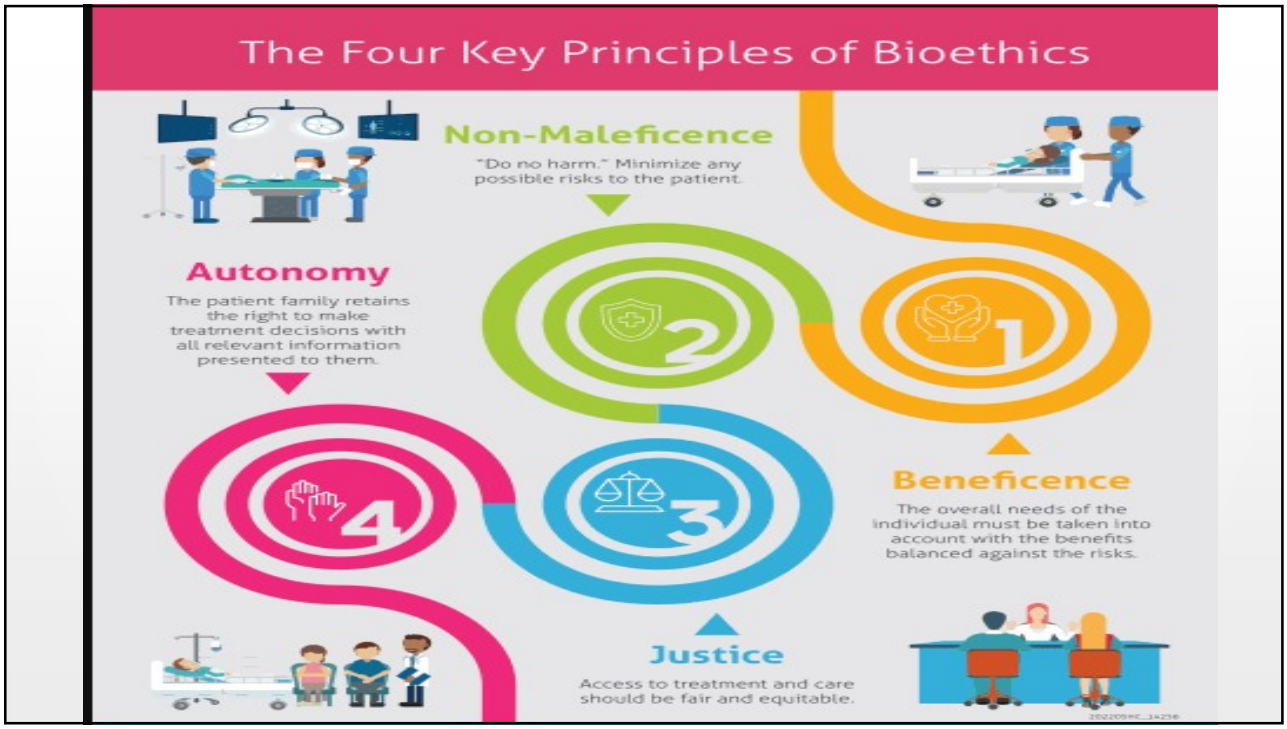

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