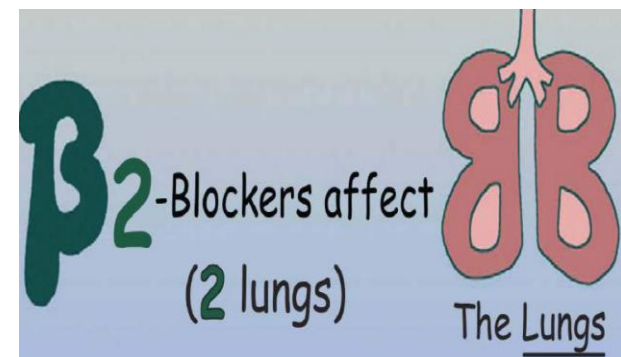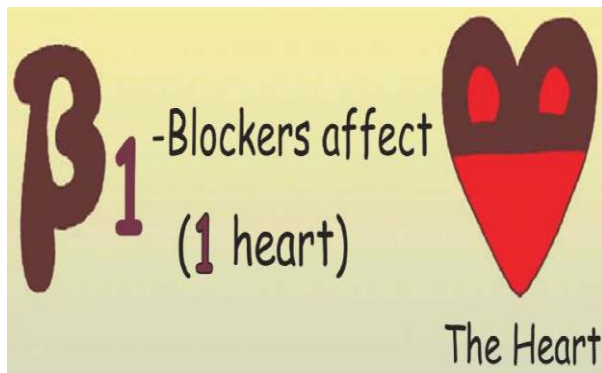# β- *Adrenoceptors blockers*

**Prof. Hanan Hagar**
**Pharmacology Unit**
**College of Medicine**

*By the end of this lecture, the student should be able to*

- **Outline the mechanisms of action of B-blockers**

- **Classify B-receptor blockers into selective & non- selective**

- **Know the pharmacokinetic aspects & pharmacodynamic effects of  B- adrenergic blockers.**

- **Identify the specific uses of non selective and selective B -adrenergic blockers.**

# Classification of β- Adrenoceptors Blockers

| Selective β1 antagonists | Non selective β- Antagonists |
|---|---|
| **Acebutolol, Atenolol** | Blocks β1& β2 receptors |
| **Bisoprolol, Betaxolol** | Oxprenolol |
| **Celiprolol** | Propranolol, Pindolol |
| **Esmolol, Metoprolol** | Sotalol, Timolol (STOP) |

**Mixed α, β receptors blockers**

➢ **Carvedilol**

➢ **Labetalol**



BETA-BLOCKERS
RX metroprolol (Lopressor)
(Ends in OLOL)
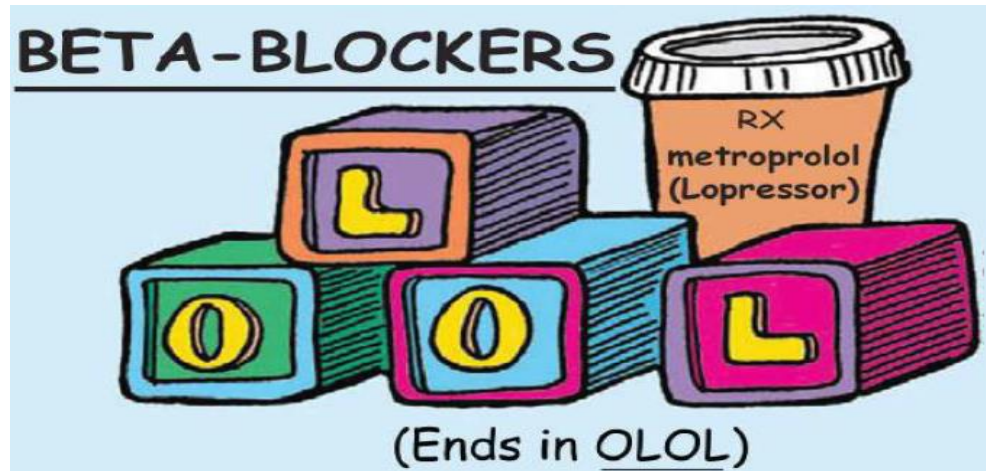
# β ADRENOCEPTOR BLOCKERS

## Pharmacodynamic Classification

**1** - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

### According to selectivity

**Non-Selective**

Block $\beta_1$ & $\beta_2$

Propranolol, Sotalol, Timolol (Eye)

**Selective**

Block $\beta_1$

Atenolol, Bisoprolol, Metoprolol, Esmolol

**Labetalol, Carvedilol (mixed $\alpha$, $\beta$ blockers)**

**2** - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

### According to presence of agonistic/antagonistic action; Intrinsic Sympathomimetic Activity ( ISA )

**Without ISA**

Atenolol, Bisoprolol, Metoprolol
Propranolol, Sotalol, Timolol, carvedilol

**With ISA (may activate beta receptors)**

Acebutolol, Pindolol, Oxprenolol, Celiprolol

**3** - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

### According to presence of membrane stabilizing effects i.e. Block Na Channels Quinidine-like action Antiarrythmic action

Propranolol, labetalol

# β ADRENOCEPTOR BLOCKERS

## Pharmacokinetic Classification
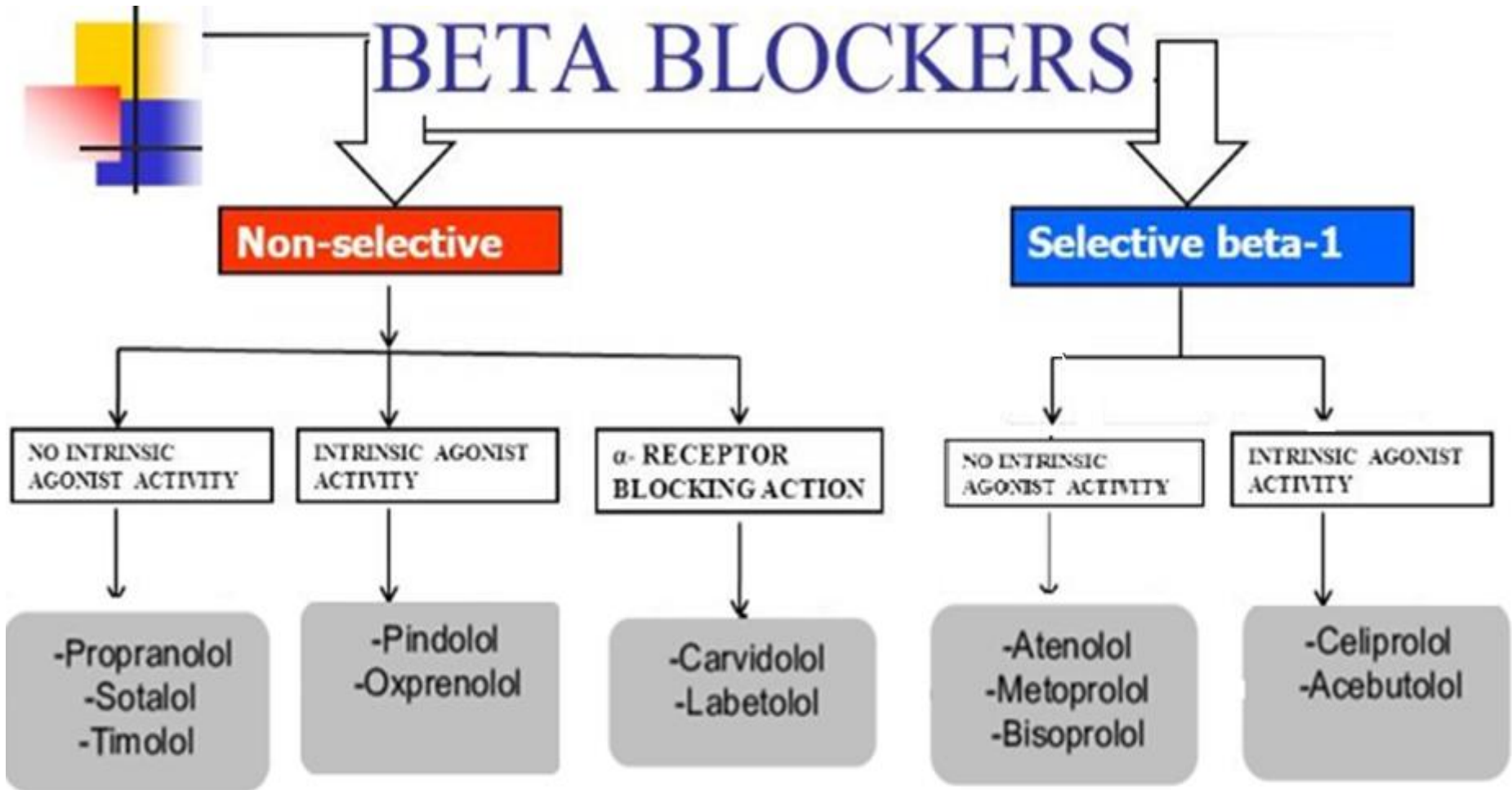
According to their lipid solubility

**Lipophylic**                                                   **Hydrophilic**

|  | Lipophilic | Hydrophilic |
|---|---|---|
| Oral absorption | Complete | Irregular |
| Liver metabolism | Yes | No |
| $t_{1/2}$ | Short | Long |
| CNS side effects | High | low |
|  | Metoprolol Propranolol, Timolol Labetalol , Carvedilol | Atenolol, Bisoprolol, Esmolol Sotalol |

**CNS depressant effects i.e. Sedative effect➤ ↓ Anxiety**

# β ADRENOCEPTOR BLOCKERS



BETA BLOCKERS

## Non-selective

### NO INTRINSIC AGONIST ACTIVITY
-Propranolol
-Sotalol
-Timolol

### INTRINSIC AGONIST ACTIVITY
-Pindolol
-Oxprenolol

### α- RECEPTOR BLOCKING ACTION
-Carvidolol
-Labetolol

## Selective beta-1

### NO INTRINSIC AGONIST ACTIVITY
-Atenolol
-Metoprolol
-Bisoprolol

### INTRINSIC AGONIST ACTIVITY
-Celiprolol
-Acebutolol

## *Pharmacokinetis of β–blockers:*

- **Most of them are lipid soluble**
- **Lipid soluble β–blockers**
  - **well absorbed orally.**
  - **are rapidly distributed, cross readily BBB**
  - **Have CNS depressant actions**

  **e.g. Metoprolol, propranolol, timolol, labetalol, carvedilol**
- **Most of them have half-life from 3-10 hrs except Esmolol (10 min. given intravenously).**
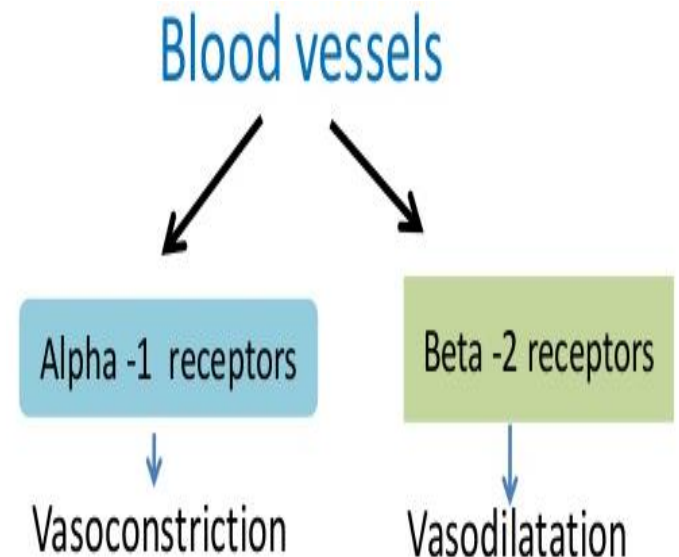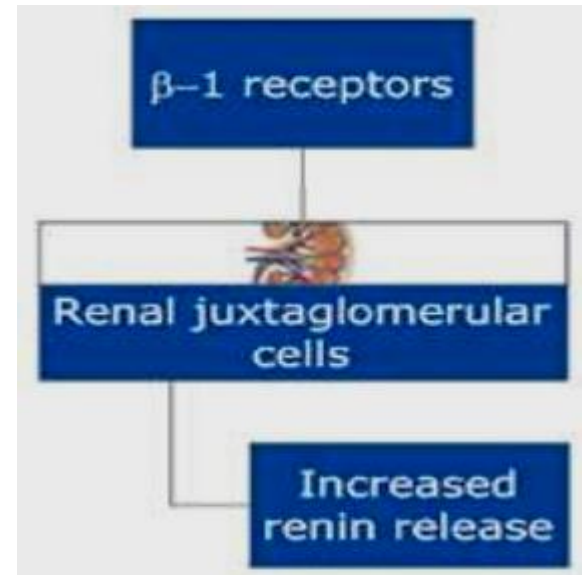- **Most of them are metabolized in liver & excreted in urine.**

| Drug | Half-life |
|---|---|
| Esmolol | 10 min |
| Acebutolol | 3-4 h |
| Pindolol | 3-4 h |
| Metoprolol | 3-4 h |
| Propranolol | 4-6 h |
| Timolol | 4-6 h |
| Labetalol | 4-6 h |
| Carvedilol | 7-10 h |
| Nadolol | 14-24 h |
| Nebivolol | 10-30 h |

# β–*receptors*

## B Receptor location

| Receptor | Location |
|----------|----------|
| β1 | Heart, JG cells in kidney |
| β2 | Bronchi, blood vessels, liver, skeletal muscle |
| β3 | Adipose tissue |

**JG = juxtaglomerular cells**

β–1 receptors

Renal juxtaglomerular cells

Increased renin release

## Blood vessels

Alpha -1 receptors → Vasoconstriction

Beta -2 receptors → Vasodilatation

# *Pharmacological effects of β–agonists*

| TISSUE | RECEPTOR TYPE | ACTION |
|---|---|---|
| Heart | | |
| • Sinus and AV | β1 | ↑Automaticity |
| • Conduction pathway | β1 | ↑Conduction velocity, automaticity |
| • Myocardial fibrils | β1 | ↑Contractility, automaticity |
| Vascular smooth muscle | β2 | Vasodilation |
| Bronchial smooth muscle | β2 | Bronchodilation |
| Kidneys | β1 | ↑Renin release |
| Liver | β2 | ↑Glycogenolysis and gluconeogenesis |
| Adipose tissue | β3 | ↑Lipolysis |
| Skeletal muscle | β2 | Tremor |

# Pharmacological effects of β–agonists

**β₁ (Heart):**

➢ **Increase heart Rate → Positive chronotropic effect.**

➢ **Increase in contractility → Positive inotropic action.**

➢ **Increase in conduction velocity → Positive dromotropic.**

**β₂:** **relaxation of smooth muscles**

**β₂ : Hyperglycemia**

**β₂ : ↑ Release of glucagon from pancreas**

**β₂ α1: Glycogenolysis & gluconeogenesis in liver**

**B3 : ↑ Lipolysis by adipose tissue**

**Pre-synaptic β2 Receptors: ↑ release of NE**
**( Positive feed back mechanism).**

# *Pharmacological actions of β–Adrenergic blockers:*

**CVS:** Negative inotropic, chronotropic, dromotropic ➡ ⬇ CO

**Antianginal effects (ischemic heart disease):**

- ↓ Heart rate (bradycardia)
- ↓ force of contraction ➡ ⬇ cardiac work
- ↓ Oxygen consumption due to bradycardia

**Anti-arrhythmic effects:**

⬇excitability, ⬇ automaticity

& ⬇ conductivity (due to its sympathetic blocking).

All β–Adrenergic blockers mask hypoglycemic manifestations in diabetic patients ➡ **COMA**

Hypoglycemia
↓
Adrenaline
↓
β- 2 receptors in liver
— Propranolol
↓
glycogenolysis
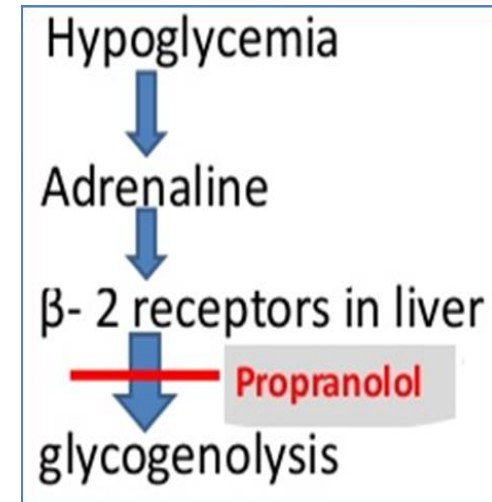
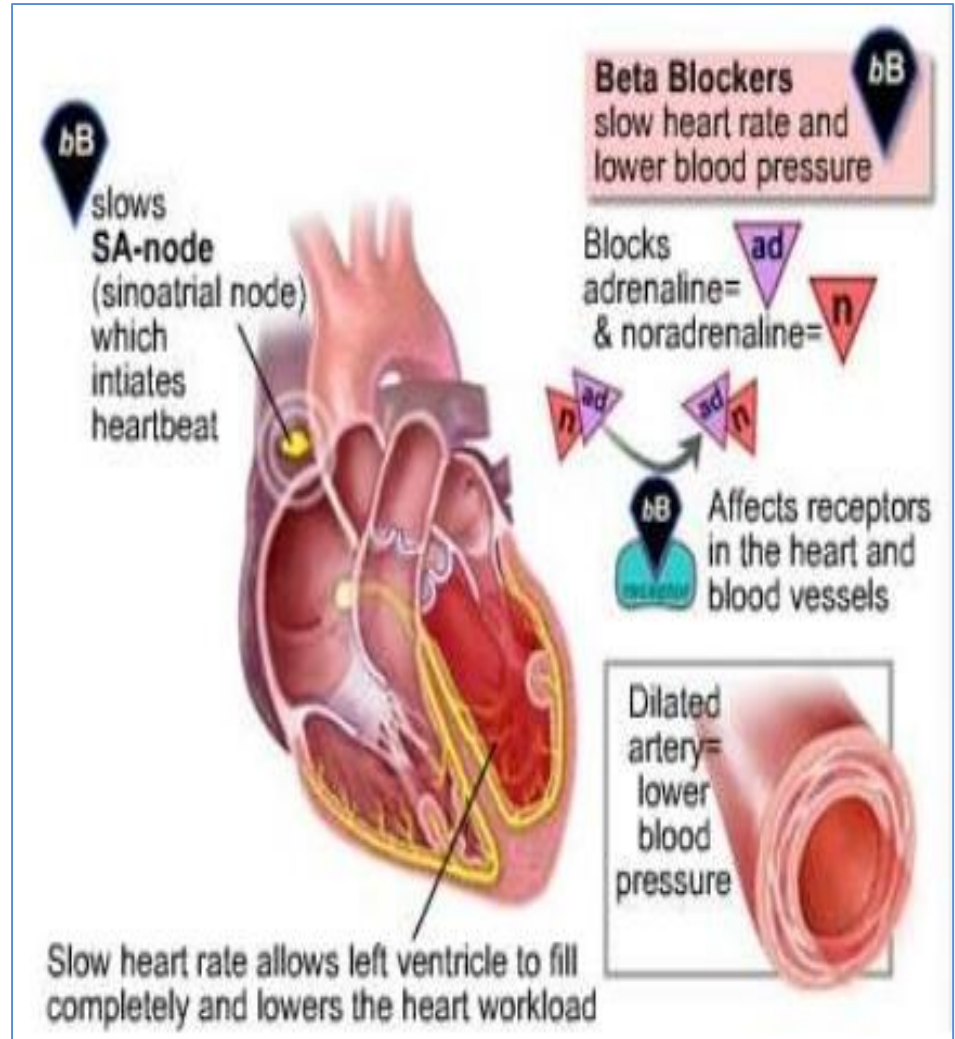# *Pharmacological effects of β–blockers on CVS*

## Sympathetic Stimulation
⬇ ( Heart )
## Beta -1 receptors

**Beta Blockers**

Myocardial contractility
Heart Rate
Cardiac output
Cardiac work
Oxygen consumption

**Beta Blockers** slow heart rate and lower blood pressure

bB slows **SA-node** (sinoatrial node) which intiates heartbeat

Blocks adrenaline= ad & noradrenaline= n

bB Affects receptors in the heart and blood vessels

Dilated artery= lower blood pressure

Slow heart rate allows left ventricle to fill completely and lowers the heart workload

# *Pharmacological actions of β–Adrenergic blockers:*

## Blood vessels $\beta_2$

⬆ peripheral resistance (PR) by blocking vasodilatory effect $\beta_2$

⬇ blood flow to organs ➡ cold extremities

contraindicated in peripheral diseases like Reynaud's disease

## Blood pressure

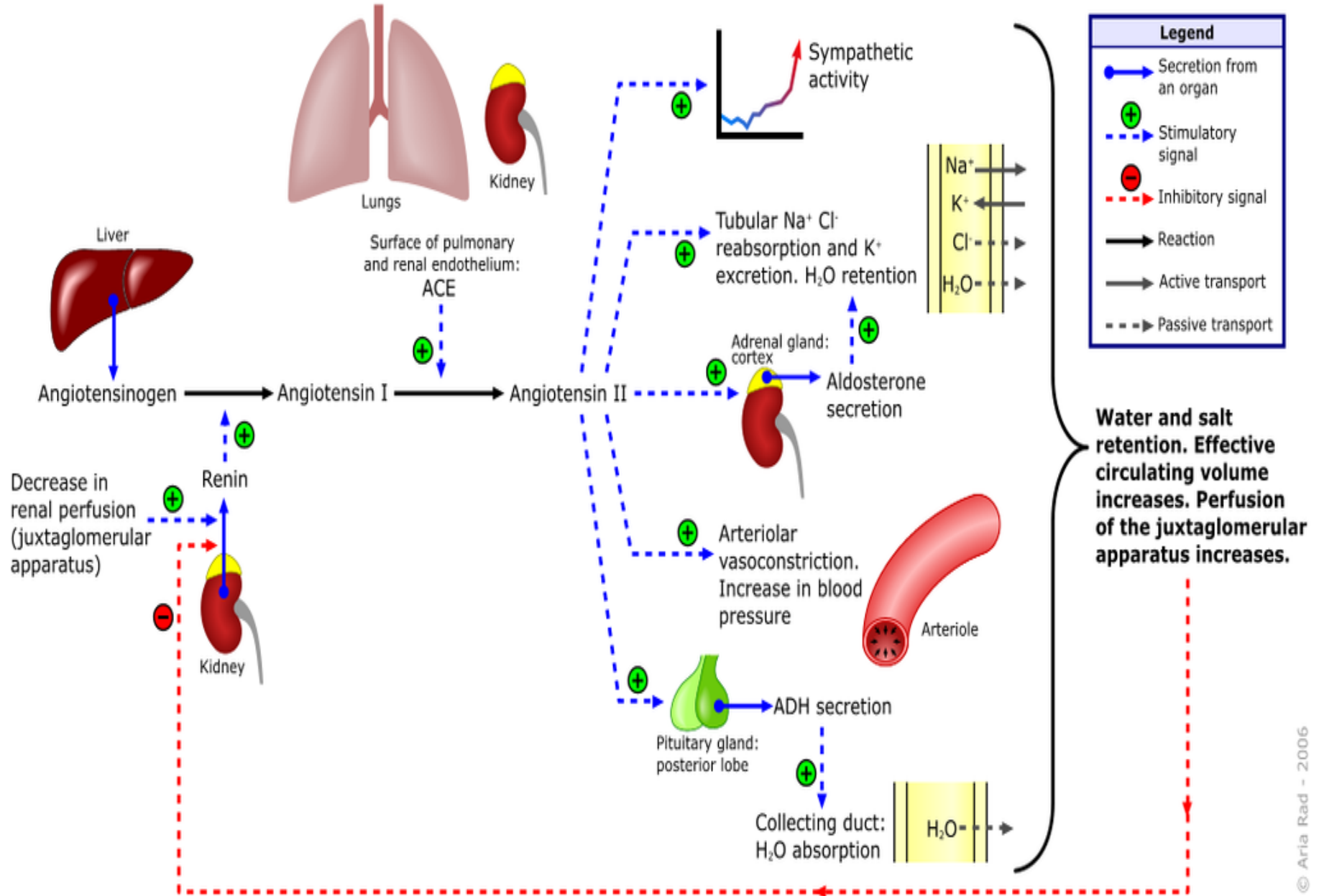Antihypertensive ➡ ⬇ BP in hypertensive patients due to effects

on:

- Inhibiting heart properties ➡ ⬇ cardiac output ($\beta_1$)

- β Blockade ⬇ renin secretion ⬇ Ang II & aldosterone secretion ($\beta_1$).

- Presynaptic inhibition of NE release from adrenergic nerves

# Renin-angiotensin-aldosterone system

# *Pharmacological actions of β−Adrenergic blockers:*

**Respiratory tract: β$_2$**

- **Bronchoconstriction**
- **contraindicated in asthmatic patients.**

**Eye:**

↓ **aqueous humor production from ciliary body**

↓ **Reduce intraocular pressure (IOP)**

**e.g. timolol as eye drops**

**Intestine: ⬆ Intestinal motility**

# *Pharmacological actions of β—Adrenergic blockers:*

## Metabolic effects:

- **Hypoglycemia**

  **↓ glycogenolysis in liver**

  **↓ glucagon secretion in pancreas**

- **↓ lipolysis in adipocytes**

- Na$^+$ retention 2$^{ndry}$ to ↓BP ➤↓renal perfusion



Hypoglycemia
↓
Adrenaline
↓
β- 2 receptors in liver
―――― Propranolol
↓
glycogenolysis
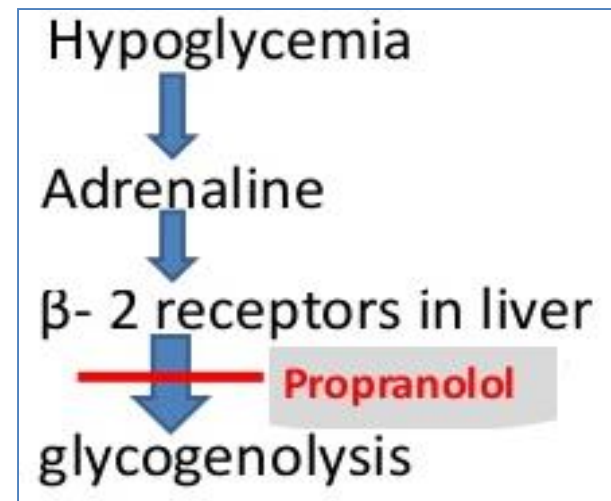
# *Clinical Uses of β–receptor blockers*

- **Cardiovascular disorders**
  - **Hypertension**
  - **Arrhythmia**
  - **Angina pectoris**
  - **Myocardial infarction**
  - **Congestive heart failure**

- **Pheochromocytoma**

- **Chronic glaucoma mainly timolol**

- **Hyperthyroidism (thyrotoxicosis)**

- **Migraine headache prophylaxis**

- **Anxiety (somatic symptoms)**

# Clinical Uses of β–receptor blockers

## In Hypertension:

e.g. Propranolol, atenolol, bisoprolol

**Labetalol:** α, β blockers in hypertensive pregnant & hypertensive crisis.

## In cardiac arrhythmias:

In supraventricular & ventricular arrhythmias.

e.g. Bisoprolol and carvedilol are preferred

## Angina pectoris:

- ↓ heart rate, ↓ cardiac work & oxygen demand.
- ↓ the frequency of angina episodes.

# Clinical Uses of β–receptor blockers

## Congestive heart failure:

### e.g. carvedilol:

- **antioxidant** and non selective α,B blocker
- ↓ myocardial remodeling & ↓risk of sudden death.



Heart Failure

Decreased Cardiac output

Sympathetic activation

Beta-1 receptors

Myocardium

myocyte hypertrophy, myocyte apoptosis detrimental remodelling

JG cells kidney Renin release
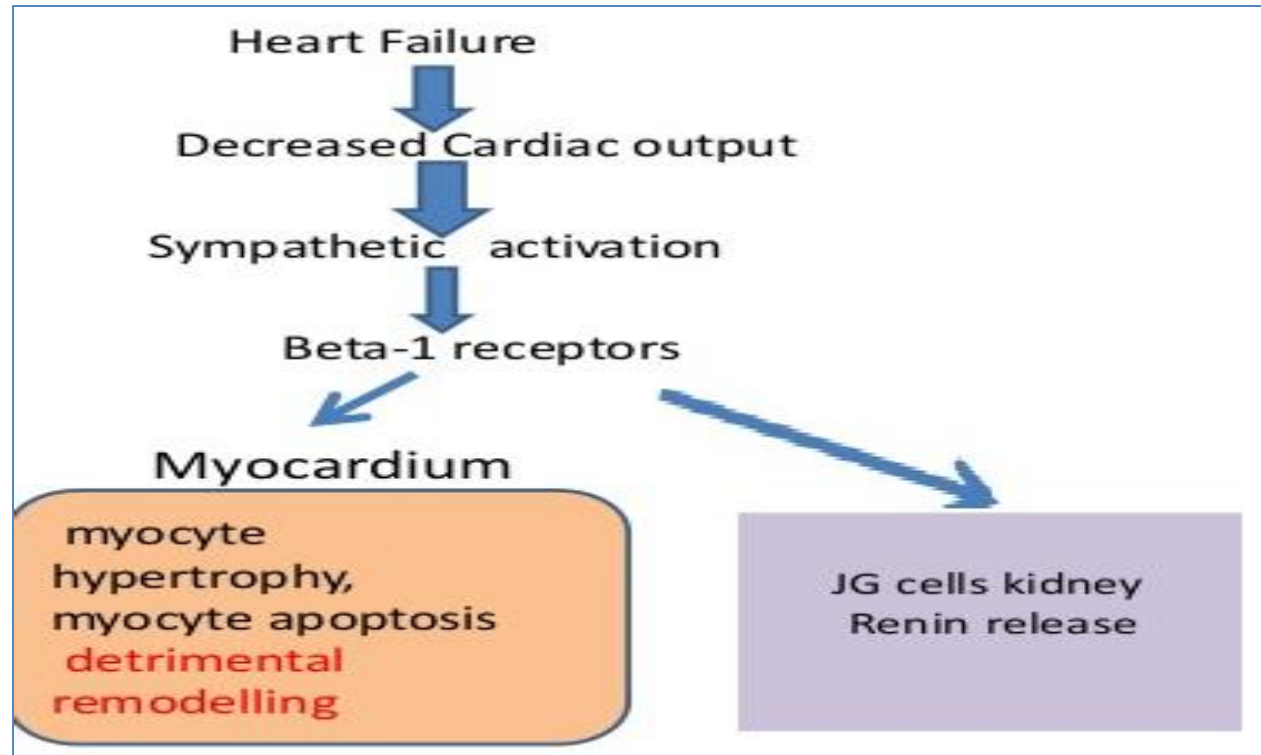
# Clinical Uses of β–receptor blockers

**Myocardial infarction:**

Have cardio-protective effect

⬇ infarct size

⬇morbidity & mortality ➡

⬇ myocardial O2 demand.

• Anti-arrhythmic action.

• ⬇ incidence of sudden death.

# In glaucoma

**e.g. Timolol as eye drops**

- Decreases secretion of aqueous humor by ciliary body.
- Decreases Intraocular pressure (IOP)
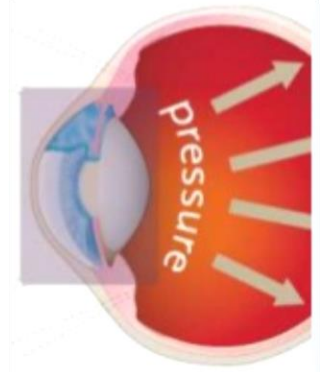


# In Hyperthyroidism

- Protect the heart against sympathetic over stimulation
- Controls symptoms;
  - Tachycardia
  - Tremors
  - Sweating



Hyperthyroidism caused by thyroid adenoma

Hyperfunctioning thyroid (goiter)
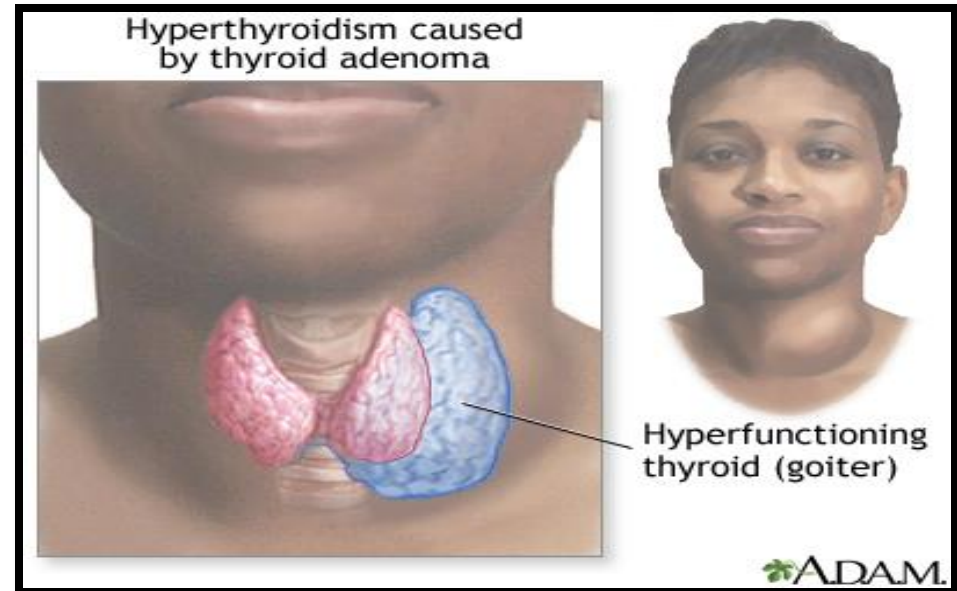
# In anxiety (Social and performance type)

## e.g. Propranolol

**Controls symptoms due to sympathetic system stimulation as tachycardia, tremors, sweating.**

## Migraine:

**Prophylactic**

↓ reduce episodes of chronic migraine

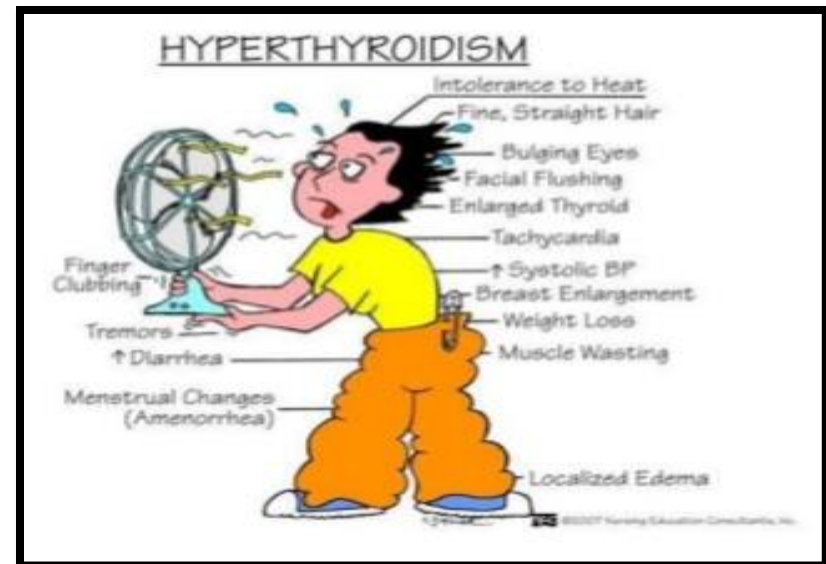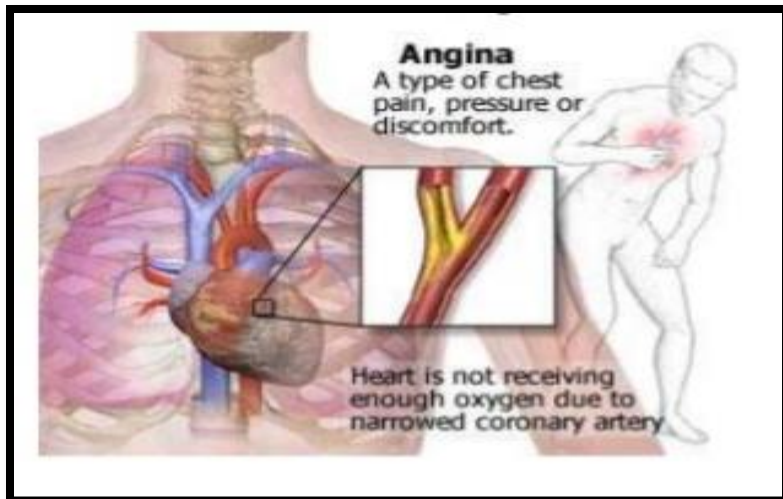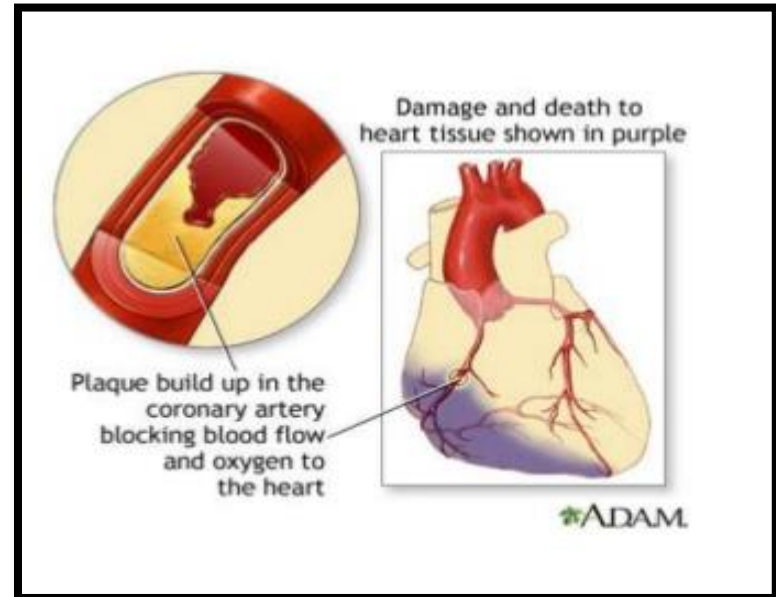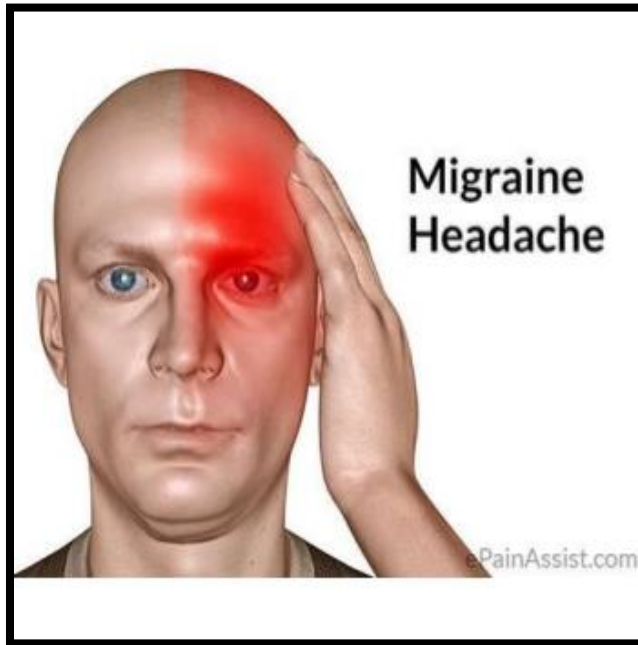↓ catecholamine-induced vasodilatation in the brain vasculature

**e.g. propranolol**



## Pheochromocytoma

used with α-blockers (never alone)

- α-blockers lower the elevated blood pressure.
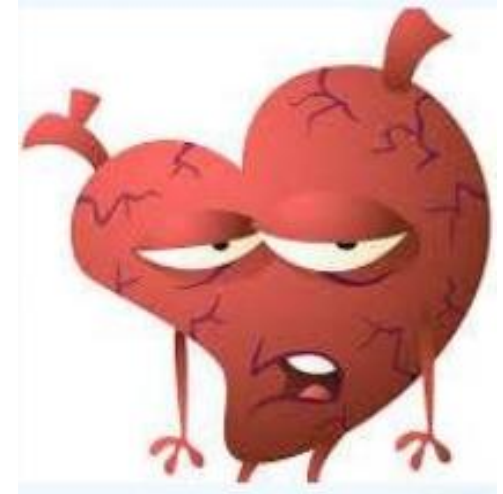- β-blockers protect the heart from NE.

# Uses of B-blockers

# *Adverse Effects of β- Adrenoceptors blockers*

**Due to blockade of β1- receptor:**

- **Bradycardia, hypotension, heart failure**

# Adverse Effects of β- Adrenoceptors blockers

**Due to blockade of β2- receptor:**
**only with non-selective β blockers**

- **Hypoglycemia**

- **⬆ TG ➜hypertriglyceridemia**
- **Bronchoconstriction**
  **(# Asthma, emphysema).**

- **cold extremities & intermittent claudication (due to vasoconstriction).**

- **Erectile dysfunction & impotence**
- **Coronary spasm ➜ in variant angina patients**


Broncho-constriction


Sexual dysfunction
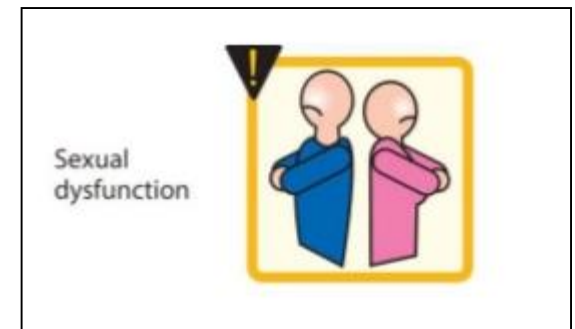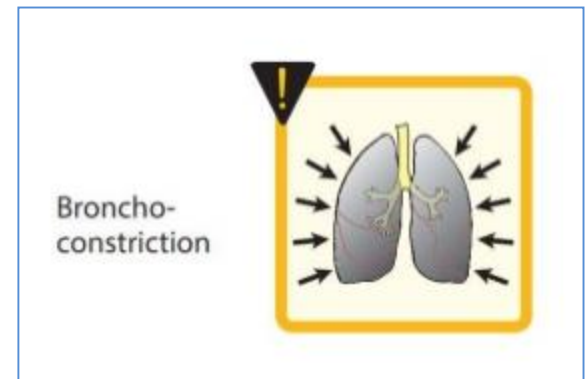
# *Adverse Effects of β- Adrenoceptors blockers*

- **Depression, and hallucinations.**

- **Gastrointestinal disturbances.**

- **Sodium retention**

- **Fatigue**

Fatigue

- **All β–Adrenergic blockers mask hypoglycemic manifestations i.e. tachycardia, sweating, ➡ COMA**

# Precautions

**Sudden stoppage will give rise to a withdrawal syndrome:**

✓ **Rebound angina, arrhythmia, myocardial infarction &**

✓ **Hypertension**

**WHY ?** ➤ **Up-regulation of β-receptors.**

✓ **To prevent withdrawal manifestations** ➤ **drug withdrawn gradually.**



Arrhythmias (upon abrupt withdrawal)
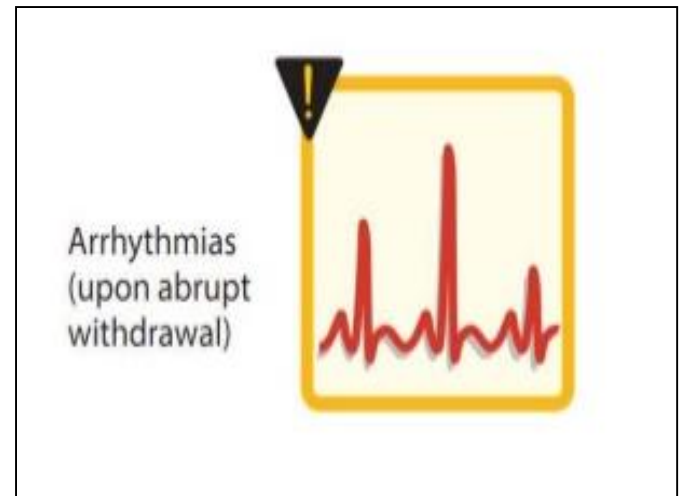
# *Contraindications of β- Adrenoceptors blockers*

- **Heart Block** (beta blockers can precipitate heart block).

- **Bronchial Asthma** (safer with cardio-selective β-blockers).

- **Peripheral vascular disease** (safer with cardio-selective β-blockers).

- **Diabetic patients** ➜ Masking of hypoglycemia / **GIVEN CAUSIOUSLY**

- **Hypotension**

- **Alone in pheochromocytoma** (must be given with an α-blockers).

**PROPRANOLOL**

- **Non-Selective Competitive Blocker of $\beta_1$ & $\beta_2$**

- **Membrane stabilizing action/ quinidine-like /local anesthetic effect**

- **sedative actions /No ISA**

**Pharmacokinetics**

**Lipophilic**

- **completely absorbed**

- **70% destroyed during 1st pass hepatic metabolism**

- **90-95% protein bound**

- **cross BBB and excreted in urine.**

- **Can be given p.o or parenteral**

# Pharmacological actions

- **Membrane Stabilization**: Block Na channels ➤ direct depressant to myocardium➤ has local anesthetic effect **(anti-arrhythmic effects).**

- **β-blocking Effect:** ➤**(anti-arrhythmic effects).**

- **CNS Effect: Has sedative action** ↓ tremors & anxiety ➤ used to protect against social anxiety performance anxiety.

## PROPRANOLOL

**Cardiovascular system**

**Heart by blocking $\beta_1$ :**

- **Inhibit heart properties ➤ ↓ cardiac output**

- **Has anti-ischemic action ➤ ↓ cardiac work + ↓ $O_2$ consumption**

- **Has anti-arrhythmic effects ➤ ↓ excitability, automaticity & conductivity + by membrane stabilizing activity.**

## PROPRANOLOL

**Blood Pressure** (by blocking $\beta_1$ & $\beta_2$ ):

**Has antihypertensive action by➤**

- Inhibiting heart properties ➤ ⬇ **cardiac output**
- B blockade : ⬇ **renin & RAAS system**
- Presynaptic inhibition of NE release from adrenergic nerves
- Inhibiting sympathetic outflow in CNS

## PROPRANOLOL

**Actions** — **Mainly by $\beta_2$ blockade**

- **Blood Vessels:** Vasoconstriction ➤ ↓blood flow specially to muscles, other organs except brain ➤ cold extremities

- **Bronchi:** Bronchospasm specially in susceptible patients

- **Intestine:** ↑ Intestinal motility

- **Metabolism:**
  - In liver: ↓ Glycogenolysis ➤ Hypoglycemia
  - In pancreas: ↓ Glucagon secretion
  - In adipocytes: ↓ Lipolysis
  - In skeletal muscles: ↓glycolysis

- **On peripheral & central nervous systems:**
  - Has local anesthetic effect ↓ tremors & ↓ anxiety

## PROPRANOLOL

### INDICATIONS

- **Hypertension**

- **Arrhythmias**

- **Angina**

- **Myocardial infarction**

- **Migraine [*Prophylaxis*]**

- **Pheochromocytoma; used with $\alpha$-blockers (never alone)**

- **Chronic glaucoma**

- **Tremors**

- **Anxiety:** *(specially social & performance type)*

- **Hyperthyroidism**

# *Labetalol*

✓ Blocks  $\alpha_1$  & $\beta$

✓ Rapid acting, non-selective with ISA

✓ Has local anesthetic effect, **Given p.o and i.v**

✓ Does not alter serum lipids or blood glucose

✓ Produce peripheral vasodilation

✓ Decrease blood pressure

**Uses**

✓ Severe hypertension in pheochromocytoma

✓ Hypertensive crisis (e.g. during abrupt withdrawal of clonidine).

✓ Used in pregnancy-induced hypertension

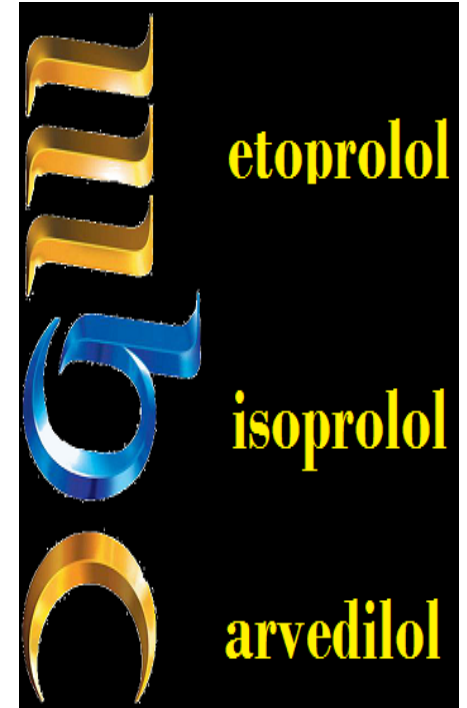**ADR;** Orthostatic hypotension, sedation & dizziness

## CARVEDILOL

# Blocks $\alpha_1$ & $\beta$

- ✓ **Non-selective with no ISA & no local anesthetic effect.**

- ✓ **Has ANTIOXIDANT action**

- ✓ **Used effectively in ➡ CONGESTIVE HEART FAILURE ➡ reverses its pathophysiological changes.**

**Adverse effects:**

**Orthostatic hypotension, Edema**

# Summary of B-blockers uses

- **Hypertension** Atenolol, Bisoprolol, Metoprolol, Propranolol

- **cardiac arrhythmia** Esmolol (ultra-short acting), Atenolol, Propranolol

- **Congestive heart failure** Carvedilol, Bisoprolol, Metoprolol

- **Myocardial infarction** Atenolol, Metoprolol, Propranolol

- **Glaucoma** Timolol

- **Migraine prophylaxis** Propranolol

- **Relief of anxiety (social & performance)** Propranolol

- **Thyrotoxicosis** Propranolol

# $\beta$-receptor blockers

| | | |
|---|---|---|
| **Propranolol** | **Non selective** <br> **B$_1$, β$_2$ blocker** | **Migraine prophylaxis** <br> **Hyperthyroidism (thyrotoxicosis)** <br> **Relieve anxiety (social performance)** |
| **Timolol** | **B$_1$, β$_2$ blocker** | **Glaucoma** |
| **Atenolol** <br> **Bisoprolol** <br> **Metoprolol** | **B$_1$ blocker** | **Myocardial infarction** <br> **Hypertension** |
| **Esmolol** | **B$_1$ blocker** <br> **Ultra short acting** | **Cardiac arrhythmia** |
| **Carvedilol** | **α, B blocker** | **Congestive heart failure** |
| **Labetalol** | **α, B blocker** | **Hypertension in pregnancy** <br> **Hypertensive emergency** |

# To increase your knowledge
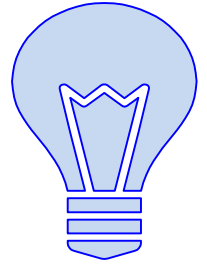
## Intermittent claudication

Peripheral artery disease most commonly affects the legs, but other arteries may also be involved. The classic symptom is leg pain when walking which resolves with rest.

## Risk factors:

Diabetes, hypercholesterolemia, hypertension