β- Adrenoceptors blockers

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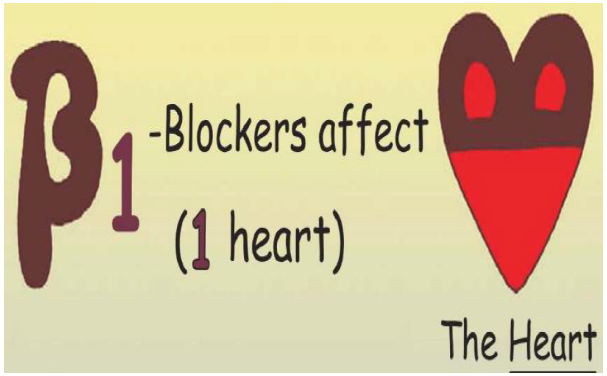
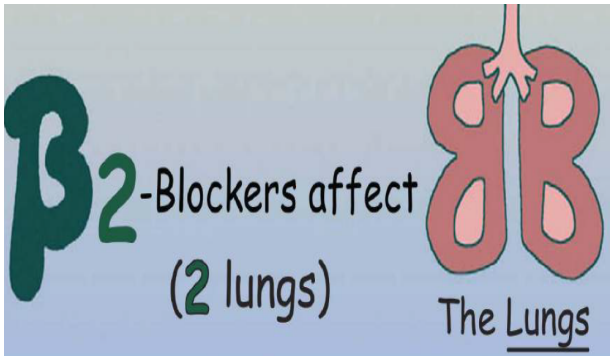




By the end of this lecture, the student should be able to

- **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

Acebutolol, Atenolol

Bisoprolol, Betaxolol

Celiprolol

Esmolol, Metoprolol

Non selective β- Antagonists

Blocks β1& β2 receptors

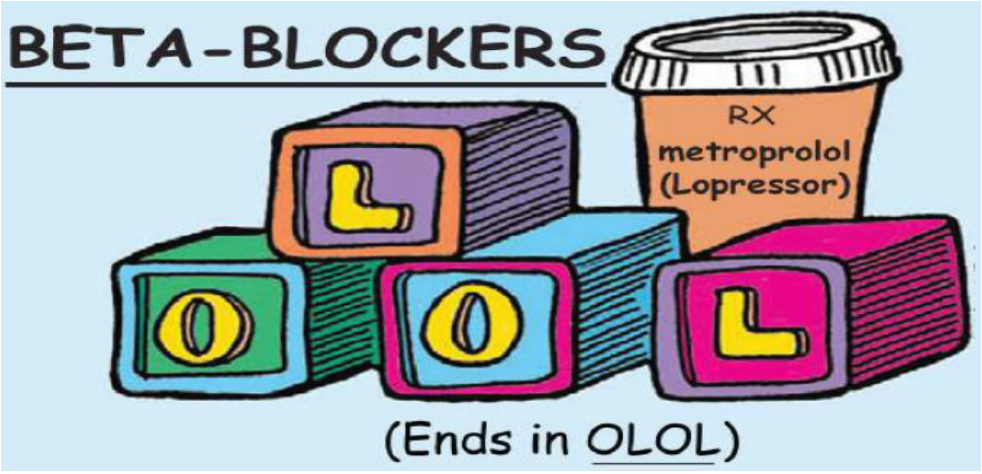
Oxprenolol

Propranolol, Pindolol

Sotalol, Timolol (STOP)

Mixed α, β receptors blockers

- **Carvedilol**
- **Labetalol**



β ADRENOCEPTOR BLOCKERS

Pharmacodynamic Classification

1

According to selectivity

Non-Selective

Block β_1 & β_2

Propranolol, Sotalol, Timolol (Eye)

Selective

Block β_1

Atenolol, Bisoprolol, Metoprolol, Esmolol

Labetalol, Carvedilol (mixed α, β 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

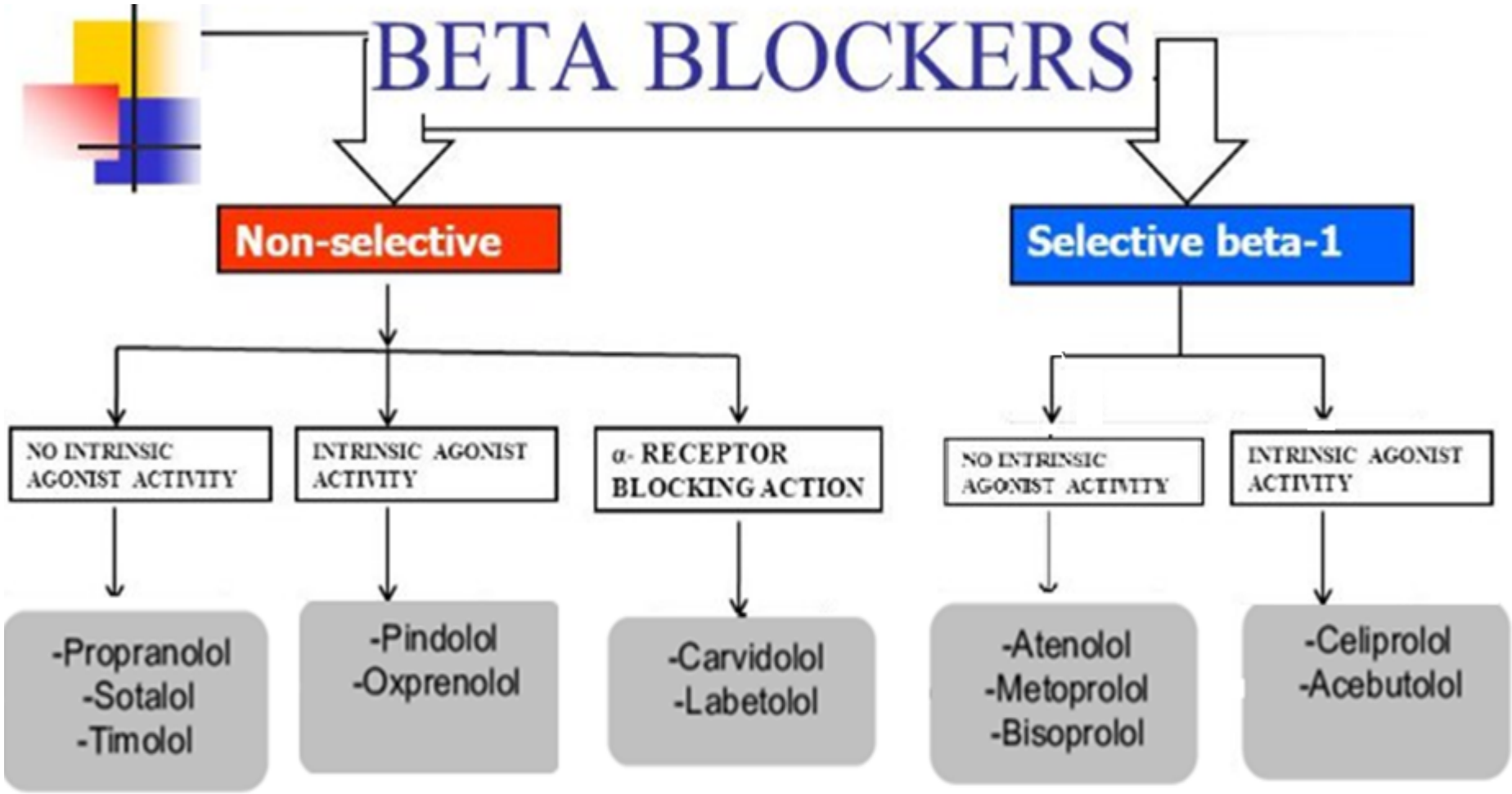
According to their lipid solubility

- 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

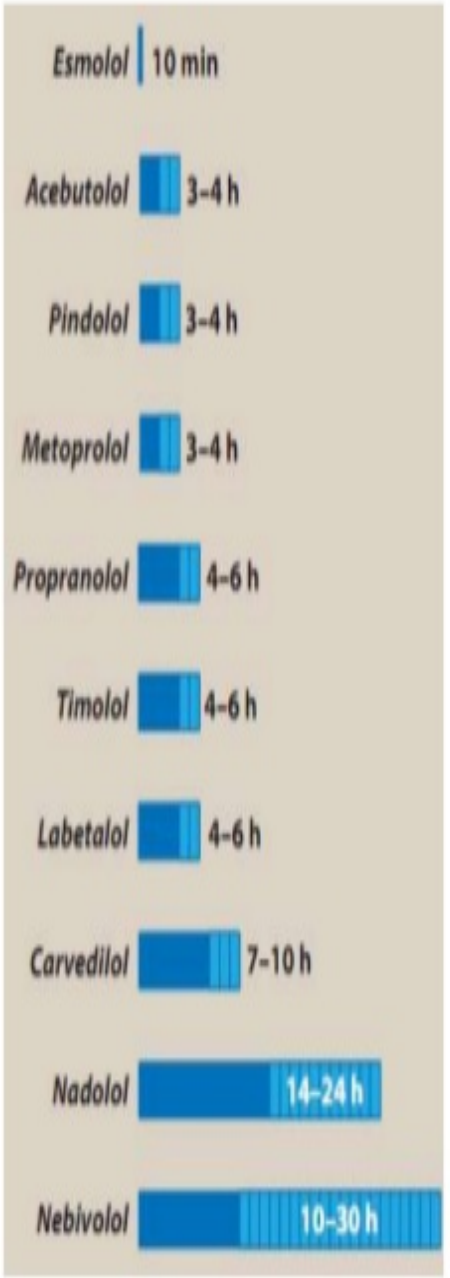
β ADRENOCEPTOR BLOCKERS



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**

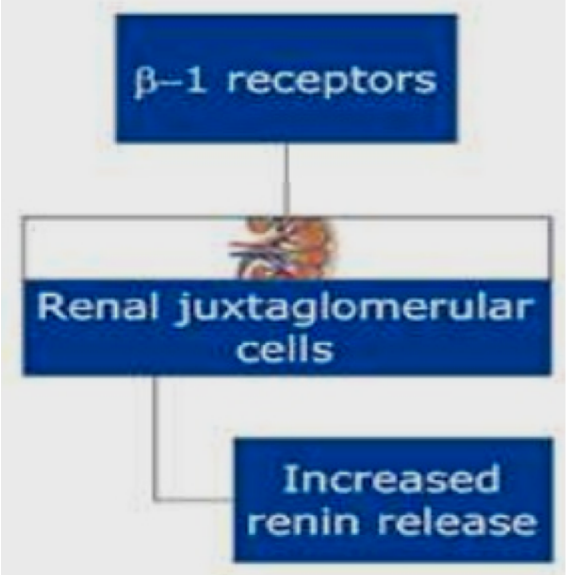
  e.g. Metoprolol, propranolol, timolol, labetalol, carvedilol
- **Most of them have half-life from 3-10 hrs except Esmolol (10 min. given intravenously).**
- **Most of them metabolized in liver & excreted in urine.**

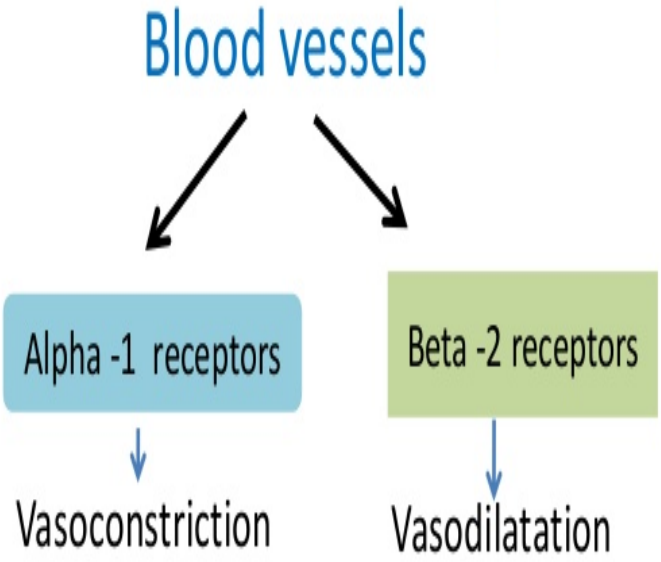


β–receptors

B Receptor location

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





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

β_1 (Heart):

- **Increase heart Rate → Positive chronotropic effect.**
- **Increase in contractility → Positive inotropic action.**
- **Increase in conduction velocity → Positive dromotropic.**

β_2: relaxation of smooth muscles

β_2 : Hyperglycemia

β_2 : ↑ Release of glucagon from pancreas

β_2 α1: Glycogenolysis & gluconeogenesis in liver

B3 : ↑ Lipolysis by adipose tissue

Pre-synaptic β2 Receptors: ↑ release of NE

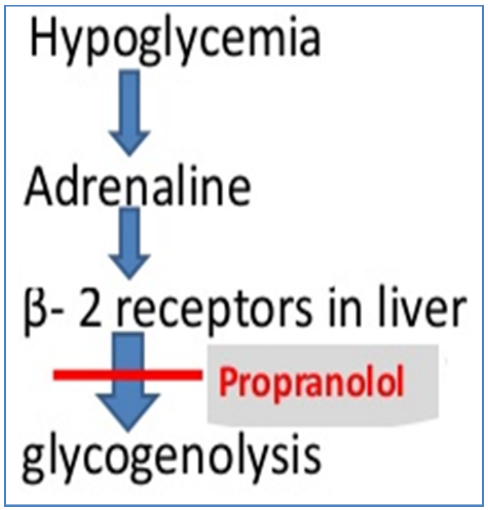
(Positive feed back mechanism).

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

Pharmacological effects of β–blockers on CVS

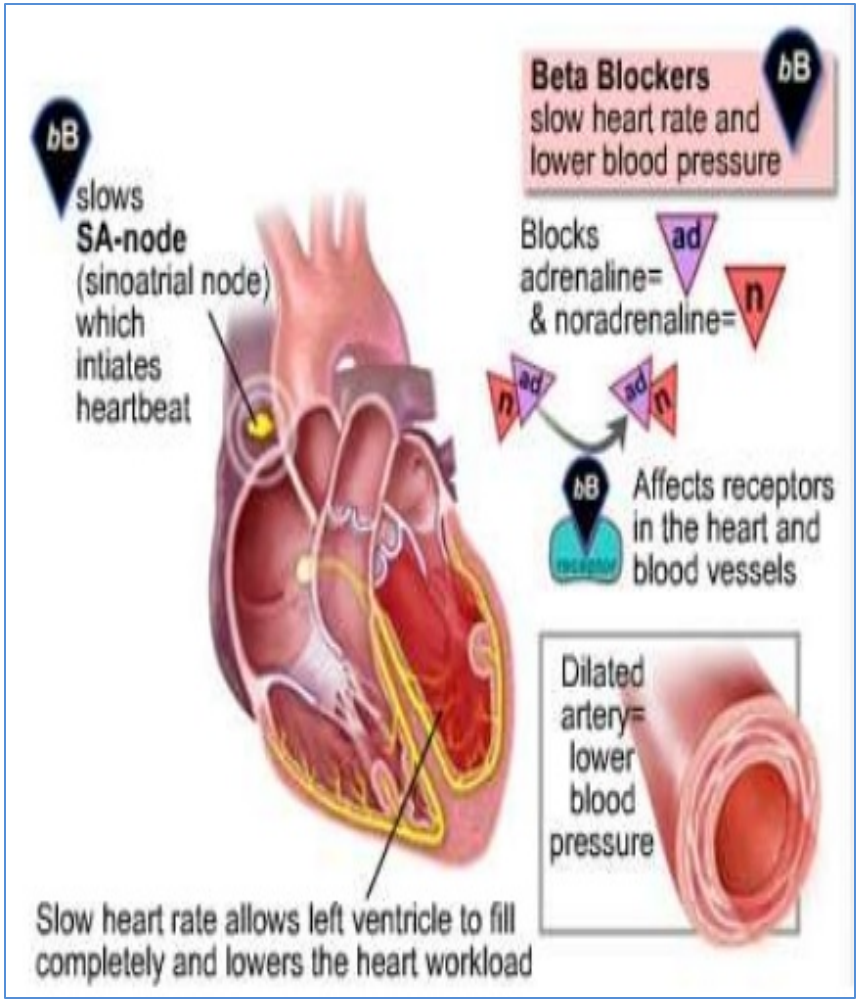
Sympathetic Stimulation

↓ (Heart)

Beta -1 receptors

↓ — Beta Blockers

- Myocardial contractility
- Heart Rate
- Cardiac output
- Cardiac work
- Oxygen consumption



Pharmacological actions of β–Adrenergic blockers:

Blood vessels β_2

↑ peripheral resistance (PR) by blocking vasodilatory effect β_2

↓blood flow to organs → cold extremities

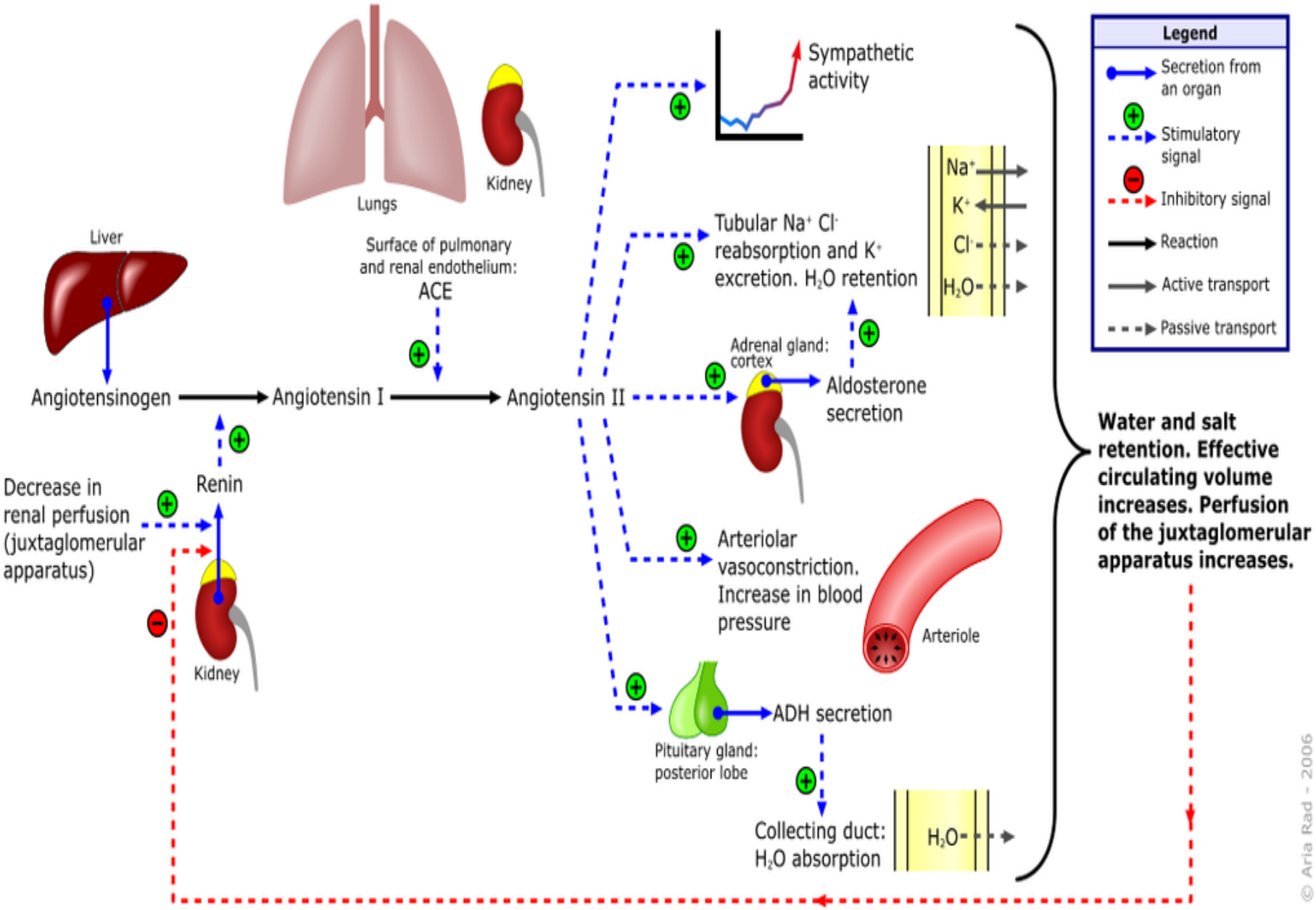
contraindicated in peripheral diseases like Reynaud's disease

Blood pressure

Antihypertensive → ↓ BP in hypertensive patients due to effects on:

- Inhibiting heart properties → ↓ cardiac output (β_1)
- β Blockade ↓ renin secretion ↓ Ang II & aldosterone secretion (β_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)

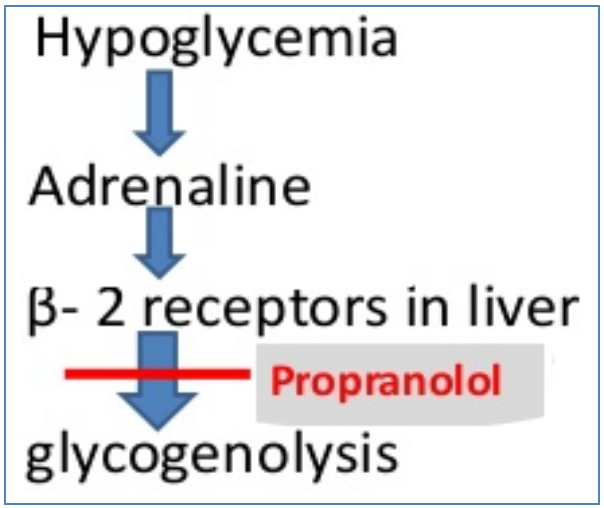
e.g. timolol as eye drops

Intestine: ↑ Intestinal motility

Pharmacological actions of β–Adrenergic blockers:

Metabolic effects:

- **Hypoglycemia**
  - **↓ glycogenolysis in liver**
  - **↓ glucagon secretion in pancreas**
- **↓ lipolysis in adipocytes**
- **Na^+ retention 2ndry to ↓BP → ↓renal perfusion**



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:

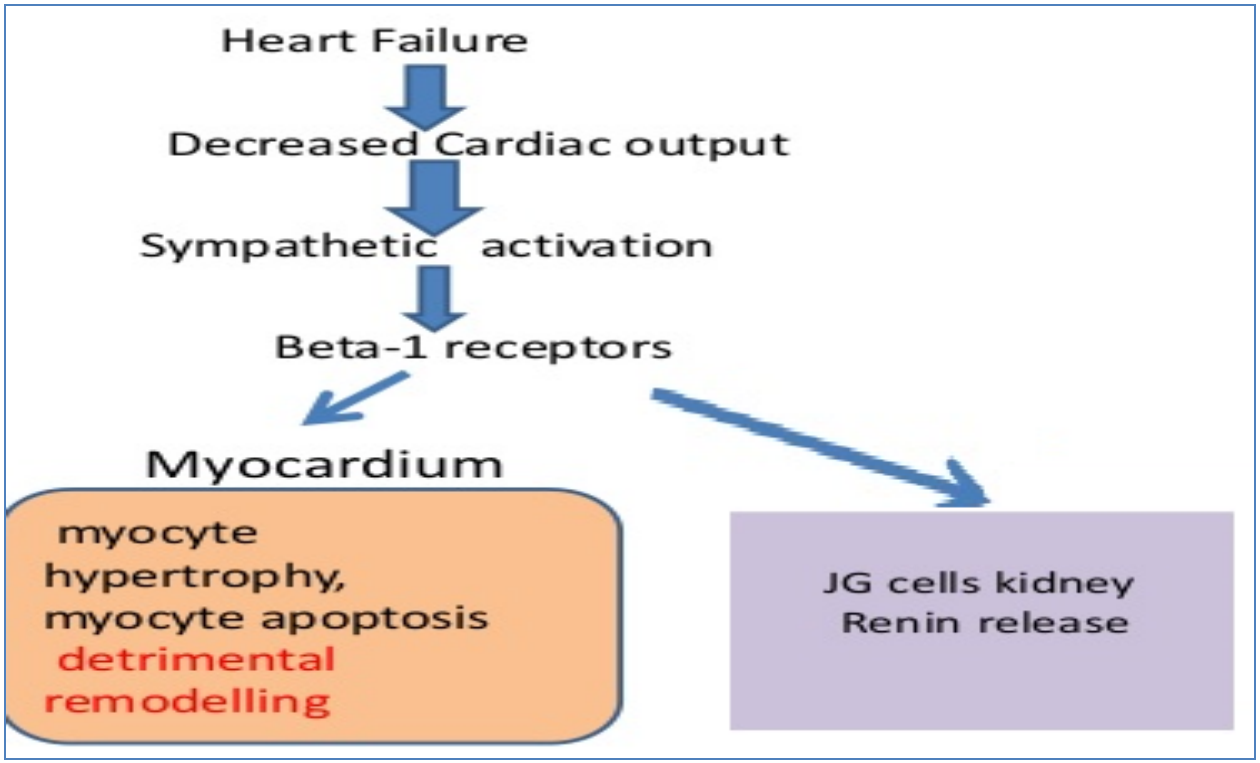
- **↓ heart rate, ↓ cardiac work & oxygen demand.**
- **↓ the frequency of angina episodes.**

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.



Clinical Uses of β–receptor blockers

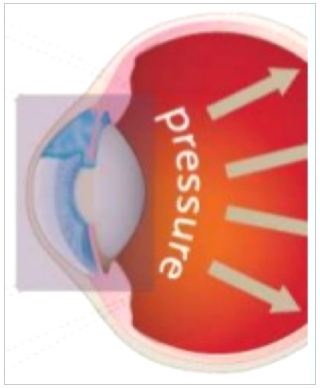
Myocardial infarction:

Have cardio-protective effect

- ↓ infarct size
- ↓morbidity & mortality →
- ↓ myocardial O2 demand.
- Anti-arrhythmic action.
- ↓ incidence of sudden death.

In glaucoma

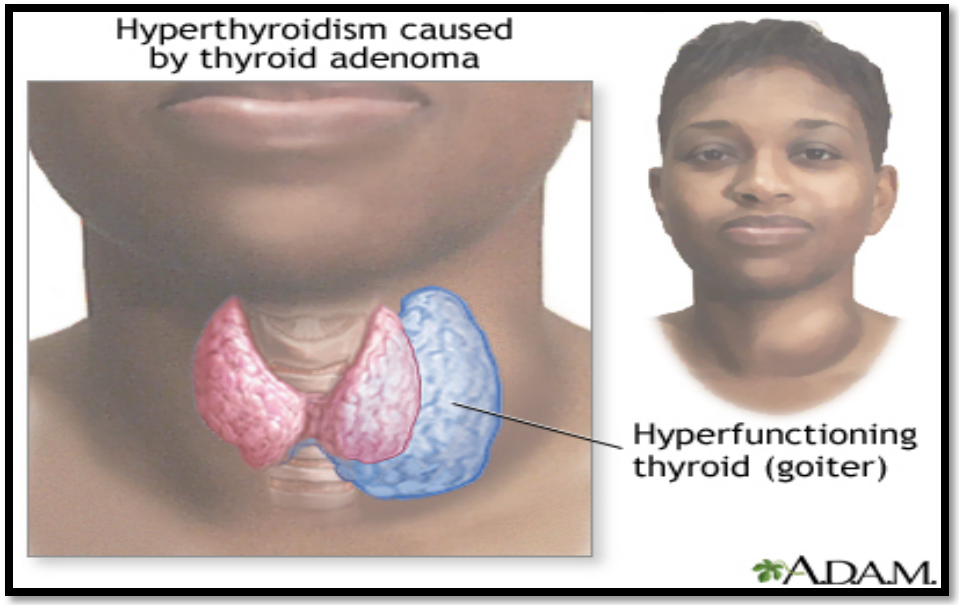
e.g. Timolol as eye drops



- 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



In anxiety (Social and performance type)

e.g. Propranolol

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

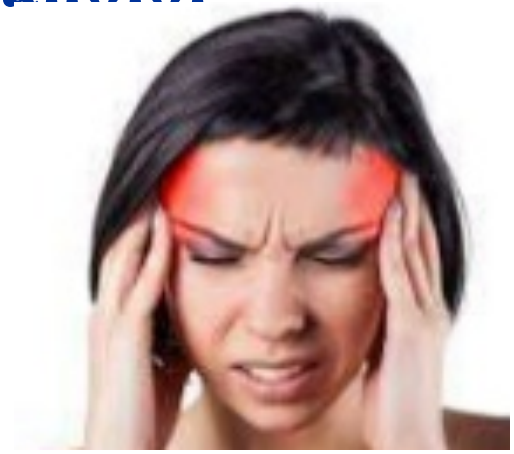
Migraine:

Prophylactic

↓reduce episodes of chronic migraine

↓catecholamine-induced vasodilatation in the brain vasculature

e.g. propranolol

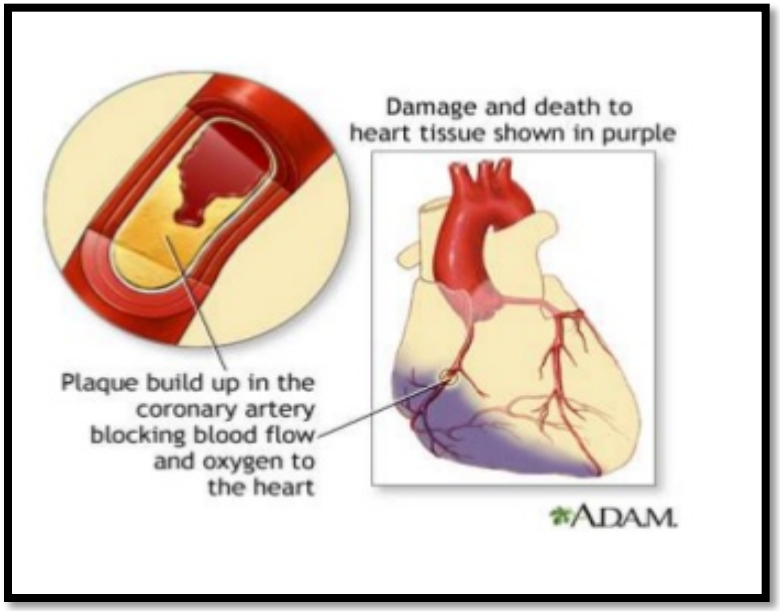


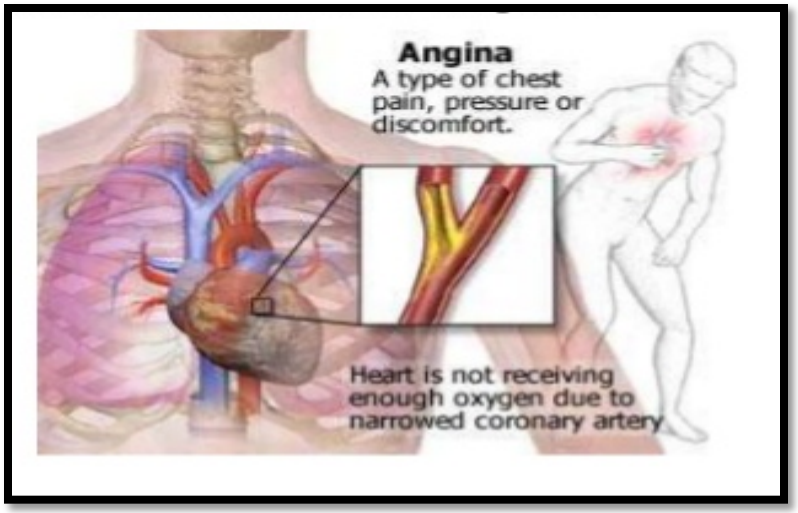
Pheochromocytoma

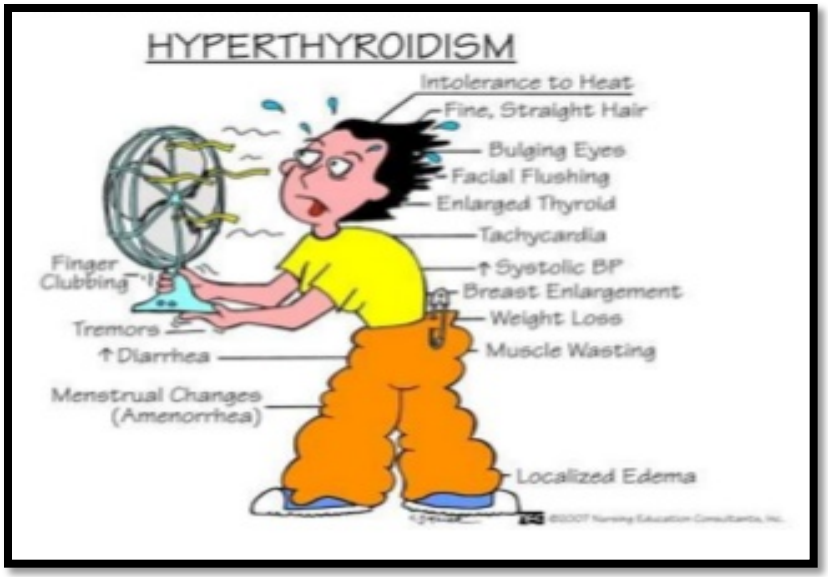
used with α-blockers (never alone)

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

Uses of B-blockers







Adverse Effects of β- Adrenoceptors blockers

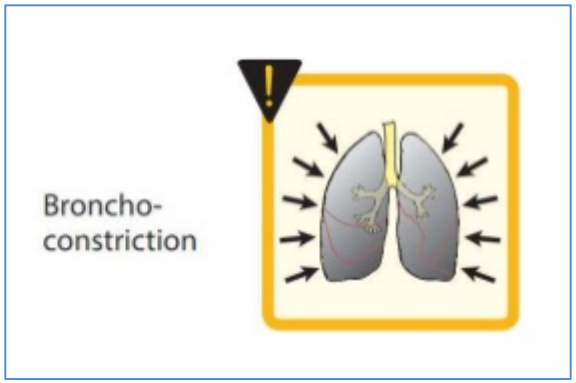
Due to blockade of β1- receptor:

- **Bradycardia, hypotension, heart failure**

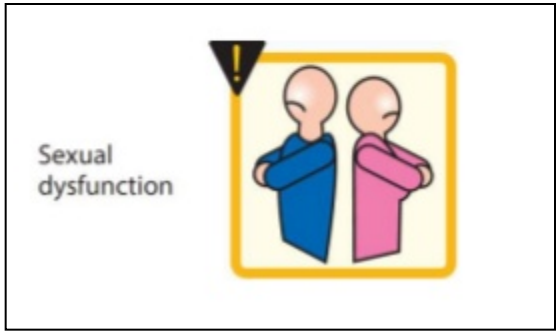
Adverse Effects of β- Adrenoceptors blockers

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**



Adverse Effects of β- Adrenoceptors blockers

- **Depression, and hallucinations.**
- **Gastrointestinal disturbances.**
- **Sodium retention**
- **Fatigue**

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

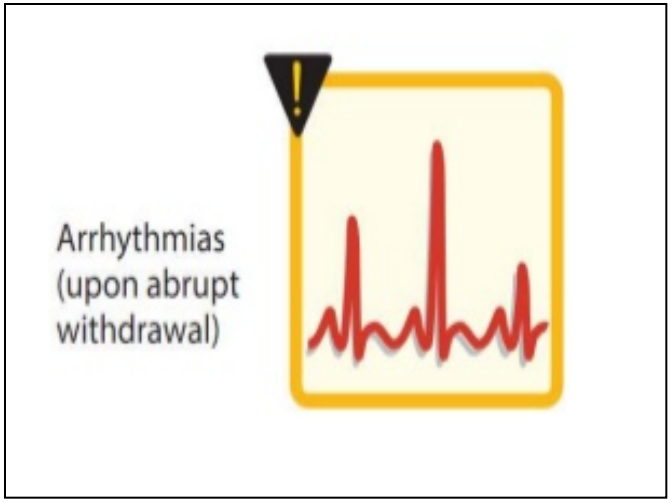
Precautions

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.



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

Prototype

- Non-Selective Competitive Blocker of β_1 & β_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

PROPRANOLOL

Prototype

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 β_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 β_1 & β_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 β_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 α-blockers (never alone)
- Chronic glaucoma
- Tremors
- Anxiety: *(specially social & performance type)*
- Hyperthyroidism

Labetalol

- ✓ Blocks α_1 & β
- ✓ 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

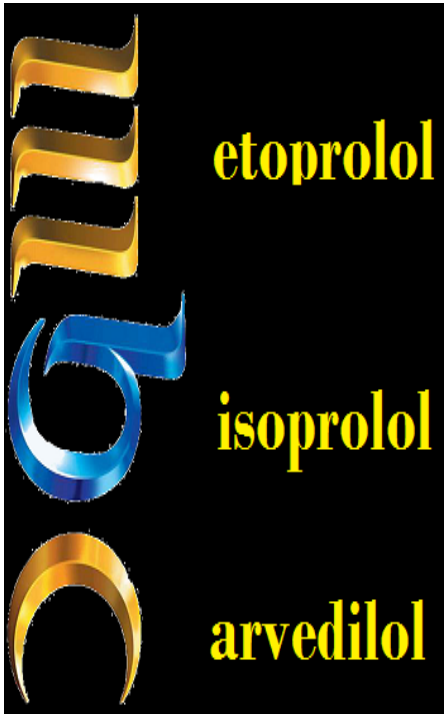
- ✓ Severe hypertension in pheochromocytoma
- ✓ Hypertensive crisis (e.g. during abrupt withdrawal of clonidine).
- ✓ Used in pregnancy-induced hypertension

ADR: Orthostatic hypotension, sedation & dizziness

CARVEDILOL

Blocks α_1 & β

- ✓ 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

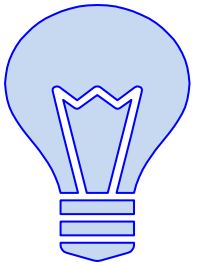
Summary of B-blockers uses

- **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

β-receptor blockers

Propranolol	Non selective B_1, β_2 blocker	Migraine prophylaxis Hyperthyroidism (thyrotoxicosis) Relieve anxiety (social performance)
Timolol	B_1, β_2 blocker	Glaucoma
Atenolol Bisoprolol Metoprolol	B_1 blocker	Myocardial infarction Hypertension
Esmolol	B_1 blocker Ultra short acting	Cardiac arrhythmia
Carvedilol	α, B blocker	Congestive heart failure
Labetalol	α, B blocker	Hypertension in pregnancy 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