Doctor 021

PHARMACOLOGY

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Alpha Adrenoceptor Antagonists Beta Adrenoceptor Antagonists Ganglion-Blocking Drugs

We'll start now the second part of our lecture, α-adrenergic receptor antagonists.

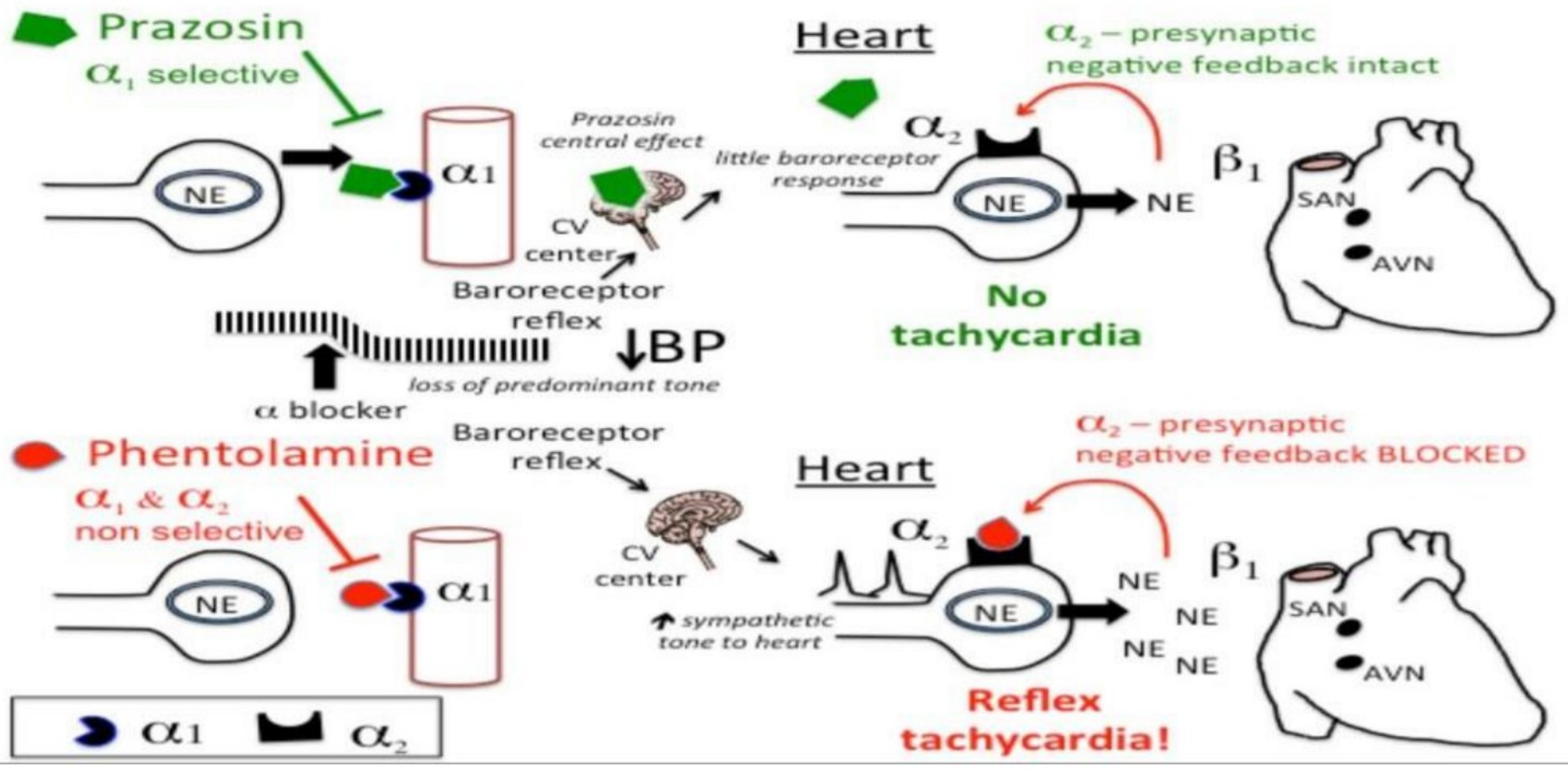
History:
α-blockers were discovered way
before β-blockers, perhaps because
there's no β-blocker in nature.

*In general, **α-blockers cause decrease in peripheral vascular resistance** and blood pressure and may cause orthostatic hypotension.

- **Prevent the pressor effects of α agonists**
- **often cause orthostatic hypotension and reflex tachycardia;**

nonselective (α 1 = α 2,) blockers cause tachycardia if blood pressure is lowered below normal.

Surprisingly, selective and non-selective have different outcomes regarding heart rate after following this scenario.



-When using phentolamine (a non-selective α blocker), α1 receptors on bloods vessels are blocked thus promoting vasodilation and decreasing blood pressure. Baro-reflex takes place and the sympathetic tone to the heart increases, causing tachycardia. α2 auto receptors are blocked, so there's no going back :(

-When using Prazosin (a selective α1 blocker), α1 receptors on bloods vessels are blocked thus promoting vasodilation and decreasing blood pressure. Baro-reflex takes place but still, there is no tachycardia. This happens thanks to our soldiers (un-inhibited auto receptors) that were not blocked by Prazosin (remember it's α1 selective).

Other effects of α-blockers include:

- **Miosis**: α1 receptors in the iris (which are responsible for mydriasis) are blocked, leaving the parasympathetic tone to work all alone.
- **Nasal stuffiness** (congestion): α1 receptors in the nasal vessels are blocked, resulting in vasodilation and congestion (feels like you have cold although you don't)
- Increasing urination: **α1 receptors in the base of bladder are blocked, reducing the resistance to the flow of urine. α blockers are used for the treatment of urinary retention due to prostatic hyperplasia**

Now we'll start taking examples, one by one.

Non-selective α blockers:

- **Phenoxybenzamine**:

- Binds covalently to α receptors, causing irreversible blockade of long duration (14-48h)

- Blocks α1& to less extent α2 receptors.

- Also inhibits reuptake of NE and blocks histamine (H1), ACh, and serotonin receptors.

- Causes little or no fall in BP in normal supine individuals (at that state the sympathetic tone is not that high), it reduces BP when sympathetic tone is high, e.g., as a result of upright posture.

- **Absorbed poorly but usually given orally** (It is not given by IV because these injections are very painful)

-**Used to treat pheochromocytoma**, which is a tumor in adrenal medulla leading to excessive production of catecholamines. It is used also to treat **peripheral vascular diseases**.

- e.g. Raynaud's phenomenon (excessive reversible vasospasm in the peripheral circulation). Prazosin or phenoxybenzamine are used but calcium channel blockers are preferable for most patients.

- Adverse effects includes orthostatic hypotension, tachycardia, Nasal stuffiness and inhibition of ejaculation.

- **Phentolamine:**

- Rapidly acting α blocker with short half-life (19 mins)

- Acts equally on α1 and α2 receptors.
- Competitive α1 and α2 antagonist

- Reduces peripheral resistance (due to blockade of α1) and causes cardiac stimulation (α2 receptors blockade enhances release of NE).

- It has **minor inhibitory effects at 5HT** (serotonin) **receptors and agonist effects at muscarinic** receptors increasing **salivary, sweat, and lacrimal** secretions. It also has agonist effect at **H1 and H2 histamine receptor** which **increase acid secretion**.

- It is used to diagnose pheochromocytoma, control hypertension due to clonidine withdrawal, and treat **cheese reaction** initiated by tyramine. It is also used **to counteract vasoconstriction caused by alpha agonists.**

- Adverse effects include severe tachycardia, arrhythmias, and myocardial ischemia.

Selective α1 blockers:

- **Prazosin:**

- Highly selective α1 blocker and less potent at α 2 receptors.

- Relaxes both arterial and venous vascular smooth muscles and smooth muscle in the prostate, due to blockade of α1 receptors, with no or little tachycardia.

- Extensively metabolized only 50% is available after oral administration , with short half-life (3 hours).

- Has a **favorable effect on plasma lipids**, so it **increases HDL/LDL ratio**.

- Used for **hypertension and benign prostatic hyperplasia (BPH) Blocks a1 in bladder trigone & prostate & decreases tone & improve urine flow**

- **Adverse effects** include **first dose phenomenon**, a sudden hypotensive state when taking the first dose**. i.e. postural hypotension with initial doses** So, it's advised to take the very first dose at bedtime.

- **Terazosin**: same as above **(high bioavailability),** but with longer half-life (9-12) hours.

- **Doxazosin**: has the longest half-life (22 hours).

- **Tamsulosin**: **Uroselective α1A blocker** (α1A are **predominant in bladder base and prostate**). So, it is the best option to treat BPH with no effect on blood pressure and heart rate **((No effect on BP and heart rate. High bioavailability and a half-life of 9–15 hours)).** However, it can cause **dizziness and retrograde ejaculation**.

--Prazosin, doxazosin, and terazosin are all effective.

--Tamsulosin is preferred in patients who have orthostatic hypotension with other α 1-receptor antagonists

Yohimbine

- an indole alkaloid, α2-selective antagonist.
- It Blocks other receptors: 5HT receptor (serotonin receptor), and dopamine receptor.
- Increases ADH release.
- Enhances sexual activity (aphrodisiac effect).
- Sometimes (rarely) used in the treatment of orthostatic hypotension because it promotes NE release through blockade of presynaptic α2 receptors.

Remember that orthostatic hypotension is the decreased blood pressure after standing following supine position, when there is no enough vasoconstriction to retain the blood in the circulation, blood goes down and central blood volume disappears, less blood reach the brain, which results in falling down.

Presynaptic α2 receptors act as normal feedback inhibition mechanism to decrease the release of NE. when Yohimbine blocks these receptors, more NE will be released, so it causes vasoconstriction and solves the problem.

- Was widely used to improve male erectile dysfunction but has been superseded by phosphodiesterase-5 inhibitors like sildenafil (viagra).

β- Adrenoceptor Antagonists

The doctor mentioned some history regarding the discovery of β-blockers that is not mentioned in the slides ☻

β-blockers are discovered after the discovery of alpha blockers, when two scientists were working on isoproterenol and they substituted the two OH present on catechol nucleus by two chlorine atoms, so the compound became **dichloroisoproterenol** which is nonselective β-blocker, so it's the first developed β-blocker with high intrinsic activity (partial agonist activity) and low beta blocking activity. The second developed beta blocker is **pronethalol** and is stopped because of carcinogenic activity on rats. The third is **propranolol** which has low intrinsic activity and high beta blocking activity, still used until now.

First generation: non selective β-blockers, they block β1 and β2 equally.

Second generation: Cardioselective β1, the first one is practolol but it's stopped because of its side effects (toxic) .

Third generation: Vasodilator β blockers (**Extra**: third-generation beta blockers can cause vasodilation through blockade of alpha-adrenergic receptors), and at the same time they decrease cardiac output, contractility and heart rate by blockade of β receptors in the heart. After vasodilation, compensatory vasoconstriction might develop (by reflex increase of sympathetic tone over blood vessels).

Notes:

- ✓ all the benefits in the treatment with β-blockers come from blocking β1 receptors, blocking β2 is responsible for the side effects.

- ✓ The selectivity of β blockers to β1 or β2 is dose-related, and the **selectivity tends to diminish at higher drug doses**. For instance, low doses of β1 blockers are not supposed to cause bronchoconstriction.

Other major differences relate to their lipid solubility. Highly lipid soluble drugs have better absorption, fast metabolism and shorter half-life, can cross the BBB and have central side effects (they might cause depression and nightmares).

Most drugs are well absorbed after oral administration, peak concentrations 1–3 hours after ingestion.

Another variation is **the local anesthetic (membrane-stabilizing) effects,** these effects are present in some β blockers such as propranolol, however, whatever the dose is high it will never achieve a concentration that causes local anesthesia, so this action is not important.

However, the concentration in plasma is too low for the anesthetic effects.

Most drugs are well absorbed after oral administration; peak concentrations 1–3 hours after ingestion

Lipophilic β blockers	Hydrophilic β blockers
• Propranolol, metoprolol, oxprenolol, carvedilol. • readily absorbed from GI, metabolized in liver. • hepatic failure prolongs their t1/2. • large volume of distribution, and penetrate BBB well.	• acebutolol, atenolol, bisoprolol, nadolol, sotalol. • less readily absorbed, not extensively metabolized. • long plasma half-lives which are prolonged in renal failure.

Pharmacodynamics of β blockers:

➢ Effects on the Cardiovascular System

Very valuable in hypertension, angina and chronic heart failure and following myocardial infarction (MI).

Heart: ↓ Heart rate, ↓Stroke volume (the volume of blood ejected by one contraction), ↓ Cardiac output, ↓ AV conduction velocity, ↓ O2 consumption.

- ✓ cardiac output = stroke volume X heart rate
- ✓ the mechanism of action for patients with ischemia is to decrease O2 consumption by decreasing cardiac output.

Blood vessels: ↓BP both diastolic and systolic after continuous treatment.

So they decrease the peripheral resistance, and this effect can result from:

1) Blockade of presynaptic β2 receptors in the heart and decrease NE release.

2) nonselective and β1 selective blockers inhibit the mechanism of release of renin (which leads to decrease angiotensin 2 that is considered vasoconstrictor).

Notice that there are two types of presynaptic receptors in the heart:

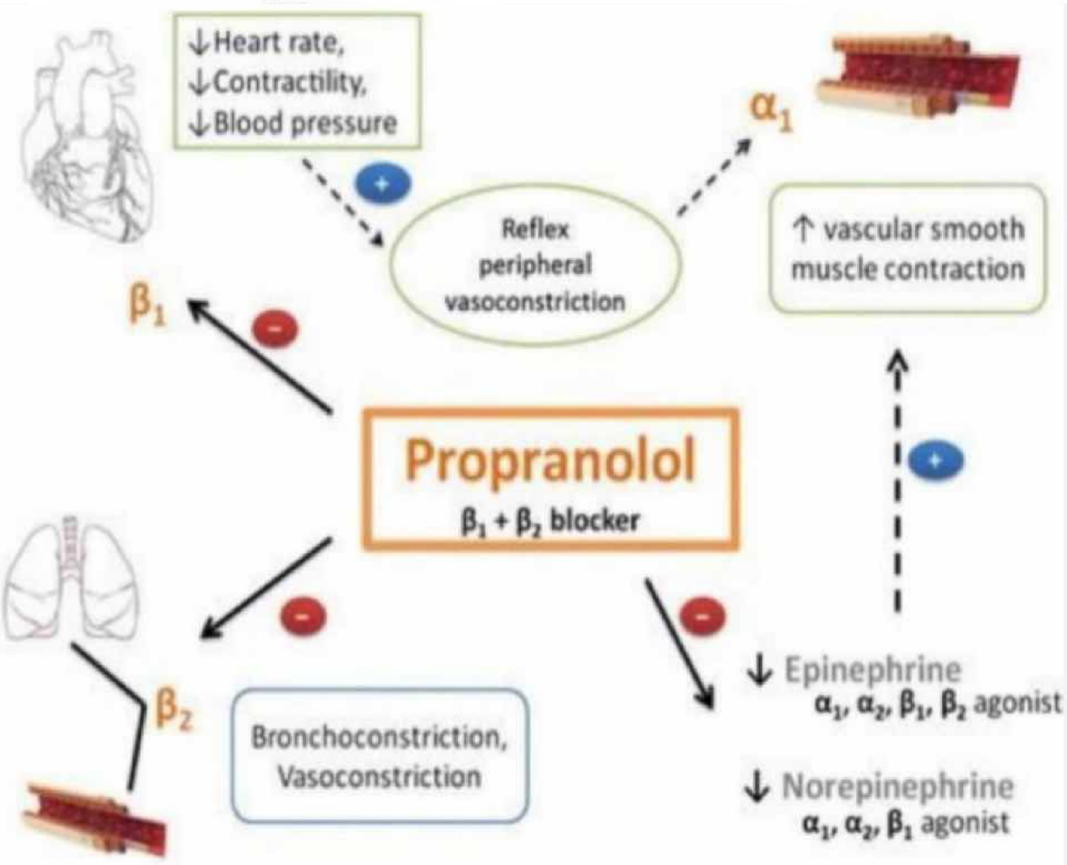
α2 receptors ➡ Inhibit NE release **β2 receptors** ➡ Increase NE release

Note: At first, the decrease in cardiac output evokes reflex peripheral vasoconstriction, so they **don't cause immediate hypotension in healthy individuals with normal BP**, but **continuous treatment may cause decreased BP**.

-Nonselective and β1-block → Inhibit renin Also, an inverse agonist(↓ resting Heart Rate)

➢ Effects on the Respiratory Tract

β2 blockade in lungs can produce bronchoconstriction and **increase in airway resistance, particularly in patients with asthma** (not noticed in normal people).



- ✓ β1 blockers are safer than nonselective β-blockers. However, β1-selective blockers are not sufficiently specific to completely avoid interactions with β2 receptors. **Consequently, these drugs should generally be avoided in patients with asthma. Many patients with chronic obstructive pulmonary disease (which involves asthma) may tolerate these drugs because the benefits exceed the risk, e.g. in patients with concomitant ischemic heart disease, may outweigh the risks.**

➢ Effects on the Eye

Reduce intraocular pressure in glaucoma by decreasing aqueous humor production. Glaucoma is treated by:

1) **reduction of aqueous humor secretion.**
2) **enhancement of aqueous out-flow.**

Drugs useful in reducing intraocular pressure: Cholinomimetics (pilocarpine, physostigmine, demecarium, etc), α agonists (epinephrine), β blockers, prostaglandin F2 analogs, diuretics.

Prostaglandin analogs and β blockers are the most popular (effective with minimal side effects).

➢ Metabolic and Endocrine Effects

- **β-receptor antagonists increase LDL (the bad cholesterol) and triglycerides, and decrease HDL (the good cholesterol) by inhibiting lipolysis. Long term treatment of β-blockers might expose the patient to type 2 diabetes.**
- **Glycogenolysis in the liver is inhibited after β2-receptor blockade.**

✓ **So β–blockers should be used with caution in type 1 insulin-dependent diabetic patients, these patients suffer from hypoglycemia and associated symptoms (tremors, sweating and tachycardia),** if they are given beta blockers the recovery of hypoglycemia will be delayed (no glycogenolysis), also no symptoms will appear which will worsen the condition.

◆ Specific Agents

➢ Propranolol

- **Prototype of β-blocking drug, High lipid solubility** (very good absorption and reach the brain).
- **Has low and dose-dependent bioavailability** (bioavailability increases with increasing the dose). -- **First-pass metabolism**
- **First-pass effect varies among individuals.**
- **A long-acting form of propranolol is available, prolonged absorption of the drug may occur over a 24-hour period**. Short-acting form is given twice daily.

Note: All beta blockers give duration of action that exceeds the expected duration according to their half-life.

- **No effect on α and M receptors but may block some serotonin receptors in the brain, though the clinical significance is unclear.**
- **It has no partial agonist action at β receptors**, strong local anesthetic effect.

- **Propranolol has been used extensively in patients with thyroid storm (severe hyperthyroidism) to control supraventricular tachycardias that often precipitate heart failure.**
- **The β antagonists are beneficial due to blockade of adrenoceptors & in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine.**
- **β antagonists reduce certain tremors. 18 Low doses of propranolol, particularly when taken prophylactically, is useful in musicians with performance anxiety ("stage fright").**
- **Propranolol may be used in symptomatic treatment of alcohol withdrawal in some patients.**
- **Propranolol reduces the frequency and intensity of migraine headache.**
- **Metoprolol , atenolol, timolol, and nadolol are also effective, mechanism is not known**

➢ Nadolol

Has a very long duration of action (24 hours), completely excreted unchanged in kidneys.

➢ Timolol

Has no local anesthetic activity, used topically to treat glaucoma and other therapies.

Note: We can't use propranolol to treat glaucoma because it causes local anesthesia in the eyes.

Sufficient timolol may be absorbed from the eye to cause serious adverse effects on the heart and airways in susceptible individuals

➢ Sotalol

Nonselective that also exhibits Class II and Class III antiarrhythmic properties.

Extra: Antiarrhythmic agents are a group of pharmaceuticals that are used to suppress abnormal rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.

✦ There are four classes of antiarrhythmics:

Class 1 → Na^+ channel blockers.

Class 2 → β-blockers.

Class 3 → K^+ channels blockers.

Class 4 → Ca^{+2} channels blockers.

Sotalol
Nonselective, has a **marked class III antiarrhythmic** effects, due to **potassium channel blockade** (treats both ventricular & supraventricular arrhythmias).

✓ Class 3 is used to treat ventricular arrythmia, while others are used to treat super ventricular arrhythmia.

◆ Cardioselective β Blockers (β1-selective antagonists)

- **less effects on bronchioles, carbohydrate metabolism, lipids.**
- **Lower incidences of Cold hands and feet** (one of the major side effects of propranolol and other nonselective beta blockers).

  Note: This side effect happens due to blockade of β receptors in the blood vessels of muscles which results in restriction of blood flow. **(remember that there are inhibitory β2 receptors in the smooth muscles of blood vessels of skeletal muscles, these receptors when activated cause relaxation)**

- **Less liable to impair exercise tolerance.**

  If someone takes nonselective beta blockers and then performs exercise he will feel tired after shorter period than usual, because exercise needs high cardiac output. Impairment of exercise tolerance is **less in β1 selective blockers**, because the blood

  vessels of skeletal muscles can still be activated by epinephrine and dilate.

- **Safer in patients who experience bronchoconstriction in response to propranolol, but their β1 selectivity is modest, so they should be used with great caution in patients with asthma.**

  However, the benefits may exceed the risks, e.g. in patients with myocardial infarction.

- **Beta1-selective antagonists are preferred in patients with diabetes or peripheral vascular disease since β2 receptors are important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).**

1. **Metoprolol**

- **High lipid solubility.**
- **Less likely to worsen asthma (cardioselective).**
- **used to treat angina and hypertension and also used to treat or prevent Myocardial Infarction (AMI) without bradycardia.**

2. **Atenolol**

- **Low lipid solubility.**
- **Longer duration action, One dose/day.**
- **Side effects related to CNS are less prominent, No effect on bronchus, carbohydrate metabolism, lipids.**
- **Most commonly used in Hypertension and angina.**

3. **Nebivolol**

- ➢ The most highly selective β 1 blocker.
- ➢ ↑ endothelial NO release (vasodilating effect) Antioxidant ,can protect the vascular wall from free radicals that damage blood vessels.

4. **<u>Bisoprolol</u>**

- ✓ low lipid solubility. Longer duration of action. One dose/day used to treat hypertension, coronary heart disease, arrhythmias.

- ✓ Clinical trials have demonstrated that at least three β antagonists, metoprolol, bisoprolol, and carvedilol are effective in reducing mortality in selected patients with chronic heart failure.

- ✓ gradual dose increments in patients who tolerate them may prolong life. They have a beneficial effects on myocardial remodeling and decrease the risk of sudden death.

5. **<u>Esmolol</u>**

- Ultra-short–acting β 1-selective blocker.
- Contains an ester linkage; esterases in red blood cells rapidly metabolize it.
- Has a short half-life (about 10 minutes).
- Given by continuous IV infusions
- Esmolol may be safer in critically ill patients who require a β -adrenoceptor antagonist.
- Esmolol is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis and myocardial ischemia in acutely ill patients.

NO MATTER WHAT, JUST KEEP GOING

BEST OF LUCK ツ

V2

⇒ Page 5

--Prazosin, doxazosin, and terazosin are all effective.

--Tamsulosin is preferred in patients who have orthostatic hypotension with other α 1-receptor antagonists

⇒ page 8

-Nonselective and β1-block → Inhibit renin Also, an inverse agonist(↓ resting Heart Rate)