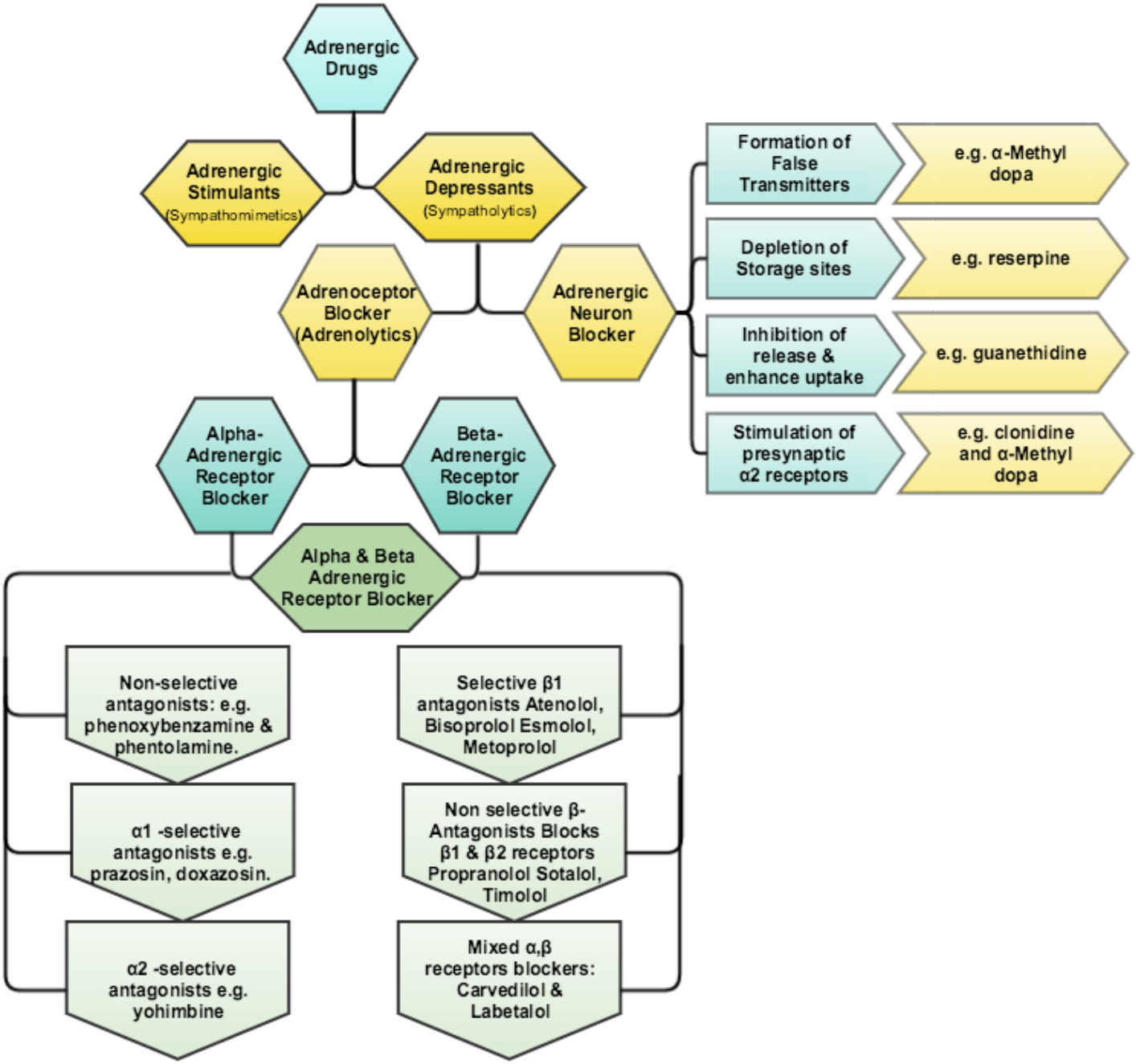
# PHARMACOLOGY

## CVS block- Drugs summary

PHARMACOLOGY
435

# lectures 1,2 : adrenergic blockers



# Adrenergic neuron blockers


**α-methyl dopa**

- formation of false transmitters (methyl norepinephrine)
- stimulation of presynaptic α2 receptors to inhibit **NE** release (as clonidine)
- acts centrally
- **Drug of choice in: hypertension in pregnancy (pre-eclampsia - gestational hypertension)**

**Reserpine**

- depletion of storage sites
  reserpine = depletes reserves

**Guanethidine**

- inhibtion of release and enhance uptake

**Clonidine**

- stimulation of presynaptic α2 receptors to inhibit **NE** release (as α-methyl dopa)
- acts centrally (on the brain)
- little used as antihypertensive agent due to **rebound hypertension** upon abrupt withdrawal. This can be treated with labetalol.

**Apraclonidine**

- used in **open angle glaucoma**. Acts by decreasing aqueous humor formation.

# α adrenergic antagonists

| Drug | Receptor selectivity | action: | Therapeutic use |
|---|---|---|---|
| Phenoxybenzamine (irreversible-long acting 24h)<br>Phentolamine (reversible-short acting 4h) | Non-selective (α1 – α2) | • Postural hypotension<br>• Decrease peripheral vascular resistance<br>• Increase cardiac output (α2 block)<br>• Precipitate in arrhythmias and angina | Used Before surgical removal of Pheochromocytoma to protect against hypertensive crisis.<br>Contraindicated in: Patient with decreased coronary perfusion |
| Prazosin (short half-life)<br>Doxazosin (long half-life)<br>Terazosin (long half-life) | α1 selective blockers | • Vasodilatation due to relaxation of arterial and venous smooth muscles<br>• Fall in arterial pressure with less tachycardia than with non-selective α blockers | 1-Benign prostatic hyperplasia<br>2-Hypertension with prostate enlargement<br>3-Reynaud's disease |
| Tamsulosin | α1A (present in prostate) | • Relaxation of smooth muscles of bladder neck and prostate → improve urine flow<br>• Minimal effect on blood pressure | Benign prostatic hypertrophy (BPH) |
| Yohimbine | α2 | ↑nitric oxide in corpus cavernosum → vasodilatation → erectile process | Aphrodisiac in erectile dysfunction |

## Adverse effects* of non-selective α blockers (phenoxybenzamine – phentolamine):

- Postural hypotension
- Tachycardia
- Headache
- Nasal stuffiness and congestion
- Vertigo and drowsiness
- Male sexual dysfunction (inhibits ejaculation)

*α1 antagonists have the same adverse effects but to a lesser degree.

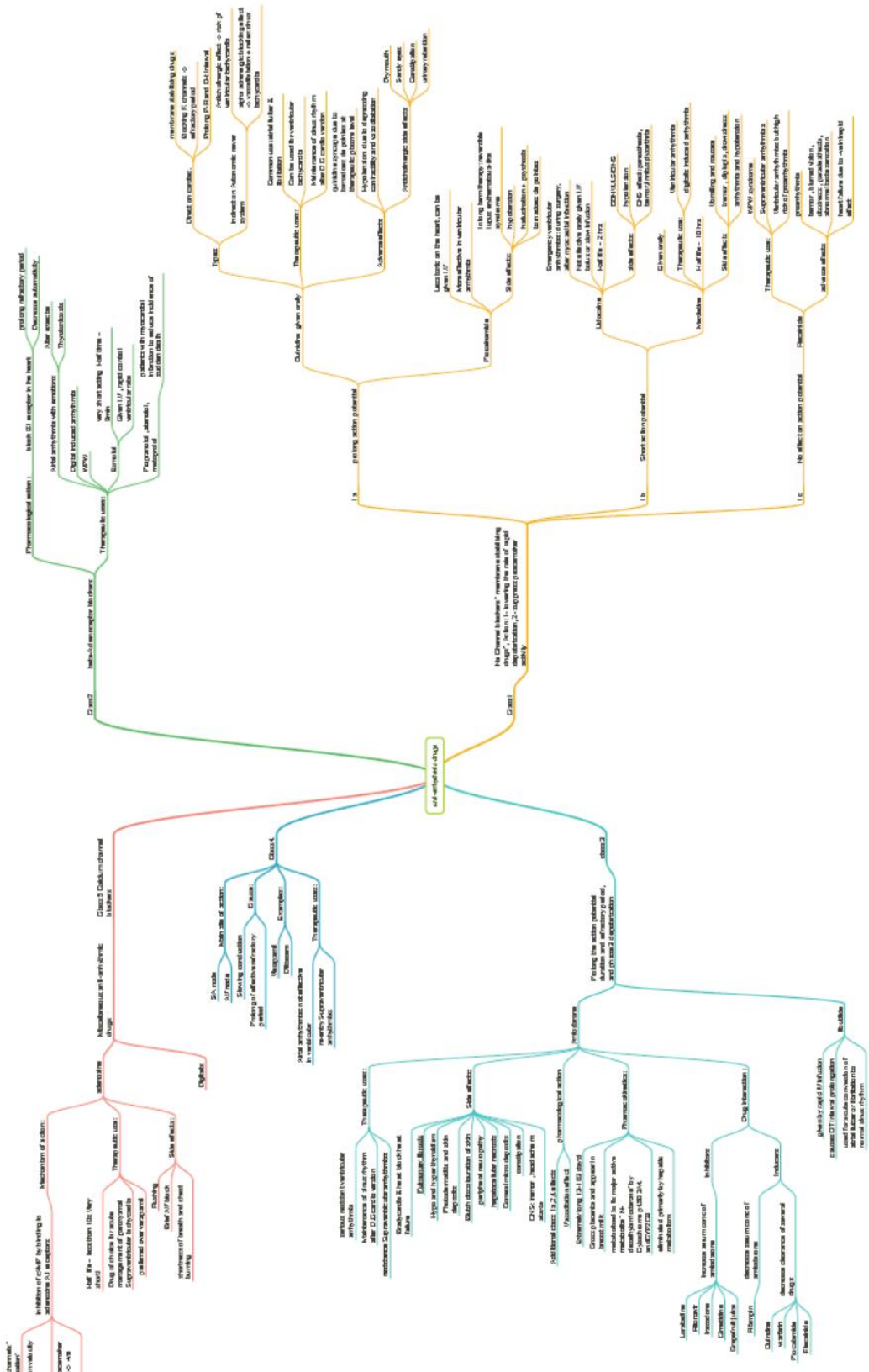
# β- Adrenoceptors blockers

| DISEASE | | DRUG (s) | mechanism of action |
|---|---|---|---|
| CVS | Hypertension | Labetalol (by injection)<br>Atenolol, Bisoprolol > Metoprolol, Propranolol | • ↓ cardiac output<br>• ↓ renin and RASS system<br>• Inhibition of presynaptic NE release<br>• Inhibition of sympathetic outflow in CNS<br>• Treatment of hypertensive pregnant & hypertensive crisis |
| | Cardiac Arrhythmias | Esmolol (ultra-short acting, $T\frac{1}{2} = 10\ min$),<br>Atenolol, Propranolol<br>(Bisoprolol and carvedilol are preferred) | • Propranolol: Membrane stabilization (block Na channel →local anesthetic effect/ antiarrhythmic effect: ↓ excitability, ↓automaticity , ↓ conductivity)<br>• treatment of supraventricular & ventricular arrhythmias |
| | Angina pectoris | Beta blockers<br>e.g. propranolol | • anti -ischemic action : ↓heart rate, ↓ cardiac work & oxygen demand, ↓the frequency of angina episodes. |
| | Congestive Heart Failure | Carvedilol (antioxidant action)<br>Bisoprolol, Metoprolol | • Decrease myocardial remodeling<br>• decrease risk of sudden death. |
| | Myocardial Infarction | Atenolol, Metoprolol, Propranolol | • Have cardio-protective effect: ↓ infarct size ,↓ morbidity & mortality ,↓ myocardial O2 demand.<br>• Anti-arrhythmic action (Quinidine-like action)<br>• Decrease the incidence of sudden death . |
| Chronic Glaucoma | | Timolol (eye drop) ,<br>propranolol | ↓aqueous humor production from ciliary body<br>↓intraocular pressure (IOP) |
| Hyperthyroidism (thyrotoxicosis) | | Beta blockers<br>(e.g. Propranolol) | • Protect the heart against sympathetic overstimulation<br>• Controls symptoms; tachycardia, tremors, sweating. |
| Anxiety (Social and performance type) | | Propranolol (orally or parenteral) | • Propranolol is Lipid soluble , thus has CNS effect →sedative action → Control anxiety symptoms (tachycardia, tremors, sweating) |
| Migraine (prophylaxis) | | propranolol | ↓reduce episodes of chronic migraine<br>↓catecholamine-induced vasodilatation in the brain vasculature (antagonize the sympathetic effect) |
| Hypertensive crisis of Pheochromocytoma | | Labetalol (has to be combined with α blockers) | α-blockers lower the elevated blood pressure.<br>β-blockers protect the heart from NE. |

# β- Adrenoceptors blockers

| | |
|---|---|
| **Pharmaco-kinetis** | • **Most of them are lipid soluble (Metoprolol, propranolol, timolol, labetalol, carvedilol), these are well absorbed orally, rapidly distributed, cross readily BBB & Have CNS depressant actions**<br>• **Most of them have a half-life from 3-10 hrs except Esmolol (10 min. given by I.V.).**<br>• **Most of them metabolized in liver & excreted in urine.** |
| **Adverse Effects:** | **selective β1-blockers (Due to blockade of β1- receptor):**<br>**Bradycardia, hypotension, heart failure**<br>**Since there is NO change in lipid or glucose & NO bronchoconstriction, they're SAFE FOR:**<br>• **Asthma & COPD**<br>• **Raynaud's phenomenon and PVD**<br>• **Diabetics/ Dyslipidemias**<br>• **Variant Angina**<br>**Note: Selectively present in low doses, Lost in high doses** |
| | **Non selective β-blockers (Due to blockade of β2- receptor):**<br>• **Depression + Hallucinations**<br>• **GI disturbances (↑ Intestinal motility)**<br>• **Bronchoconstriction, specially in susceptible patients**<br>• **Sodium retention 2ndry to ↓BP → ↓renal perfusion**<br>• **hypoglycemia, ↓ Lipolysis , ↑TG (hyperglyceridemia)**<br>• ↑ peripheral resistance (PR) by blocking vasodilatory effect → Vasoconstriction → ↓blood flow to organs **except brain** → **cold extremities & intermittent claudication** ($\beta_2$)<br>• **Erectile dysfunction & impotence**<br>• **Coronary spasm (in variant angina patients)** |
| | **Mixed alpha & beta receptor blockers:**<br>• Carvedilol: **Edema**<br>• Labetalol **(membrane stabilizing effect with ISA): Orthostatic hypotension, Sedation and dizziness** |
| | **All β-blockers:**<br>• **Masked hypoglycemic manifestations i.e. tachycardia, sweating… →Coma** |
| **Contra-indications** | • **Heart Block (because beta blockers can precipitate heart block).**<br>• **Bronchial Asthma, emphysyma & Peripheral vascular disease (safer with cardio-selective β1 blockers).**<br>• **Diabetic patients → Masking of hypoglycaemia / must be GIVEN CAUSIOUSLY**<br>• **Hypotension**<br>• **Alone in pheochromocytoma (must be given with α-blockers).**<br>• **peripheral diseases like Reynaud's disease** |
| **Precautions** | **Sudden stoppage will give rise to a withdrawal syndrome:**<br>**Rebound angina, arrhythmia, myocardial infarction & Hypertension**<br>**WHY ? Due to Up-regulation of β-receptors** (increase number of β-receptors)<br>**To prevent withdrawal manifestations → drug withdrawn gradually.** |

# Mind map- lectures 3,4: Antiarrhythmic Drugs



Note: Class 5 aren't Calcium channel blockers. Class 4 are.

[For a better version, click here]

# Drugs summary- lectures 3,4: Antiarrhythmic Drugs

## CLASS I (Na+ channel blockers)

### IA

**Action:**
-Prolong action potential duration by: Slow phase 0.

- Slow conduction

#### Quinidine (Given orally)

**Uses:**
-atrial flutter & fibrillation (common use).
-Can be used in ventricular tachycardia.
-maintaining sinus rhythm after D.C. cardio version.

**ADRs:**
- quinidine syncope due to torsades de pointes
- Dry mouth.
- Blurred vision.
- Urinary retention.
- Constipation.
- Hypotension.

**Mechanism of action:**
Cardiac ( Direct):
(Membrane stabilizing effect)
- Block K+ channel
- Prolong PR & QT intervals
- Widens QRS complex.

ANS ( Indirect):
-Anticholinergic effect (Increase conduction through the A.V. node)
*α-adrenergic blocking effect

#### Procainamide (Can be given IV)

Similar to quinidine **except** :
- less toxic on the heart.
- More effective in ventricular than in atrial arrhythmia.

- No anticholinergic or α-blocking actions

**ADRs:**
- Lupus erythematosus-like syndrome ( in long term therapy).
- Hypotension .
- Torsades de pointes.
- Hallucination & psychosis .

### IB

**Action:**
- Decrease action potential duration by shortening phase 3 (repolarization)

#### Lidocaine (given IV bolus or slow infusion)

**Uses:**
Treatment of emergency ventricular arrhythmia (e.g. during surgery, following acute myocardial infarction).
**Not effective in:**
- Oral administration.
- In atrial arrhythmia.
**T1/2:**
2 hours

**ADRs:**
-Hypotension
-Similar to other local anesthetics.
CNS adverse effects:
-paresthesia.
- tremor.
- Dysarthria.
- tinnitus.
- confusion.
- Convulsion.

#### Mexiletine ( effective orally)

**Uses:**
- Ventricular arrhythmia.
- Digitalis-induced arrhythmia.

**T1/2:**
- 10 hours

**ADRs:**
- Nausea
- Vomiting
- Tremor
- Drowsiness
- Diplopia
- Arrhythmia
- Hypotension

### IC

**Action:**
- Slow phase 0 (depolarization

- No effect on action potential duration.

#### Flecainide

**Uses:**
- Supraventricular arrhythmia.
- Wolff-Parkinson-White syndrome
- Very effective in ventricular arrhythmia.
- Should be reserved for ventricular arrhythmia.

**ADRs:**
- Proarrhythmia.
- Heart failure due to -ne inotropic effect.
- CNS adverse effects: Dizziness, tremor, blurred vision, abnormal taste sensation, paraesthesia.

# Drugs summary- lectures 3,4: Antiarrhythmic Drugs

## CLASS II (β- ADRENOCEPTOR BLOCKERS)

**Action:**

a- Block β1 receptor in the heart.
b- Reduce sympathetic effect on the heart.
c- 1-decrease automaticity of SA node and ectopic pacemaker.
2-prolong refractory period of AV node.

### Esmolol

Very short acting (half-life= 9min.)
Given IV fro rapid control of ventricular rate ( atrial flutter or fibrillation).

### Propranolol Atenolol Metoprolol

used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias.

**Uses:**

- Atrial arrhythmia associated with emotion.
- WBW.
- Digitalis-induced arrhythmia.

## CLASS III

**Action:**

Prolong the action potential duration by prolong phase 3.

### Amiodarone

**pharmacological actions:**

- prolongs action potential duration and therefore prolongs refractory period ( Main effect )
- additional class Ia, II & IV effects
- vasodilating effects ( due to its α- & β- adrenoceptor blocking effects and its calcium channel blocking effects )

**Therapeutic uses:**

1- main use : serious resistant ventricular arrhythmias
2- maintenance of sinus rhythm after D.C. cardio version
3- resistant supraventricular arrhythmias ( e.g. WPW ).

**Adverse effects:**

- bradycardia & heart block, heart failure
- pulmonary fibrosis
- hyper- or hypothyroidism
- photodermatitis & skin deposits ( patients should avoid exposure to the sun)
- may cause bluish discoloration of the skin.
- CNS: tremor, headache, ataxia, paresthesia
- constipation
- corneal micro deposits
- hepatocellular necrosis
- peripheral neuropathy

**Pharmacokinetics:**

- long t1/2 = (13 - 103 days)
- metabolized to its major active metabolite N-desethylamiodaron-e by cytochrome P450 3A4 and CYP2C8
- eliminated primarily by hepatic metabolism
- cross placenta and appear in breast milk

**Drug Interactions:**

1 - As amiodarone is metabolized by CYP3A4 & CYP2C8. drugs (or substances) that inhibit these enzymes will increase serum concentration of amiodarone
e.g. : Loratadine, Ritonavir, Trazodone, Cimetidine, Grapefruit juice.
2 - drugs that are inducers of these enzymes will decrease serum concentration of amiodarone
e.g. : Rifampin
3 - Reduces clearance of several drugs e.g. quinidine, warfarin, procaiamide,flecainide

### Ibutilide

- Given by rapid I.V. infusion.
- Used for the acute conversion of atrial flutter or fibrillation to normal sinus rhythm.
- Causes QT interval prolongation.
- May cause torsades de pointes.

# Drugs summary- lectures 3,4: Antiarrhythmic Drugs

## Class IV

**Action**:
calcium channel blockers.
main site of action is A.V node & S.A node.
cause:
- slowing of conduction
- prolongation of effective refractory period

Verapamil

Diltiazem

### Therapeutic uses :

1- atrial arrhythmias
2- re-entry supraventricular arrhythmias. e.g. WPW
3- NOT effective in ventricular arrhythmias

## CLASS V (MISCELLENIOUS ANTIARRHYTHMIC DRUGS)

**Drugs:**

Adenosine

Digitalis

**Mechanism of action : (of Adenosine)**

-inhibits cAMP by binding to adenosine A1 receptors, causing the following actions:
1 - Opening of potassium channels (hyperpolarization).
2 - decreasing conduction velocity mainly at AV node. ( negative dromotropic effect )
3- inhibiting phase 4 pacemaker action potential ( SA node).
( negative chronotropic effect ).

**Therapeutic uses : (of Adenosine)**

- half-life = less than 10 sec.
- drug of choice for acute management of paroxysmal supraventricular tachycardia
- preferred over verapamil – safer and does not depress contractility

**Adverse effects: (of Adenosine)**

- flushing in about 20% of patients
- shortness of breath and chest burning in 10% of patients ( bronchospasm )
- brief AV block ( contraindicated in heart block)

| Classification of Drug | | Mechanism of Action | Comment | Examples |
|---|---|---|---|---|
| Class 1 | A1 | Na Channel Blocker (membrane stabilizing drugs) | Slow phase 0 (in ventricular muscle) | Quinidine and Procainamide |
| | A2 | | Shorten Phase 3 (in ventricular muscle) | Lidocaine and Mexiletne |
| | A3 | | Markedly slow phase 0 (in ventricular muscle) | Flecainide and Propafenone |
| Class 2 | | β- adrenoceptor blockers | Marked slow phase 0 (in ventricular muscle) | Esmolol, Propranolol, Atenolol, and Metoprolol |
| Class 3 | | K Channel Blocker | Inhibit phase 4 (in SA and AV nodes) | Aminodarone and Ibutilide |
| Class 4 | | Ca Channel Blocker | prolong Phase 3 (in ventricular muscle) | Verapamil and Diltiazem |
| **Miscellaneous antiarrhythmic drugs** (Does not undergoes specific class.*we can call it Class5) | | | It is a large group of antiarrhythmic drugs | Adenosine and Digitalis |

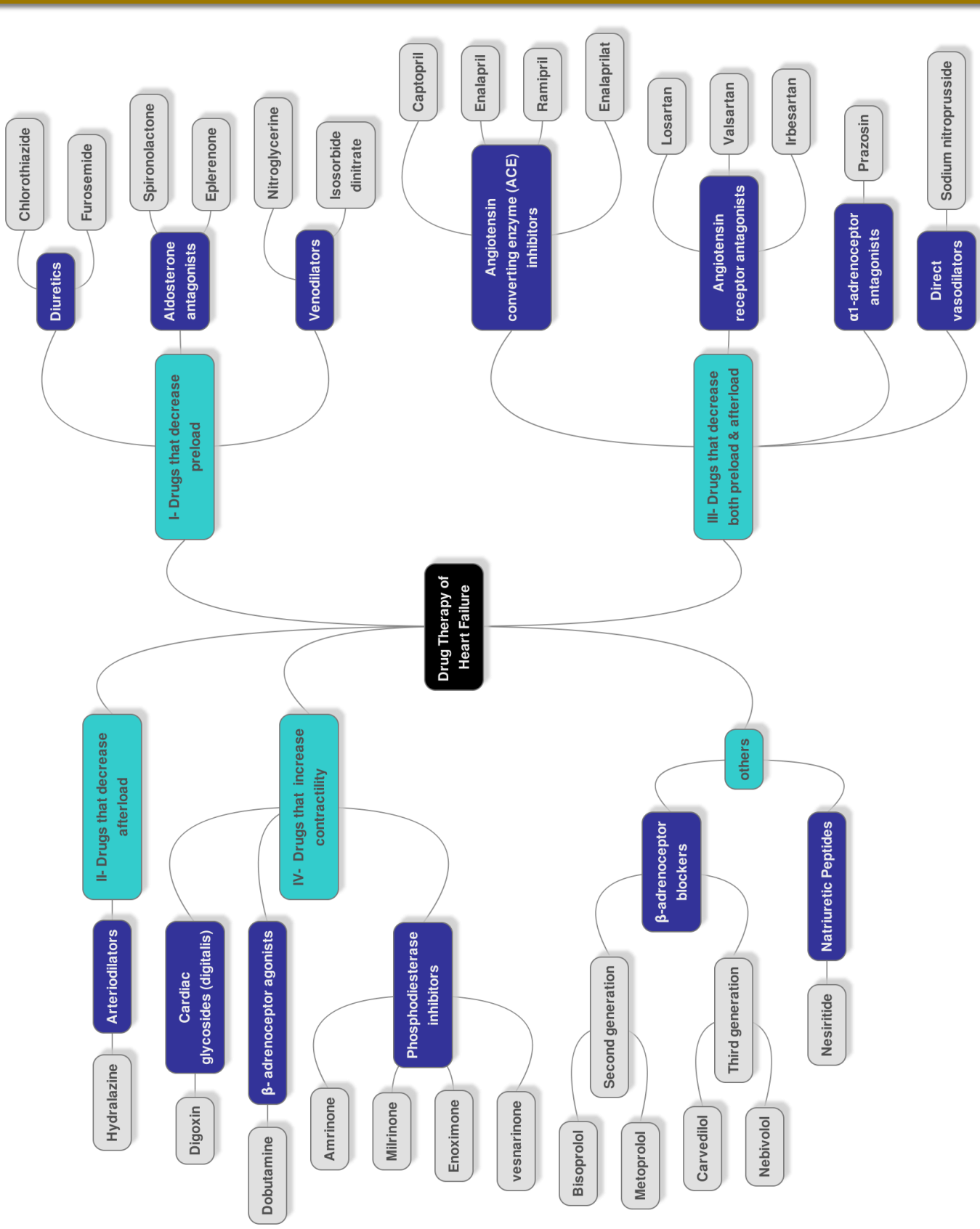
# anti-arrhythmia drugs

| Condition | Drug of choice |
|---|---|
| **Ventricular arrhythmia** | Emergency " After MI "<br>1st choice —> **Lidocaine** ( Ib)<br>2nd choice —>**Procainamid** (Ia) |
| | Normal state:<br>**Mexiletine** (Ib) |
| | Resistance: **Amiodarone** (III) **Flecainide** (Ic) *Pro-arrhythmia |
| **Atrial arrhythmia** | Emergency:<br>- Acute arrhythmia (atrial fib. to normal sinus) —> **Ibutilide** (III)<br>- Acute arrhythmia (Sympathatic) —> **Esmolol** (II) |
| | Not emergency:<br>- Sinus tachycardia & **prophylactic** for pts who had MI —><br>**Propranolo**, **Atenolol** & **Metanolo** (II)<br>- **Verapamile** & **Diltiazem** (IV)<br>- **Quinidine** |
| | Resistance: **Flecainide** (Ic) |

| Condition | Drugs |
|---|---|
| **Treatment of WPW** | **Flecainamide** (Ic) , **Beta blockers** (II) & **Amiodarone** (III)<br>* (IV) are contraindicated with WPW pts. |
| **Cause torsade de pointes** | **Quinidine**, **Procainamide** (Ia) + **Amiodarone**, **Ibutilide** (III)<br>* باختصار، كل الأدوية اللي تسبب Prolongation of QT interval |
| **used as Digitalis induced arrhythmia** | **Mexiletine** (Ib) , **Beta blockers** (II) |
| **Membrane stabilizing** | **Propranolol** (II), **class I** , **Labetalol** |

Done by: Atheer Alnashwan

# mind map- lectures 5,6: treatment of heart failure




For a more detailed mind map (therapeutic use), click here.

# Drugs summary- lectures 5,6: Treatment of heart failure

| Group | Diuretics | Veno-dialators | Aldosterone antagonists | Arterio-dialators |
|---|---|---|---|---|
| *Action* | *Decrease preload* | | | *Decrease afterload* |
| *Mechanism of action* | • reduce salt and water retention<br>• which decrease ventricular preload and venous pressure<br>• reduction of cardiac size<br>• Improvement of cardiac performance | *Dilate venous blood vessels and ↓ preload* | antagonist of aldosterone receptor | *dilate arterial blood vessels to ↓ peripheral vascular resistance* |
| *Drugs* | 1- Chlorothiazide<br>first-line agent in heart failure therapy<br>used in volume overload (pulmonary and/ or peripheral edema)<br>used in mild congestive heart failure<br>2- Furosemide<br>a potent diuretic used for immediate reduction of pulmonary congestion & severe edema associated with :<br>- acute heart failure<br>- moderate and severe chronic failure | Nitroglycerine & Isosorbide dinitrate<br>used I.V. for severe heart failure when the main symptom is dyspnea due to pulmonary congestion | 1-Spironolactone<br>• nonselective antagonist of aldosterone receptor<br>• a potassium sparing diuretic used in congestive heart failure<br>• improves survival in advanced heart failure<br>2- Eplerenone<br>a new selective aldosterone receptor antagonists | Hydralazine<br>Used when the main symptom is Rapid fatigue due low cardiac output |

# Drugs summary- lectures 5,6: Treatment of heart failure

<table>
<tr><th>Group</th><th colspan="3">Angiotensin converting enzyme inhibitors</th><th>Angiotensin receptor blockers</th><th>α-adrenoceptor blockers</th><th>Direct vasodilators</th></tr>
<tr><td>Action</td><td colspan="6">Decrease both ( preload and after load )</td></tr>
<tr><td>Mechanism of action</td><td colspan="3">1st line for hypertension & chronic heart failure therapy along with diuretics.<br>inhibit ACE → reduce synthesis of AgII → activation of Bradykinin system which is a potent vasodilator.<br>↓ preload and afterload</td><td>Blocks AT1 receptors decrease the action of AgII<br>(more potent effect than ACE)</td><td>block α- receptors in arterioles and venules</td><td></td></tr>
<tr><td>Useful Effects</td><td colspan="4">1-Decrease peripheral resistance (Afterload )<br>2-Decrease Venous return (Preload)<br>3- Decrease sympathetic activity<br>4- Inhibit cardiac and vascular remodeling</td><td>reduce blood pressure by decreasing both afterload & preload which help heart failure patients</td><td></td></tr>
<tr><td>Drugs</td><td>Captopril</td><td>Enalapril</td><td>Rampril</td><td>Losartan, Valsartan, Irbesartan</td><td>Prazosin</td><td>Sodium nitroprusside</td></tr>
<tr><td colspan="4">Rapidly absorbed from GIT after oral administration<br>Food reduce their bioavailability</td><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3">- I.V acute or severe refractory HF<br>-Acts immediately<br>- Effect lasts 1 – 5 min</td></tr>
<tr><td colspan="2">Short duration of action<br>Not a prodrug</td><td>Prodrugs converted to their active metabolites in the liver<br>Long T1/2<br>(given once daily)</td></tr>
<tr><td colspan="4">Enalaprilat<br>(active metabolite of Enalapril )<br>Used I.V in hypertensive emergency</td></tr>
<tr><td>Adverse effect</td><td colspan="4">1- acute renal failure<br>2- hyperkalemia<br>3-hypotension in hypovolemic patients<br>4- Dry cough<br>5- angioneurotic edema<br>6-Dysgeusia</td><td></td><td></td><td></td></tr>
<tr><td>Contra-indications</td><td colspan="4">• during the second and third trimesters of pregnancy<br>• renal artery stenosis</td><td></td><td></td><td></td></tr>
</table>

# Drugs summary- lectures 5,6: Treatment of heart failure

| Group | Cardiac glycosides (Digitalis) | Phosphodiesterase-III inhibitors | β – adrenocepters agonists |
|---|---|---|---|
| ***action*** | ***Increase contractility (+ve inotropic)*** | | |
| ***Drugs*** | ***Digoxin*** | ***Amrinone / Milirone***<br>***Enoximone / vesnarinone (new drugs)*** | ***Dobutamine***<br>***(selective β1 agonist)*** |
| ***Mechanism of action*** | ***Inhibit NA/K ATPase enzyme (the Sodium pump)***<br>*1- inhibit Na/K pump directly*<br>*2- indirect inhibition of Na/Ca exchange*<br>*3- facilitate Ca influx*<br>*4- ↑ Ca release from ER & T tubules*<br>*Net result : increase the intracellular Calcium* | **Inhibit Phosphodiesterase isoenzyme 3 in cardiac and blood vessels to inhibit cAMP degradation (↑cAMP)**<br><br>**1- in heart: ↑ Ca which ↑ contraction**<br>**2- in peripheral vessels dilatation of arteries and veins (reduction of preload and afterload)** | |
| ***Pharmacol - ogical action*** | **1- increase the force of myocardial contraction to increase cardiac output ( +ve inotropic effect )**<br>**2- slow heart rate by vagal stimulation (-ve chronotropic effect)** | | |
| ***Pharmaco-kinetics*** | **- narrow therapeutic index**<br>**- 40-80 % absorbed orally (variable bioavailability)**<br>**- 85% excreted unchanged in urine** | | |
| ***Therapeutic uses*** | **- congestive heart failure**<br>**- Atrial arrhythmias:**<br>• **Atrial flutter**<br>• **Atrial fibrillation**<br>• **Supraventricular tachycardia** | **Milrinone : Acute heart failure (intravenously), not safe nor effective in the longer treatment (> 48hours)**<br>**Amrinone not used now because it causes thrombocytopenia** | **Treatment of acute heart failure in Cardiogenic shock**<br>**(I.V in severe cases)** |
| ***Adverse effects*** | **1) digitalis-induced arrhythmias (any type of arrhythmias for example bigeminal rhythm )**<br>**2) GIT side effects (The earliest signs of toxicity)**<br>**3) CNS side effects especially in old age**<br>**Factors that increase toxicity:**<br>**- Renal diseases**<br>**- Hypokalemia**<br>**- Hypomagnesemia**<br>**- Hypercalemia** | **1) GIT upsets (Nausea ,vomiting)**<br>**2) thrombocytopenia**<br>**3) live toxicity**<br>**(Milrinone has LESS hepatotoxic and less bone marrow depression than amrinone)** | |

# Drugs summary- lectures 5,6: Treatment of heart failure

| Group | β-adrenoceptor blockers | Natriuretic Peptides |
|---|---|---|
| *Drugs* | Second generation: Bisoprolol, Metoprolol<br>β1 receptors blockers (cardio selective)<br>Third generation: Carvedilol , Nebivolol<br>have vasodilator actions ( α- blocking) | Nesiritide |
| *Mechanism of action* | β-blockers:<br>1- attenuate cardiac remodeling (cardiac dilatation & hypertrophy)<br>2- slow heart rate, which allows the left ventricle to fill more completely<br>3- decrease renin release<br>reduce mortality and morbidity of patients with HF | Nesiritide is a purified preparation of human BNP (which is normally secreted by the ventricular myocardium in response to stretch) manufactured by recombinant DNA technology.<br>It increases cyclic-GMP in vascular smooth muscle, leading to smooth muscle relaxation and reduction of preload and afterload |
| *Therapeutic uses* | reduce the progression of chronic heart failure, not used in acute heart failure | indicated for the treatment of patients with acutely decompensated heart failure who have dyspnea at rest or with minimal activity |

| Condition | Drugs |
|---|---|
| **Acute HF** | – Dobutamine (if w\cardiogenic shock)<br>– Amrinone & Milrinone (ADRs: Thrombocytopenia, Liver toxicity)<br>– Furosemide (Reduce pulmonary congestion & Sever edema) *K+ supplementation.<br>– Beta agonist (+ve ionotropic)<br>– Sodium nitroprusside (Vasodilators) |
| **HF + Dyspnea** | Nitroglycerine (Venodilators) (Reduce **preload**) |
| **HF + Rapid fatigue** | Hydralazine (Arteriodilators) (Reduce **afterload**) |
| **1st line treatment of chronic HF** | **ACEIs + Diuretics** |

Done by: Atheer Alnashwan

Mind map – drugs for heart failure

# mind map- lectures 7,8: Antihypertensive Drugs

## Antihypertensive Drugs

### DIURETICS

- Thiazides
  - Hydrochlorothiazide
  - In Mild hypertension
- Loop diuretics
  - Furosemide
  - -Sever & Moderate hypertension
  - -Sever heart failure
- Potassium-sparing diuretics
  - Amiloride as well as spironolactone
  - - Not potent antihypertensive, mainly used in Heart failure)

### β- Adrenoceptor Blockers

**monotherapy in mild to moderate hypertension, In severe cases used in combination with other drugs.**

- non cardio selective(β1 & β2)
  - **Propranolol**
  - **Nadolol**
  - contraindicated in asthmatic patients
- cardio selective(β1)
  - **Bisoprolol**
  - **Atenolol**
  - **metoprolol**
- α–β adrenergic blockers
  - **Labetalol**
  - **carvidalol**

### α1-Adrenoceptor blockers

- **•Added to β- blockers for treatment of hypertension of pheochromocytoma**
- Prazosin &
- Terazosin
- Doxazosin

Due to the postural hypotension, α1-adrenoceptor blockers are not commonly used for Rx of HTN

### Ca++ CHANNEL BLOCKERS

**Treatment of chronic hypertension with oral preparation**

- **•Nifedipine used for Raynaud's phenomena**
- **•Nicardipine can be given by I.V. route & used in hypertensive emergency**

- Dihydropyridine
  - It is more selective as vasodilator than a cardiac depressant. This group is specifically used for treatment of hypertension.
  - **e.g. Nifedipine, Nicradipine, Amlodipin (Ankmlor)**
- Verapamil
  - It is more effective as cardiac depressant , therefore commonly used as antiarrhythmic .
- Diltiazem
  - Intermediate action. Used mainly for angina pectoris

# mind map- lectures 7,8: Antihypertensive Drugs

## Antihypertensive Drugs

### Centrally acting sympatholytic drugs

- α methyl dopa
  - Indirect α 2 agonist
  - Safely used in hypertensive pregnant women
- Clonidine
  - Direct α2-agonist
  - Sudden withdrawal causes rebound hypertension

### Vasodilators

- Minoxidil
  - K- channel opener, Arteriodilator
  - 1.severe hypertension
    2.correction of baldness (by Hypertrichosis)
- Na nitropruside
  - Release of (NO), Arterio & venodilator
  - 1.Hpertensive emergency
    2.Severe heart failure
  - ADRs: cyanide toxicity, methemoglobinemia
- Hydralazine
  - Direct , Arteriodilator
  - 1.Moderate -severe hypertension.
    2.Hypertensive pregnant woman
    3. Heart failure (CHF)
  - Cause lupus-erythematosus-like syndrome
- Diazoxide
  - 1.Hpertensive emergency
    2. Treat **hypoglycemia** (contraindicated for diabetics

### ACE INHIBITORS

Cause Acute renal failure, contraindicated in renal artery stenosis

**Note that ACE I all end with the suffix "-pril"**

- **Drugs include captopril, lisonopril, enalapril, ramipril, fisonopril**

**USES:**

- **Hypertension**
- **Heart failure**
- **Diabetic nephropathy**

### BLOCKERS OF AT1 RECEPTOR

Adverse effects:
As ACEI except cough ,wheezing, and angioedema. Because it has no effect on bradykiniin

**Note that all end with the suffix "-sartan"**

- **Drugs include:**
  - **losartan**
  - **valosartan**
  - **irbesartan**

**Clinical Uses:**
hypertension.
(Especially in asthmatic patients)

# Drugs summary- lectures 7,8: Antihypertensive Drugs

| Classification | Examples | Important notes |
|---|---|---|
| **Diuretics** | Hydrochlorothiazide, Furosemide ,potassium sparing diuretics (Amiloride, & spironolactone) | • K-sparing diuretics reduce K loss in the urine<br>• **Hydrochlorothiazide & Furosemide** decrease the B.P by decreasing volume of blood & cardiac output<br>• Furosemide is indicated for hypertension with renal impairment |
| **ACE Inhibitor** | captopril, lisonopril, enalapril, ramipril,& fisonopril | • Cause and increase the risk of renal failure thus contradiction in patient with renal diseases & Pregnant women |
| **Angiotensin receptor Blockers** | Losartan, valosartan, & irbesartan | Same ADRs & contraindications as ACEI, except for cough and angioedema, thus indicated for asthmatic hypertensive patients. |
| **Calcium channel blockers** | Verapamil, Diltiazem, Nicardipine & Nifedipine | • **Treat chronic hypertension**<br>• Nicardipine is used in hypertensive emergency<br>• side effects :<br>Verapamil → Constipation<br>Nifedipine → reflex tachycardia. |
| **Vasodilators** | Hydralazine, Minoxidil, Diazoxide, & Na nitropruside | • **Hydralazine** used in Hypertensive pregnant woman. ADRs: lupus erythematous like syndrome.<br>• **Minoxidil** Cause: (Hypertrichosisis) increase hair growth, That's why it is contradicted in female.<br>• **Na nitropruside** Cause: Cyanide toxicity & used in hypertensive emergency |
| **β- Adrenoceptor Blockers** | Nadolol, Bisoprolol, Atenolol, metoprolol, Labetalol, & carvidalol | • In severe cases used in combination with other drugs.<br>• They decrease cardiac output & renin release<br>• Mask the symptoms of Hypoglycemia in diabetic patients. |
| **α- Adrenoceptor Blockers** | Prazosin, Doxazosin & Terazosin | • Prazosin is short-acting, causes first dose hypotension & postural hypotension<br>• Doxazosin is **Preferred, because of its long half- life** |
| **Centrally acting sympatholytic** | Clonidine & α methyl dopa | **clonidine** can lead to rebound hypertension<br>**α methyl dopa** : Safe in Pregnant woman |

# Drugs summary – lectures 9,10: Antihyperlipidemic drugs

| | 1. Drugs targeting exogenous pathways | |
|---|---|---|
| Drug | Ezetimibe | Bile acid sequestrants (resins)<br>Cholestyramine, Colesevelam and Colestipol |
| Mechanism | Selectively inhibits absorption of dietary and biliary cholesterol in the small intestine → ↓ pool of cholesterol available to the liver upregulate LDL receptor. | (Bind bile acids [BA] → preventing their enterohepatic recycling & ↑ fecal excretion (10 folds). that will ↑ hepatic C uptake & ↓ plasma & tissue C . |
| Pharmaco-logical action | ↓ LDL 20%<br>↓ TG 8%<br>↑ HDL 1-4% | ↓ LDL 15-30%<br>↑ HDL 3-5%<br>↑ TG & VLDL |
| Indications | As Monotherapy, Primary prevention of low risk of CHD ,<br>As Combination Therapy; is safe (With statinsOr With other lipid lowering drugs As fibrates ). | As Monotherapy: rarely, if statin is contraindicated<br>As combination with statins in type IIa Hyperlipoproteinemia |
| ADRs & Interaction | • GIT disturbance, headache, fatigue,<br>• artheralgia and myalgia. | • clinically safe as they are not systemically absorbed, but May ↓ absorption of fat soluble vitamins ( A, D, E, K)<br>• They also ↓ absorption of some drugs, except for Colesevelam |
| Contra-indications | | • Biliary obstruction<br>• Chronic constipation<br>• Severe hypertriglyceridemia |

## Adjuvants in Hyperlipidemia

| The adjuvant | **Omega -3-FA** (found in fish oils containing highly unsaturated FA) | **β---Sitosterol** (found in plants with structure similar to cholesterol) |
|---|---|---|
| **Mechanism & Effect** | decreases TG & gives Some vascular protection | Compete with dietary & biliary cholesterol Absorption.<br>decrease LDL levels +10% |
| **Indication** | **treatment of very high TGs** | Given as food supplement before meal in **Hypercholesterolemia** |

## Antihyperlipidemic drugs Combinations

| Synergistic combination | Contraindicated combination | Should be taken with breaks in between. |
|---|---|---|
| Statin & ezetimibe. | Statins & Fibrates, because the incidence of myopathy may increase | Resins: decreases the absorption of statins and ezetimibe. |

# Drugs summary – lectures 9,10: Antihyperlipidemic drugs

| | 2. Drugs targeting endogenous pathways | | |
|---|---|---|---|
| | **Statins** | | **Fibrates** |
| **Drug** | **Simvastatin- Lovastatin Atorvastatin - Pravastatin Rosuvastatin** | **Niacin (Nicotinic Acid)** | **Clofibrate, Fenofibrat, Gemfibrozil** |
| Mechanism | competitive inhibitors of HMG-CoA reductase, which catalyzes a rate-limiting step in de novo hepatic cholesterol synthesis | promotes hepatic apoA-I production and slows hepatic clearance of apoA-I and HDL | They increase gene transcription for lipoprotein lipase (LPL) → ↑catabolism of TG |
| Pharmaco-logical action | ↓LDL 18-55%<br>↑ HDL 5-10%<br>↓ TG & VLDL 10-30% | ↓LDL (15-30),<br>↑ HDL (15-35)<br>↓ Triglyceride (20-50) | ↓LDL (5-20),<br>↑HDL (10-20)<br>↓Triglyceride (20-50) |
| Indications | first-line drugs when LDL-lowering drugs are indicated, as they have additional Pleiotropic effects.<br>❖ Monotherapy :<br>1. Type IIa Hyperlipoprotinemia. If there is no control, combine (sequestrants / ezatimibe, niacine,.. ) to decrease cholesterol .<br>2. In all ischemic insults<br>❖ Combination therapy<br>1. Mixed dyslipidemias<br>2. In diabetics and patients with insulin resistance | • Type IIA hypercholestrolemia – Type IIB hypercholesterolemia & any combined hyperlipidemia<br>• Patient with hypertriglyceridemia & low HDL-C.<br>• Hyperchylomicronemia.<br>• mixed dyslipidemia | 1st-line defense for:<br>• Mixed dyslipidemia (i.e. raised serum TG and C )<br>• Patients with low HDL and high risk of atheromatous disease ( often type 2 diabetic patients )<br>• Patients with severe resistant dyslipidemia ( combination with other lipid lowering drugs ). |
| ADRs | • Hepatotoxicity, raised concentrations of liver enzymes (↑ serum aminotransferases)<br>• Teratogenicity, statins should be avoided during pregnancy<br>• Myalgia & Myopathy (↑ Creatine kinase) | • Sensation of warmth & cutaneous flushing (can be avoided by low dose of Aspirin).<br>• reactivation of peptic ulcer<br>• hepatotoxicity.<br>• Hyperglycemia<br>• ↑ uric acid. | • Myositis: Rhabdomyolysis ➔Acute renal failure, especially in alcholics & patients with renal impairment.<br>• Gallstones, especially Clofibrate |
| Drug interaction | Pravastatin and fluvastatin are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system. | | - increase risk of myopathy when combined with statins<br>- Displace drugs from plasma proteins |

# Drugs summary – lecture 11: Thrombolytic drugs

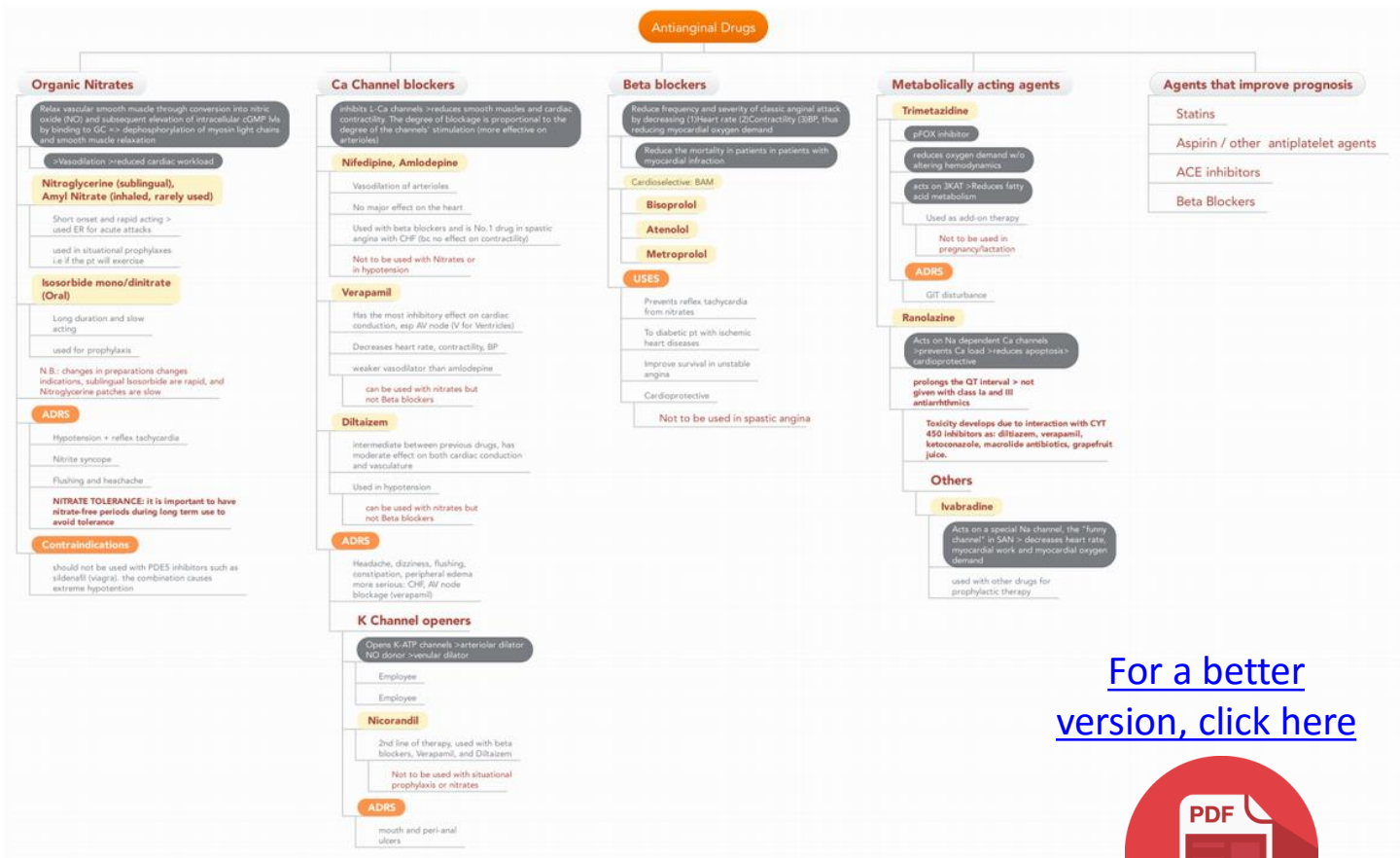
## Thrombolytic drugs (plasminogen activators)

| Types | Fibrin Specific<br>AKA: Tissue plasminogen Activators (t-PA) | | | Non fibrin-specific | | |
|---|---|---|---|---|---|---|
| Action | They activate mainly plasminogen bound to clot surface (**non-circulating plasminogen in tissue**). | | | Activate **both** plasminogen bound to clot surface and circulating plasminogen in blood. | | |
| Examples | **A**lteplase | **R**eteplase | **T**enectepla se | **S**treptokinas **e (SK)** | **A**nistrepla **se** | **U**rokinase |
| Origin | A Recombinant Form Of Human tPA. | Prepared By Recombinant Technology | | Streptokinase is a Bacterial protein. | acylated plasminogen combined with SK | Human enzyme obtained from **urine** or **kidney** |
| $T_{1/2}$ | 5 Min | 15 Min. | 30 Min | >20 minutes | **70-120 min** | IV infusion. |
| administration | IV Bolus Followed By An Infusion. | Two I.V. Bolus Injections | Single IV Bolus. | I.V infusion | bolus I.V. injection | **12-20 min** |
| Price | - | | | **the cheapest** | more **expensive** | Very Expensive |
| ADRs | • **Less risk of bleeding than Non fibrin-specific thrombolytics , because of selectivity to fibrin (no** systemic plasminogen activation**)**<br>• **Not antigenic:** Can be used in patients with antistreptococcal antibodies (due to either recent infection or use of SK). | | | **Antigenicity Allergy Bleeding**. | **More effective and has less ADRs than SK** | No anaphylaxis (not antigenic) |
| Uses | • ST-elevation Myocardial Infarction **(STEMI)**<br>• Pulmonary Embolism | | approved for Acute Myocardial Infarction (**AMI**) | Venous or arterial thrombosis | | lyses of acute massive **pulmonary emboli** |
| Contraindications | **Absolute contraindications include:**<br>➢ Active internal bleeding<br>➢ Cerebral hemorrhagic stroke<br>➢ Recent intracranial trauma or neoplasm<br>➢ Major surgery within two weeks | | | **Relative contraindications include:**<br>➢Active peptic ulcer<br>➢Severe uncontrolled hypertension. | | |
| Antidote | **Fibrinolytic Inhibitors (Antiplasmins)** inhibit plasminogen activation and **promote clot stabilization. E.g.** Aminocaproic Acid & tranexamic acid **&** Aprotinin | | | | | |

# Drugs summary – lectures 12,13: Antianginal drugs:

## Antianginal drugs

| Agents that improve symptoms and ischemia | Agents that improve prognosis |
|---|---|
| 1. Organic nitrates<br>• Short acting nitrates<br>• Long - acting nitrates.<br>2. Calcium channel blockers<br>3. Potassium channel openers<br>4. β-adrenoceptor blockers<br>5. Metabolically acting agents<br>6. Others (Ivabradine)<br>* All used for Prophylactic therapy to Halt progression, Prevent acute insults (ACSs), Improve survival. except for Short acting nitrates which are indicated for attacks & situational prophylaxis | 1. Aspirin / Other antiplatelets<br>2. Statins<br>3. ACE Inhibitors<br>4. β-AD blockers<br><br>*They help in<br>1.Halt progression<br>2.Prevent acute insult<br>3.Improve survival |

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# lectures 12,13: Antianginal drugs:

## 1. Organic nitrates

| Types | Short acting | Long acting |
|---|---|---|
| Drugs | Nitroglycerine [GTN] | Isosorbide mono & dinitrate |
| Indications | • Sublingual tablets or spray for variant angina - Acute symptom relief of stable angina - Situational prophylaxis "as before exercise"<br>• I.V. Preparations: in unstable angina, refractory AHF, AMI | • For long-term Persistent prophylaxis of stable angina.<br>• CHF ➔ Isosorbide mononitrate + hydralazine [if contraindication to ACEIs] |
| Mechanism | 1. Nitric oxide binds to guanylate cyclase in vascular smooth muscle cell to form cGMP.<br>2. cGMP activates PKG to produce relaxation | |
| Hemodynamic effect | 1. Venous vasodilation → ↓preload<br>2. Coronary vasodilation → ↑myocardial perfusion<br>3. Arteria vasodilatation → ↓afterload<br>4. Shunting of flow from normal area to ischemic area by dilating collateral vessel | |
| NIRATE TOLERANCE | Loss of vasodilator response of nitrates on use of long-acting preparations (oral, transdermal) or continuous intravenous infusions, for more than a few hours without interruption.<br>Mechanism:<br>1-Compensatory neurohormonal counter-regulation<br>2-Depletion of free-SH groups<br>Nitrate tolerance can be overcome by:<br>1.Smaller doses at increasing intervals (Nitrate free periods twice a day).<br>2.Giving drugs that maintain tissue SH group like Captopril. | |
| ADRs | • Throbbing headache<br>• Flushing in blush area<br>• Tachycardia & palpitation<br>• Postural hypotension, dizziness & syncope<br>• Rarely methemoglobinema | |
| Contra-indications | • Known **sensitivity** to organic nitrates, Uncorrected hypovolemia<br>• Glaucoma: nitrates➔ ↑ aqueous humour formation<br>• **Head trauma or cerebral haemorrhage** Increase ➔intracranial pressure<br>• Concomitant administration of PDE5 Inhibitors | |

# lectures 12,13: Antianginal drugs:

## 2. Calcium channel blockers (CCBs)

| | | |
|---|---|---|
| Classification (Heterogeneous) | Dihydropyridines: Nifedipine , Nicardipine & Amlodepine | More Selective to VSMCs |
| | Phenylalkylamines :Verapamil | More selective to cardiomyocyte |
| | Benzthiazepines :Diltiazem | Intermediate in action |
| Mechanism | Calcium channel blockers → Bind to L Type Ca channels → decrease their frequency of opening in response to depolarization → ↓entry of Ca → ↓ Ca from internal stores → No Stimulus-Contraction Coupling → **RELAXATION** | |
| Antianginal actions | **↓ Cardiomyocyte Contraction** | **↓VSMC Contraction** / Coronary dilatation |
| | ↓cardiac work through their –ve inotropic & chronotropic action (verapamil & diltiazem) → **↓myocardial oxygen demand** | 1-↓ After load → ↓cardiac work → **↓myocardial oxygen demand** / **↑myocardial $O_2$ supply** |
| Indications | ➢ IN STABLE ANGINA; Regular prophylaxis<br>➢ IN VARIANT ANGINA→ Attacks prevented<br>➢ IN UNSTABLE ANGINA→ Seldom added in refractory cases<br>➢ Long acting Dihydropyridene (Amlodepine) is a useful antianginal if with CHF, because the don't decrease cardiac contractility. | |
| Precaution | • Short acting dihydropyridine (Nifedipine , Nicardipine) should be AVOIDED → ↓ BP → ↑symathetic activation →reflex tachycardia + syncope →impair coronary filling→ ischemia ….. | |
| Combinations | • nitrates + Verapamil & diltiazem<br>• beta-adrenoceptor blockers + Long acting dihydropyrdine (amlodepine) | |

## 3. $K^+$ CHANNEL OPENERS

| | | |
|---|---|---|
| Drugs | Nicorandil | |
| Mechanism (dual) | **1.Opening of $K_{ATP}$ channels (more arteriolar dilator)** | **2. Acting as NO donner; as it has a nitrate moiety (more venular dilator)** |
| | On VSMCs :$K^+$ channel opening → Hyperpolarization→ VASODILATATION | On VSMCs : NO donner→ ↑ cGMP/ PKG → **VASODILATATION** |
| | On Cardiomyocyte : K channel opening→ Repolarization → **↓Cardiac work** | |
| Indications | 1. Prophylactic 2nd line therapy in stable angina<br>2. refractory variant angina | |
| ADRs | • Flushing, headache,<br>• Hypotension, palpitation, weakness<br>• Mouth & peri-anal ulcers, nausea and vomiting | |

# lectures 12,13: Antianginal drugs:

## 4. β1 Adrenergic Blockers

| | | |
|---|---|---|
| β1 Blockers | Atenolol, Bisoprolol, Metoprolol | |
| Antianginal mechanism | ↓ Heart rate by<br>1-↑ Duration of diastole<br>2-↑ Coronary blood flow<br>3-↑oxygen supply | ↓Heart contractility by<br>1.↓Workload<br>2.↓$O_2$ consumption |
| 1-Indication | Stable | 1-Regular prophylaxis → Cardio-selective are better to spare $b_2$-AR<br>2-They are 1st choice on prolonged use → ↓ incidence of sudden death specially due to ventricular tachycardia → by their antiarrhythmic action. |
| | Variant | **contraindicated → as it has no vasodilator action. They may** worsen symptoms and aggravate condition. |
| | Unstable | **halts progression to AMI → improve survival** |
| | AMI | **Reduce infarct size, reduce morbidity & mortality** |
| Precautions | **β- blockers should be withdrawn gradually. sudden stoppage** → give rise to withdrawal manifestations: Rebound angina, arrhythmia, myocardial infarction & hypertension Due → Up-regulation of β-receptors. | |
| | **Given to diabetics with ischemic heart disease** if Benefits are more than hazards | |

## 5. Metabolically Acting Agents

| | | |
|---|---|---|
| Trimetazidine | Mechanism | 1.$O_2$ requirement of glucose pathway is lower than FFA pathway<br>2.During ischemia, oxidized FFA levels rise, blunting the glucose pathway<br>3.Reduces O2 demand without altering hemodynamics |
| | Indication | Used whenever needed as add-on therapy |
| | ADRs | GIT disturbances |
| | Contraindications | 1-Hypersensitivity reaction<br>2-In pregnancy & lactation |
| Ranolazine | Mechanism | Inhibits the late sodium current which increases during ischemia |
| | Contraindications | 1-It prolongs the QT interval so not given with Class Ia & III antiarrhthmics<br>2-Toxicity develops due to interaction with CYT 450 inhibitors |

## 6. Others (Ivabradine)

| | |
|---|---|
| Ivabradine | Selectively blocks $I_f$ ($I_f$ is an inward Na+/K+ current that activates pacemaker cells of the SA node) |
| | Reduces slope of depolarization, slowing HR, reducing myocardilal work & O2 demand |

# THANK YOU FOR CHECKING OUR WORK

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