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Summary

Hypertension:

1- Mild hypertension:

- Propranolol
- Metaprolol
- Atenolol
- Bisoprolol
- Thiazide diuretics (as initial therapy):
  - Hydrochlorothiazide
  - Chlorothiazide
  - Chlorthalidone

2- Moderate Hypertension:

- Propranolol
- Metaprolol
- Atenolol
- Bisoprolol
- Hydralazine (ADR: lupus erythematous like syndrome)
- Minoxidil (contraindicated in women)

3- Severe hypertension:

- Hydralazine
- Minoxidil

4- Chronic hypertension in diabetics we use:

- Dihydropyridine (Nifedapine, Nicardipine and amlodipine)
- ARBs (Losartan, valsartan, Candesartan and Telmisartan) (first line)
- ACE inhibitors

5- Hypertension with angina:

- Dihydropyridine (Nifedapine, Nicardipine and amlodipine)
- Verapamil
- Diltiazem

6- Pregnancy induced

→ α-methyl dopa (first-line)

- If they told you the patient used a drug which she forgot the name of, and when she stopped it she got hypertension again, what is the drug she previously used?
  Clonidine
- Why did she get hypertension again?
  Because clonidine causes rebound hypertension upon withdrawal.

→ Labetalol

→ Hydralazine

7- **Prevention of a hypertensive crisis prior to removal of Pheochromocytoma (tumor derived from the adrenal medulla + made of catecholamine-secreting cells)**

→ **Phenoxibenzamine or Phentolamine**

- What if the patient had coronary perfusion? We avoid using this drug.
- They both could cause arrhythmia and angina, so if they said the drug used lead to angina, that's your clue it's one of these two.
- **What are these drugs ADR?**
  - Postural hypotension
  - Tachycardia
  - Headache
  - Nasal stuffiness and congestion
  - Vertigo and drowsiness
  - Male sexual dysfunction (inhibits ejaculation)

→ Labetalol.

8- **Hypertensive crisis due to clonidine abrupt withdrawal:**

→ Labetalol.

9- **Hypertension with impaired pulmonary function:**

- Selective beta 1 antagonists (atenolol, bisoprolol, esmolol and metaprolol)

10- **Emergency hypertension:**

- Labetalol: it can rapidly decrease blood pressure.
- **Enalaprilat**
- Diazoxide (contraindicated in diabetics)
- Sodium nitropruside
- Nicardipine

11- **Hypertension with renal disease:**

- Clonidine
- Furosemide (renal impairment)
- ARBs (Losartan, valsartan, Candesartan and Telmisartan) (first line)
- ACE inhibitors

12- **Hypertension with decrease in K, what should we use?**

- Spironolactone
- Amiloride
  - Those two are used in combination with loop diuretics and thiazides to decrease potassium loss induced by them.

13- **Resistant hypertension:**

- Clonidine

Hypoglycemia:

- Diazoxide

Baldness:

- Minoxidil

Raynaud's phenomenon:

- Prazosin
- Doxazosin
- Terazosin
- All have same ADR as drug above ↑.
- Beta 2-blockers decrease blood flow to organs, so they're **contraindicated** in this disease and shouldn't be used. However Beta 1-blockers are good.

Benign prostatic hypertrophy (BPH):

- Tamsulosin.
- Same ADR as drug above.

Erectile dysfunction:

- Yohimbine

Cardiac Arrhythmias:

- **Supraventricular arrhythmias:**
  - **AV nodal reentry:**
    - Metaprolol
    - Verapamil
    - Alternative to them? Digoxin
  - **Acute Supraventricular tachycardia:**
    - Diltiazem
    - Alternative to it? Adenosine
  - Bisopoprolol
  - Carvedilol
  - Flecainide (last resort, if all else fails)
  - If it was paroxysmal what is the drug of choice? **Adenosine**
    - **ADR?**
      - Flushing
      - Bronchospasm, contraindicated in asthma
      - Brief A.V block (thus contraindicated in heart block)

- **Ventricular arrhythmias:**
  - **Acute ventricular tachycardia:**
    - Lidocaine
    - Amiodarone
  - **Ventricular fibrillation:**
    - Amiodarone
    - Epinephrine
    - Alternative to them? Lidocaine
  - **Bisopoprolol**
  - **Carvedilol**
  - **Procainamide (better than quinidine)**
    - **ADR?**
      - Lupus erythematosus-like syndrome (in long term therapy).
      - Hypotension.
      - Torsades de pointes.
      - Hallucination & psychosis.
  - **Emergency → Lidocaine**
    - **ADR?**
      - Hypotension
      - CNS ADR:
        - Parasthesia
        - Tinnitus
        - Dysarthria
        - Tremors
        - Confusion
        - Convulsion
  - Mexiletine (chronic treatment)
    - **ADR?**
      - GIT:
        Nausea, vomiting
      - CNS:
        Tremor, drowsiness, diplopia
      - CVS:
        Arrhythmias & hypotension
  - Flecainide (last resort, if all else fails) why? Might lead to proarrhythemia.
    - **ADR?**
      - Proarrhythmia
      - CNS:
        Dizziness, tremor, blurred vision, abnormal taste sensations (Dysgeusia), paraesthesia
      - Heart failure due to -ve inotropic effect.

- Amiodarone → For seriously resistant ventricular arrhythmia (also as a last resort)
    - **ADR:**
        - Peripheral nephropathy
        - Pulmonary fibrosis (common)
        - Constipation
        - Photodermatitis (avoid the sun)
        - Hyper/hypo thyroidism
        - Hepatocellular necrosis (long use)
        - Bluish discoloration of skin
        - Cardiac bradycardia, heart failure.
        - Corneal micro deposits
        - CNS: Headache, tremor, ataxia, paraesthesia

- **Digitalis-induced** → **Mexiletine**
- **Bradyarrhythmia:**
    - Atropine → Sinus bradycardia after MI.
    - Emergency heart block what do we use? Atropine + Isoprenaline but with caution.
- **Atrial arrhythmias:**
    - **Atrial Fibrillation:**

      Most commonly:
        - Metaprolol
        - Amiodarone
        - Diltiazem
        - Anticoagulant therapy:
            - Alternative to it? Digoxin.
    - **Atrial Flutter:**

      Most commonly:
        - Verapamil.
        - Metaprolol.
        - Alternative to these two? Digoxin.
    - **Atrial flutter and fibrillation:**
        - **Quinidine.**
            - **ADR?**
                - Quinidine syncope due to torsades de pointes
                - Dry mouth.
                - Blurred vision.
                - Urinary retention.
                - Constipation.
                - Hypotension.
        - **Esmolol** → Rapid control
        - **Ibutilide** → Acute conversion of atrial flutter or fibrillation to normal sinus rhythm
            - **ADRs?**
                - Torsades De pointes

- **WPW:**
    - Flecainide.
    - Amiodarone.
    - Verapamil.
    - Diltiazem.

Angina Pectoris:

→ **Beta blockers (decrease frequency of episodes)**

→ **Chronic stable angina:**

- **Propranolol**
- Selective beta 1 antagonists (atenolol, bisoprolol, esmolol and metaprolol) ***First line***

Myocardial infarction:

→ **Beta blockers (decrease frequency of episodes)**

- Have cardio-protective effect
- Decrease infarct size
- Decrease morbidity & mortality
- Decrease myocardial O2 demand.

→ **If the patient already had an MI, what do we give him?**

- Atenolol, propranolol, metaprolol. Why? To reduce incidence of sudden death due to ventricular arrhythmias

→ **Acute MI:**

- Tenecteplase

→ **ST-elevation MI:**

- Alteplase
- Reteplase

→ **Nitroglycerine (IV).**

Note:

- Selective Beta 1 blockers loose their selectivity at high doses and affect beta 2.
- Norepinephrine activates alpha 1 and beta 1.
- Epinephrine activates beta 1 and beta 2.

Stopping beta-blockers abruptly might lead to?

Rebound:

- Angina
- Arrhythmia
- MI
- Hypertension

  Due to up-regulation of beta-receptors.

Maintaining sinus rhythm after DC:

- Quinidine
- Amiodarone

Is the patient asthmatic?

- Don't use Beta-blockers.

Is the patient diabetic (Type 1)?

- Don't use Beta-blockers.

Anxiety:

- **Propranolol**

Migraines:

- **Propranolol** → Prophylaxis, not helpful in acute conditions.

Heart Failure:

1. **Congestive heart failure:**
   - **Carvedilol:**

     Decreases risk of sudden death & myocardial remodeling.
   - **Spironolactone (Improves survival in advanced heart failure) (Potassium sparing)**
   - **Eplerenone**
   - **Digoxin**
2. **Chronic heart failure:**
   - ACE inhibitors (**Captopril, Enalapril, Ramipril**) are first line therapy drugs + diuretics.
     i. When should we avoid ACE inhibitors?

     When patient is pregnant or suffering from renal arterial stenosis.
   - **β-adrenoceptor blockers: (Reduce progression)**
     - Second generation:
     - Cardioselective (β1-receptors) e.g. Bisoprolol, Metaprolol
     - Third generation:

       Have vasodilator actions (α- blocking effect) e.g. Carvedilol, Nebivolol
   - Isosorbide mononitrate & Hydralazine (Second line treatment)

3. **Mild congestive heart failure:**
   - First line: **Chlorothiazide**

     * Used in volume overload (pulmonary and/ or peripheral edema)
4. **Acute Heart failure:**
   - **Furosemide**

     * Used for immediate reduction of pulmonary congestion & severe edema.
   - **Sodium nitroprusside**
   - **Dobutamine**: in cardiogenic shock.
   - **Milrinone.**

If you were told a patient was given a drug that later on caused an extreme fall in platelet count or thrombocytopenia, what is that drug?

- **Amrinone.**
- **Nitroglycerine (IV).**

5. **Moderate chronic failure:**
   - **Furosemide**
6. **Severe chronic failure:**
   - **Furosemide**
   - **Nitroglycerine**
   - **Isosorbide dinitrate**
   - **Sodium nitroprusside**

- Used I.V. for severe heart failure when the main symptom is **dyspnea** due to pulmonary congestion
- Dilate venous blood vessels and reduce preload

- When the main symptom is rapid fatigue due to low cardiac output, which drug do we use?
  - **Hydralazine.** (Reduces vascular peripheral resistance)
- When the patient is African American suffering from advanced heart failure due to left ventricular systolic dysfunction, what should we add to their therapy?
  - Venodilaters:
    - **Nitroglycerine**
    - **Isosorbide dinitrate**
  - Hydralazine.
- When patients are intolerant of an angiotensin converting enzyme inhibitor and an angiotensin II receptor blocker due to renal dysfunction, what drug should we consider?
  - **Hydralazine.**
- Patients with acutely decompensated heart failure who have dyspnea at rest or with minimal activity are indicated for which treatment?
  - **Nesiritide.**

Venous or arterial thrombi:

- **Streptokinase (cheapest one).**
  - **ADR?**
    - Antigenicity.
    - Allergic reaction (causing rashes, fever, hypotension)
    - Bleeding
  - What if the patient had had a recent streptococcal infection OR previous administration of the drug (within 6 months). What should we do?
    We avoid this drug. And use other thrombolytic.

- **Anistreplase:**

  Works like SK but with less severity of ADR.

Pulmonary emboli:

- **Urokinase (acute massive ones).**
- **Alteplase.**
- **Reteplase.**

If a toxic dose of thrombolytics was given and resulted in bleeding, what do we use?

- **Aminocaproic acid**
- **Tranexamic acid**
- **Apotinin**

Those are used for?

- ✓ Adjuvant therapy in hemophilia
- ✓ Fibrinolytic therapy-induced bleeding (antidote).
- ✓ Post-surgical bleeding
- ✓ These drugs work like antidotes for fibrinolytic drugs. Similar to Protamine (Antidote of the anticoagulant, heparin) or Vitamin K (Antidote of the oral anticoagulant warfarin).

Angina:

- **Stable Angina:**
  - Acute attacks:
    - Nitroglycerine.
  - Prophylaxis:
    - Isosorbide mononitrate and dinitrate. (Long term).
    - Nifedapine, Nicardipine (short acting) & Amlodipine (long acting)
    - Verapamil
    - Diltiazem
    - Nicorandil (Second line therapy)
  - Prolonged use of Beta-1 blockers (Atenolol, bisoprolol and metaprolol) reduces incedince of sudden death.
    - **Can we develop tolerance to nitrates?** Yes. **WHEN?**

      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.

- ❖ **How? Mechanism:**
  1. Compensatory neurohormonal counter-regulation and sympathetic activation.
  2. Depletion of free-SH groups.

  Note:

  For the action of Nitrates we need sulfur.
- ❖ **How to overcome tolerance?**

  By: free periods (Smaller doses at increasing intervals) & Giving drugs that maintain tissue SH group e.g. Captopril
- ❖ **Contraindications:**
  - Known sensitivity to organic nitrates
  - Glaucoma.
  - Head trauma or cerebral haemorrhage
  - Uncorrected hypovolemia,
  - Concomitant administration of PDE5 Inhibitors.

- **Variant Angina:**
  - Nitroglycerine.
  - To prevent attacks:
    - Nifedapine, Nicardipine (short acting) & Amlodipine (long acting)
    - Verapamil
    - Diltiazem
  - Refractory?
    - Nicorandil (if it wasn't responding to nitrates and CCB)
  - What do we avoid? B- blockers as they may worsen the symptoms and are ineffective.
- **Unstable Angina:**
  - B1- blockers halt progression AMI (improve survival)
  - IV Nitroglycerine.
  - In refractory cases:
    - Nifedapine, Nicardipine (short acting) & Amlodipine (long acting)
    - Verapamil
    - Diltiazem
- **Trimetazidine:**

  Used whenever needed as add-on therapy to nitrates, CCBs or b-blockers

  Contraindications?
  - Hypersensitivity reaction
  - In pregnancy & lactation, because it is teratogenic.

- **Ranolazine:**

  Usually used in patients who failed other antianginal therapies but can also be used for treating chronic angina (alone or in combination with other drugs).
- **Ivrabradine:**

  Used when patients can't tolerate B-blockers as it has the same effect.

Hyperlipidemia:

- **Patients with hyperlipidemia and at risk for other ischemic insults:**
  - Statins (primary prevention)
- **Type IIa Hyperlipoprotinemia:**
  - Statins (primary prevention)
  - And if there is no control? We combine bile acid sequestrants, Ezetimibe, niacin, etc. to decrease cholesterol
- **Type IIa hypercholesterolemia:**
  - Niacin
- **Type IIb hypercholesterolemia:**
  - Niacin
- **Combined hyperlipidemia:**
  - Niacin
- **Patient with hypertriglyceridemia & low HDL – C:**
  - Niacin
- **Hyperchylomicronemia:**
  - Niacin
  - β- Sitosterol (given as food supplement before meals)

When shouldn't we use niacin?

- Gout

  (Because it increases uric acid production)
- Peptic ulcers

  (Because it causes GIT disturbance)
- Hepatotoxicity

  (Because it causes an increase in liver enzymes)
- Diabetes mellitus

  (Because it causes impairment of glucose tolerance)

- **Ischemic insults:**
  - Statins (secondary prevention) → Stabilizes plaques.

- **Mixed dyslipidemias:**
  - Fibrates (1st line)
  - Statins with fibrates or niacin. (Combination therapy)
  - Niacin

- **Patients with low HDL and high risk of atheromatous disease (usually diabetic type 2 patients) what do we use?**
  - Fibrates (1st line)
    - **What are its ADR?**
      - **Gallstones**
      - **Myositis:**
        - In alcoholics.
        - Combined with statins
        - In impaired renal function
    - **When can't we use it?**
      - Pregnancy.
      - Nursing women
      - Renal impairment
      - Gall-bladder disease
      - Alcoholics
    - **What are its interactions?**
      - Increase risk of myopathy when combined with statins (Give lower doses)
      - Displace drug from plasma proteins. E.g. oral anticoagulants (Warfarin → bleeding tendency → anticoagulant dose must be adjusted) and oral hypoglycemic drugs.

- **In diabetics and patients with insulin resistance (metabolic syndrome) what do we use?**
  - Statins (Combination therapy)
- **If the patient is pregnant?**

  Don't use statins.
- **Most important ADR of statin is?**

  Myopathies. + Fibrates increase the risk of them too!
- **Patients taking drugs metabolized by cytochrome 3A4 system what kind of statins can we use?**
  - Pravastatin.
  - Fluvastatin.

❖ **Severe resistant dyslipidemia:**

- Fibrates combined with other lipid lowering drugs

❖ **High TG:**

- Omega-3-Fa

❖ **LDL Changes:**

- **Very high LDL:**
  - **Statins**
- **Moderately elevated LDL:**
  - **Ezetimibe (As monotherapy it's used for prevention of low risk CHD)**
    - **What can we use it with?**
      - Statins in moderate/severe increase in LDL.
      - Lipid lowering drugs like fibrates.

- **People who can't tolerate any of the drugs, what can we use?**

- **Exchange bile sequestrants (resins)**
  - Cholestyramine.
  - Colesevelam
  - Colestipol
- **Features?**
  - Lower LDL
  - Raise TG (5%)
  - HDL not affected

  They might cause constipation, diarrhea or GIT bloating and discomfort however they're clinically safe.

  - Shouldn't be used when:
    - Biliary obstruction
    - Chronic constipation
    - Severe hypertriglyceridemia (because they raise TG)
  - **They interact with drugs however Colesevelam doesn't, so it's the best choice for patients with multiple drug regimens.**

Antihyperlipedemic combinations:

Indications:

1. Severe hypertriglyceridemia or severe hypercholesterolemia
2. To take lower doses of each drug
3. High LDL or VLDL not normalized with a single drug (failure of monotherapy)

Resins:

Decreases the absorption of statins and ezetimibe, Therefore, these drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after taking resins.

Statins & Fibrates:

- Contraindicated (in full dose) because the incidence of myopathy may increase
- So, use not more than ¼ maximum dose of statin and use pravastatin (Pravastatin and fluvastatin are the statins of choice in patients taking other drugs metabolized by cytochrome 3A4 system)

Statin & ezetimibe (synergistic combination):

Statin blocks synthesis of endogenous cholesterol while ezetimibe blocks exogenous cholesterol.

Lecture Mind Maps:

- Anti-arrhythmic::
  https://drive.google.com/file/d/0B8NyM96qUdjfb1ZuZ1RZSjB5dDg/view
- Heart Failure - Therapeutic uses (5,6):
  https://drive.google.com/file/d/0B8NyM96qUdjfSmc1QkRHMDQ5b1E/view
- Heart Failure (5,6):
  https://drive.google.com/file/d/0B8NyM96qUdjfcERudGx2bThiTzQ/view
- Anti-anginal (12,13):
  https://drive.google.com/file/d/0B8NyM96qUdjfRzRoeUI3bER3SzA/view

Summary Schedules

Pharmacokinetics	• **Most of them are lipid soluble (Metaprolol, propranolol, timolol, labetalol, carvedilol), these are well absorbed orally, rapidly distributed, cross readily BBB & Have CNS depressant actions** • **Most of them have a half-life from 3-10 hrs. except Esmolol (10 min. given by I.V.).** • **Most of them metabolized in liver & excreted in urine.**
Adverse effects	**Selective β2-blockers (Due to blockade of β1- receptor):** Bradycardia, hypotension, heart failure Since there is NO change in lipid or glucose & NO bronchoconstriction, they're SAFE FOR: • Asthma & COPD • Raynaud's phenomenon and PVD • Diabetics/ Dyslipidemias • Variant Angina Note: Selectively present in low doses, Lost in high doses **Non selective β-blockers (Due to blockade of β2- receptor):** • Depression + Hallucinations • GI disturbances (↑ Intestinal motility) • Bronchoconstriction, specially in susceptible patients • Sodium retention 2ndry to ↓BP → ↓renal perfusion • hypoglycemia, ↓ Lipolysis , ↑TG (hyperglyceridemia) • ↑ peripheral resistance (PR) by blocking vasodilatory effect → Vasoconstriction → ↓blood flow to organs except brain → cold extremities & intermittent claudication (b2) • Erectile dysfunction & impotence • Coronary spasm (in variant angina patients) **Mixed alpha & beta receptor blockers:** Carvedilol: Edema Labetalol (membrane stabilizing effect with ISA): Orthostatic hypotension, Sedation and dizziness **All β-blockers:** Masked hypoglycemic manifestations i.e. tachycardia, sweating →Coma
Contraindications	• Heart Block (because beta blockers can precipitate heart block). • Bronchial Asthma, emphysyma & Peripheral vascular disease (safer with cardio-selective β1 blockers). • Diabetic patients → Masking of hypoglycaemia / must be GIVEN CAUSIOUSLY • Hypotension • Alone in pheochromocytoma (must be given with α-blockers). • peripheral diseases like Reynaud's disease
Precaution	Sudden stoppage will give rise to a withdrawal syndrome: Rebound angina, arrhythmia, myocardial infarction & Hypertension WHY ? Due to Up-regulation of β-receptors (increase number of β-receptors) To prevent withdrawal manifestations → drug withdrawn gradually.

Drug	Therapeutic use
Phenoxybenzamine (Irreversible-long acting 24h)	**Used Before surgical removal of Pheochromocytoma to protect against hypertensive crisis.** **Contraindicated in:** **Patient with decreased coronary perfusion**
Phentolamine (Reversible-short acting 4h)	
Prazosin (short half-life)	**1-Benign prostatic hyperplasia** **2-Hypertension with prostate enlargement** **3-Reynaud's disease**
Doxazosin (long half-life)	
Terazosin (long half-life)	
Tamsulosin	**Benign prostatic hypertrophy (BPH)**
Yohimbine	**Aphrodisiac in erectile dysfunction**

DISEASE	DRUG (s)	Mechanism of action
Hypertension	Labetalol (by injection) Atenolol, Bisoprolol > Metoprolol, Propranolol	• ↓ cardiac output • ↓ renin and RASS system • Inhibition of presynaptic NE release • Inhibition of sympathetic outflow in CNS • Treatment of hypertensive pregnant & hypertensive crisis
Cardiac Arrhythmias	Esmolol (ultra-short acting, T1/2=10 min), Atenolol, Propranolol (Bisoprolol and carvedilol are preferred)	• Propranolol: Membrane stabilization (block Na channel →local anesthetic effect/ antiarrhythmic effect: ↓ excitability, ↓automaticity, ↓ conductivity) • Treatment of supraventricular & ventricular arrhythmias
Angina pectoris	Beta blockers e.g. propranolol	Anti -ischemic action: ↓heart rate, ↓ cardiac work & oxygen demand, ↓the frequency of angina episodes.
Congestive Heart Failure	Carvedilol (antioxidant action) Bisoprolol, Metoprolol	• Decrease myocardial remodeling • Decrease risk of sudden death.
Myocardial Infarction	Atenolol, Metoprolol, Propranolol	• Have cardio-protective effect: ↓ infarct size, ↓ morbidity & mortality, ↓ myocardial O2 demand. • Anti-arrhythmic action (Quinidine-like action) • Decrease the incidence of sudden death.
Chronic Glaucoma	Timolol (eye drop) , propranolol	• ↓aqueous humor production from ciliary body • ↓intraocular pressure (IOP)
Hyperthyroidism(thyrotoxicosis)	Beta blockers (e.g. Propranolol)	• Protect the heart against sympathetic overstimulation • 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 ↓ Catecholamine-induced vasodilatation in the brain vasculature (antagonize the sympathetic effect)
Hypertensive crisis (Pheochromocytoma)	Labetalol (has to be combined with α blockers)	α-Blockers lower the elevated blood pressure. β-Blockers protect the heart from NE.

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: - Paraesthesia. - 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.

<table>
<tr><td rowspan="2">CLASS II
(β-ADRENOCEPTOR BLOCKERS)</td><td rowspan="2">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.</td><td>Esmolol</td><td>Very short acting (half-life= 9min.)
Given IV fro rapid control of ventricular rate (atrial flutter or fibrillation).</td><td rowspan="2">Uses:
- Atrial arrhythmia associated with emotion.
- WBW.
- Digitalis-induced arrhythmia.</td></tr>
<tr><td>Propranolol
Atenolol
Metaprolol</td><td>used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias.</td></tr>
<tr><td rowspan="3">CLASS III</td><td rowspan="3">Action:
Prolong the action potential duration by prolong phase 3.</td><td rowspan="2">Amiodarone</td><td>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)</td><td colspan="2">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, paraesthesia
- Constipation
- Corneal micro deposits
- Hepatocellular necrosis
- Peripheral neuropathy</td></tr>
<tr><td>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).</td><td>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</td><td>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</td></tr>
<tr><td>Ibutilide</td><td colspan="3">•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.</td></tr>
</table>

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)

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

<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 hypotension & chronic heart failure therapy along with diuretics.
inhibit ACE → reduce synthesis of AgII → activation of Bradykinin system which is a potent vasodilator.
↓ preload and afterload</td><td>Blocks AT1 receptors decrease the action of AgII (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)
2-Decrease Venous return (Preload)
3- Decrease sympathetic activity
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 rowspan="4">Drugs</td><td>Captopril</td><td>Enalapril</td><td>Rampril</td><td>Losartan, Valsartan, Irbesartan</td><td>Prazosin</td><td>Sodium nitroprussi de</td></tr>
<tr><td colspan="3">Rapidly absorbed from GIT after oral administration
Food reduce their bioavailability</td><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3">- I.V acute or severe refractory HF
-Acts immediatel y
- Effect lasts 1 – 5 min</td></tr>
<tr><td>Short duration of action
Not a prodrug</td><td colspan="2">Prodrugs converted to their active metabolites in the liver
Long T1/2
(given once daily)</td></tr>
<tr><td colspan="3">Enalaprilat
(active metabolite of Enalapril)
Used I.V in hypertensive emergency</td></tr>
<tr><td>Adverse effect</td><td colspan="3">1- acute renal failure
2- hyperkalemia
3-hypotension in hypovolemic patients
4- Dry cough
5- angioneurotic edema
6-Dysgeusia</td><td></td><td></td><td></td></tr>
<tr><td>Contra-indications</td><td colspan="3">• during the second and third trimesters of pregnancy
• renal artery stenosis</td><td></td><td></td><td></td></tr>
</table>

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

Group	β-adrenoceptor blockers	Natriuretic Peptides
Drugs	**Second generation: Bisoprolol, Metoprolol** **β1 receptors blockers (cardio selective)** **Third generation: Carvedilol , Nebivolol** **have vasodilator actions (α-blocking)**	**Nesiritide**
Mechanism of action	**β-blockers:** **1- attenuate cardiac remodeling (cardiac dilatation & hypertrophy)** **2- slow heart rate, which allows the left ventricle to fill more completely** **3- decrease renin release** **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.** **It increases cyclic-GMP in vascular smooth muscle, leading to smooth muscle relaxation and <u>reduction of preload and afterload</u>**
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**

Classification	Examples	Important notes
Diuretics	Hydrochlorothiazide, Furosemide, potassium sparing diuretics (Amiloride, & spironolactone)	• K-sparing diuretics reduce K loss in the urine • **Hydrochlorothiazide & Furosemide** decrease the B.P by decreasing volume of blood & cardiac output • 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** • Nicardipine is used in hypertensive emergency • side effects : Verapamil → Constipation Nifedipine → reflex tachycardia.
Vasodilators	Hydralazine, Minoxidil, Diazoxide, & Na nitropruside	• **Hydralazine** used in Hypertensive pregnant woman. ADRs: lupus erythematous like syndrome. • **Minoxidil** Cause: (Hypertrichosisis) increase hair growth, That's why it is contradicted in female. • **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. • They decrease cardiac output & renin release • Mask the symptoms of Hypoglycemia in diabetic patients.
α- Adrenoceptor Blockers	Prazosin, Doxazosin & Terazosin	• Prazosin is short-acting, causes first dose hypotension & postural hypotension • Doxazosin is **Preferred, because of its long half- life**
Centrally acting sympatholytic	Clonidine & α methyl dopa	**clonidine** can lead to rebound hypertension **α methyl dopa** : Safe in Pregnant woman

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

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

Drug Class	Agents	Effects (% change)	Side Effects
HMG CoA reductase inhibitors	Lovastatin Pravastatin	**↓LDL (18-55),** ↑ HDL (5-15) ↓ Triglycerides (7-30)	Myopathy, increased liver enzymes
Cholesterol absorption inhibitor	Ezetimibe	↓ LDL(14-18), ↓ ↑ HDL (1-3) ↓Triglyceride (2)	Headache, GI distress
Nicotinic Acid (Niacin)		↓LDL (15-30), **↑ HDL (15-35)** **↓ Triglyceride (20-50)**	Flushing (+aspirin) Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity
Fibric Acids	Gemfibrozil Fenofibrate	↓LDL (5-20), ↑HDL (10-20) **↓Triglyceride (20-50)**	Dyspepsia, gallstones, myopathy
Bile Acid sequestrants	Cholestyramine	↓ LDL ↑ HDL No change in triglycerides	GI distress, constipation, decreased absorption of other drugs

Thrombolytic drugs (plasminogen activators)						
Types	**Fibrin Specific** 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**enecteplase	**S**treptokin**ase (SK)**	**A**nistre**plase**	**U**rokin**ase**
Origin	A Recombinant Form Of Human tPA.	Modified recombinant human t-PA 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**)** • **Not antigenic:** Can be used in patients with antistreptococcal antibodies (due to either recent infection or use of SK).			**Antigenicity Allergy Bleeding**.	**<u>More effective and has less ADRs than SK</u>**	No anaphylaxis (not antigenic)
Uses	• ST-elevation Myocardial Infarction **(STEMI)** • Pulmonary Embolism		approved for Acute Myocardial Infarction (**AMI**)	<u>Venous or arterial thrombosis</u>		lyses of acute massive **pulmonary emboli**
Contraindications	**Absolute contraindications include:** ➢ Active internal bleeding ➢ Cerebral hemorrhagic stroke ➢ Recent intracranial trauma or neoplasm ➢ Major surgery within two weeks			**Relative contraindications include:** ➢ Active peptic ulcer ➢ Severe uncontrolled hypertension.		
Antidote	**Fibrinolytic Inhibitors (Antiplasmins)** inhibit plasminogen activation and **promote clot stabilization. E.g.** Aminocaproic Acid & tranexamic acid **&** Aprotinin					

Antianginal drugs	
Agents that improve symptoms and ischemia	**Agents that improve prognosis**
1. Organic nitrates • Short acting nitrates • Long - acting nitrates. 2. Calcium channel blockers 3. Potassium channel openers 4. β-adrenoceptor blockers 5. Metabolically acting agents 6. Others (Ivabradine) * 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 2. Statins 3. ACE Inhibitors 4. β-AD blockers *They help in 1.Halt progression 2.Prevent acute insult 3.Improve survival

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" • I.V. Preparations: in unstable angina, refractory AHF, AMI	• For long-term Persistent prophylaxis of stable angina. • CHF ➔ Isosorbide mononitrate + hydralazine [if contraindication to ACEIs]
Mechanism	1. Nitric oxide binds to guanylate cyclase in vascular smooth muscle cell to form cGMP. 2. cGMP activates PKG to produce relaxation	
Hemodynamic effect	1. Venous vasodilation → ↓preload 2. Coronary vasodilation → ↑myocardial perfusion 3. Arteria vasodilatation → ↓afterload 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. Mechanism: 1-Compensatory neurohormonal counter-regulation 2-Depletion of free-SH groups Nitrate tolerance can be overcome by: 1.Smaller doses at increasing intervals (Nitrate free periods twice a day). 2.Giving drugs that maintain tissue SH group like Captopril.	
ADRs	• Throbbing headache • Flushing in blush area • Tachycardia & palpitation • Postural hypotension, dizziness & syncope • Rarely methemoglobinema	
Contra-indications	• Known **sensitivity** to organic nitrates, Uncorrected hypovolemia • Glaucoma: nitrates➔ ↑ aqueous humour formation • **Head trauma or cerebral haemorrhage** Increase ➔intracranial pressure • Concomitant administration of PDE5 Inhibitors	

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 ➢ IN VARIANT ANGINA→ Attacks prevented ➢ IN UNSTABLE ANGINA→ Seldom added in refractory cases ➢ 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 • 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 2. refractory variant angina	
ADRs	• Flushing, headache, • Hypotension, palpitation, weakness • Mouth & peri-anal ulcers, nausea and vomiting	

4. β1 Adrenergic Blockers			
β1 Blockers	Atenolol, Bisoprolol, Metoprolol		
Antianginal mechanism	↓ Heart rate by 1-↑ Duration of diastole 2-↑ Coronary blood flow 3-↑oxygen supply		↓Heart contractility by 1.↓Workload 2.↓O_2 consumption
1- Indication	Stable	1-Regular prophylaxis → Cardio-selective are better to spare b_2-AR 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 2.During ischemia, oxidized FFA levels rise, blunting the glucose pathway 3.Reduces O2 demand without altering hemodynamics
	Indication	Used whenever needed as add-on therapy
	ADRs	GIT disturbances
	Contraindications	1-Hypersensitivity reaction 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 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

A huge thanks to our Pharmacology team!
Done by: Nouf Altwaijri
Good Luck.