Refer to the slides from 1-16

Congenital Arrythmias		
Arrythmia	**Mutations**	**Notes**
Polymorphic Ventricular Tachycardia (Torsade de Pointes)	- 300 different mutations in at least 8 ion channel genes.	- Long QT interval. - It can be secondary due to **familial LQT** or **drug-induced** (drugs that prolong APD / QT). - Causes syncope, dizziness, and sudden death. - **Mechanism:** **a-** GF: Increased inward current. **b-** LF: Decreased outward current during the plateau. - **Risk factors:** **a-** Bradycardia **b-** Hypokalemia *(Tx: giving K^+ but not with renal failure)* **c-** Triggered upstroke *(Tx: β-blockers or Mg^{+2})* **d-** Drugs which prolong ADP *(Tx: pacemakers or isoproterenol)*
Short QT Syndrome	- GF in **K^+** channels genes: KCNH2, KCNQ1, and KCNJ2.	-
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)	- LF/GF in sarcoplasmic proteins that control **calcium**.	- Causes syncope (fainting) induced by stress, physical activity, or emotion.
Sick Sinus Syndrome	- LF in HCN4 and SCN5A.	- Problems in the SA node.
Brugada Syndrome	- LF in SCN5A.	- Ventricular fibrillation, persistent ST elevation, and incomplete right bundle branch block (5 in 10,000).
Familial Atrial Fibrillation	- GF in KCNQ1.	-

Antiarrhythmic drugs were classified into classes (Vaughan Williams classification):

Class I A

- **Na^+- channel** blockers with **intermediate** dissociation and strength.
- They increase **QRS** and **QT** interval.

Drug	Notes	Side effects
Quinidine	- Old prototype, related to Quinine *(an antimalarial drug).* - Extracted from Cinchona tree. - Antipyretic drug *(reduces fever).* - **Inhibits** alpha and muscarinic receptors. - **Slows** upstroke and conduction. - **Prolongs** APD and QRS duration. - **Uses:** Restricted to patients with have **atrial or ventricular arrhythmias.** But **not** for patients with heart failure or ischemia.	- Nausea (18%), Diarrhea (33%). - **Cinchonism**: Headache, Dizziness, and tinnitus. - **TdP** due to prolongation of QT interval and slowed conduction. - **Sudden death** *(common in all antiarrhythmic drugs but mostly from quinidine).* - Hypotension. - ↑ Serum Digoxin levels. - ↑ Warfarin effects. - Hypersensitivity, fever, rash, angioedema. - Thrombocytopenia.
Procainamide	- Oral, with short t½. - When acetylated → NAPA, with Class III actions.	- **Lupus Erythematous** in 30% of patients with Tx over 6 months.
Disopyramide	- More anticholinergic effects.	- Less diarrhea than quinidine.

Class I B

- Na^+- channels blocker with **fast** dissociation action and weak strength.
- They **decrease** QT interval.

Drug	Notes	Side effects
Lidocaine (Xylocaine)	- High affinity to bind with activated and inactivated Na^+ channels with rapid kinetics. - More effective with hyperkalemia. - Not effective in atrial arrhythmias. - Well absorbed, but ineffective orally, due to first pass effect, so **given IV**. - Well distributed, including the brain - **Uses:** **a-** Was routinely given to all **MI** patients to prevent **ventricular arrhythmias**. **b-** Acts selectively in ischemic tissue to promote conduction & **block reentry**.	- **Least cardiotoxic** of the class. However, it causes h**ypotension** with **high** doses due to depression of the myocardium. - **CNS** *(main side effects in high doses):* paresthesia, tremor, nausea *(reduced by sedatives),* slurred speech, and convulsions.
Tocainide	- Oral analog of lidocaine	- CNS, GI and blood dyscrasia.
Mexiletine	- Oral analog of lidocaine	- Neurologic side effects.
Phenytoin	- Antiepileptic drug. - **Uses:** **a-** Digitalis-induced arrhythmias. **b-** Arrhythmias after congenital heart surgery. **c-** Congenital LQT.	-

Class I C

- Na^{+}- channels blocker with **slow** dissociation action and high strength.
- They highly **increase** QRS.
- Can be **proarrhythmic**. Used mainly for **supraventricular arrhythmias**.

Drug	Notes	Side effects
Flecainide	- Potent blocker of Na^{+} and K^{+} channels. - **Negative** inotropic effect. - Effective in **supraventricular tachycardia** with normal hearts.	- Ventricular arrhythmias (**proarrhythmic**). - CNS, and sudden death.
Propafenone	- Blocks Na^{+} channels but also has β-blocking and Ca^{+2} blocking activity. - **No effect** on QT interval. - Used for **supraventricular arrhythmias.**	- Metallic taste, constipation, and arrhythmias.

Class II (β-adrenoceptor antagonism drugs)

Drug	Notes	
Propranolol	- **Membrane stabilization**, intrinsic sympathomimetic activities, and effective anti-arrhythmic activity. - Very effective, well tolerated, and documented to **reduce mortality** after acute MI by **reducing myocardial O_2 demand** and arrhythmias. - It has **CNS** manifestations as it can cross the BBB.	
Esmolol	- **No** membrane stabilization effect. - Given 2-3 times daily.	- β1 **selective**. - Short acting, used in **intraoperative** and **acute arrhythmias.**
Acebutolol	- Has **direct** membrane stabilizing effects.	

Class III (K^+ channels blockers)

Drug	Uses	Side effects
Amiodarone	- Has Class I, II, III, and IV actions: Blocks K^+ channels and markedly **prolongs** APD. Ca^{+2} blocking actions. Blocks α and β Receptors. - **Effect is due to alteration of lipid membrane.** - Given **IV** *(loading dose 10gm)* and **orally**. - **Slow** kinetics *(t½ is long 25-110 days)*, metabolized by CYP3A4 enzymes. - **Uses:** **a-** Reserved for life-threatening **atrial and ventricular arrhythmias.** **b-** Prevents conversion of ventricular arrhythmia into fibrillation.	- **Low incidence of TdP** despite significant QT prolongation. - **Peripheral vasodilator** *(only with IV)*. - Slows heart rate and AV conduction. - **Toxicity**: mainly extracardiac and dose related. **a-** Lung fibrosis (1%), this may affect the heart. **b-** CNS. **c-** Thyroid (hypo and hyper). **d-** GI and liver. **e-** Corneal deposits. **f-** Photodermatitis and discoloration of the skin which is treated by decreasing the dose. → **Blue-man syndrome** **g-** Interactions: affected by CYP3A4 activity: ↑ Digoxin and anticoagulants levels.
Bretylium Tosylate	- Originally an antihypertensive, but tolerance develops. - Releases NE, then ↓ Release / Reuptake. - Rarely used, except for **prevention of ventricular fibrillation** after failure of cardioversion and lidocaine.	- Hypotension. - Parotid swelling.
Sotalol	- β-blocker but has Class III actions. - **Uses:** Atrial and ventricular arrhythmias.	- Causes **bradycardia** and heart failure. - Prolongation of QT, thus **inducing TdP**.
Ibutilide	-	
Dofetilide	-	

Class IV (Ca^{+2} channels blockers)		
Drug	**Uses**	**Side effects**
Verapamil	- Block activated and inactivated **L-type Ca^{+2} channels.** - Effects more marked in tissues that fire frequently, less completely polarized at rest, and those dependent on Ca^{+2} (**SA node and AV node**). - **<u>Uses:</u>** **a- Paroxysmal Supraventricular Tachycardia.** **b-** Vasodilators and have **negative** inotropic effects.	- Can cause **severe AV block** in diseased hearts. - Relatively safe: Constipation, gastric discomfort, vertigo, headache, nervousness, pruritis. - ↑ Digoxin levels.
Diltiazem		

Refer to the slides from 23-32

Unclassified Anti-arrhythmic Drugs	
Drug	**Notes**
Digoxin	- Old fashioned agent for **heart failure and atrial arrhythmias**. - Direct negative chronotropic actions on SA node. - Vagotonic Effects (directly stimulates vagus nerve). - ↑ AV refractoriness.
Magnesium	- Used for **ventricular fibrillation, digoxin toxicity.** - Works on Na^+/K^+ ATPase, Na^+ channels, certain K^+ channels, and Ca^{+2} channels. - **Uses:** **a-** Effective **IV** in refractory **digitalis- induced ventricular arrhythmias only in hypomagnesemia patients.** **b-** In **TdP patients** even if serum Mg^{+2} is normal.
Potassium salts	- Used for **digitalis-induced arrhythmias with hypokalemia.** - It depresses ectopic pacemakers and slows conduction.
Adenosine	- Naturally occurring nucleoside. - Stimulates purinergic (P1) receptors. - Activates inward rectifier K^+ current and inhibits Ca^{+2} current. - Very short acting (t½ = 10s). - ↓ Phase 4 depolarization in SA node. - ↓ AV conduction. - No effect on ventricles. - **Uses**: 90-95% effective in **supraventricular tachycardia**, replaces verapamil. Less effective in the presence of adenosine receptor blockers, e.g. theophylline and caffeine. - **Side effects**: Can cause **transient flushing** (20%), chest tightness, AV block, headache, hypotension, nausea, and paresthesia.
Atropine	- Anticholinergic drug, used for **Sinus bradycardia.**
Adrenaline (EP)	- Used for **Cardiac arrest** via intracardial injection.
Isoprenaline	- β-agonist used for **Heart block**.
Calcium Chloride	- **Ventricular tachycardia** due to hyperkalemia

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