Antiarrhythmic Drugs
Normal conduction pathway:

1. SA node generates action potential and delivers it to the atria and the AV node.
2. The AV node delivers the impulse to Purkinje fibers.
3. Purkinje fibers conduct the impulse to the ventricles.

Other types of conduction that occurs between myocardial cells:
When a cell is depolarized → adjacent cell depolarizes along.
**Action potential phases**

0: Upstroke
1: Early-fast repolarization
2: Plateau
3: Repolarization
4: Diastole
Action potential of the heart:

In the atria, purkinje, and ventricles the AP curve consists of 5 phases.

In the SA node and AV node, AP curve consists of 3 phases.
Non-pacemaker action potential

Phase 0: fast upstroke
Due to Na\(^+\) influx

Phase 1: partial repolarization
Due to rapid efflux of K\(^+\)

Phase 2: plateau
Due to Ca\(^{++}\) influx

Phase 3: repolarization
Due to K\(^+\) efflux

Phase 4: resting membrane potential

N.B. The slope of phase 0 = conduction velocity
Also the peak of phase 0 = \(V_{max}\)
Phase 0: upstroke:
Due to Ca\(^{++}\) influx

Phase 3: repolarization:
Due to K\(^{+}\) efflux

Phase 4: pacemaker potential
Na influx and K efflux and Ca influx until the cell reaches threshold and then turns into phase 0

Pacemaker cells (automatic cells) have unstable membrane potential so they can generate AP spontaneously
Effective refractory period (ERP)

It is also called absolute refractory period (ARP):

- In this period the cell can’t be excited
- Takes place between phase 0 and 3
Arrhythmia /dysrhythmia: abnormality in the site of origin of impulse, rate, or conduction

If the arrhythmia arises from the atria, SA node, or AV node it is called supraventricular arrhythmia.

If the arrhythmia arises from the ventricles it is called ventricular arrhythmia.

Causes of arrhythmia:
- arteriosclerosis
- Coronary artery spasm
- Heart block
- Myocardial ischemia
Action of drugs

In case of abnormal generation:

- Decrease of phase 4 slope (in pacemaker cells)
- Raises the threshold

In case of abnormal conduction:

- ↓conduction velocity (remember phase 0)
- ↑ERP (so the cell won’t be reexcited again)
Pharmacologic Goals

- The ultimate goal of antiarrhythmic drug therapy:
  - Restore normal sinus rhythm and conduction
  - Prevent more serious and possibly lethal arrhythmias from occurring.

- Antiarrhythmic drugs are used to:
  - decrease conduction velocity
  - change the duration of the effective refractory period (ERP)
  - suppress abnormal automaticity
**Antyarrhythmic drugs**

- Most antiarrhythmic drugs are **pro-arrhythmic** (promote arrhythmia).
- They are classified according to **Vaughan William** into four classes according to their effects on the cardiac action potential.

<table>
<thead>
<tr>
<th>class</th>
<th>mechanism</th>
<th>action</th>
<th>notes</th>
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<tbody>
<tr>
<td>I</td>
<td>Na(^+) channel blocker</td>
<td>Change the slope of phase 0</td>
<td>Can abolish tachyarrhythmia caused by reentry circuit</td>
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<tr>
<td>II</td>
<td>(\beta) blocker</td>
<td>↓heart rate and conduction velocity</td>
<td>Can indirectly alter K and Ca conductance</td>
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<tr>
<td>III</td>
<td>K(^+) channel blocker</td>
<td>1. ↑action potential duration (APD) or effective refractory period (ERP). 2. Delay repolarization.</td>
<td>Inhibit reentry tachycardia</td>
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<tr>
<td>IV</td>
<td>Ca(^{++}) channel blocker</td>
<td>Slowing the rate of rise in phase 4 of SA node</td>
<td>↓conduction velocity in SA and AV node</td>
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</table>
Class I drugs

- Have moderate K\(^+\) channel blockade

- They act on open Na\(^+\) channels or inactivated only

- They ↓ conduction velocity in non-nodal tissues (atria, ventricles, and purkinje fibers)

- So they are used when many Na\(^+\) channels are opened or inactivated (in tachycardia only) because in normal rhythm the channels will be at rest state so the drugs won’t work

Class I

IA  IB  IC

So they are used when many Na\(^+\) channels are opened or inactivated (in tachycardia only) because in normal rhythm the channels will be at rest state so the drugs won’t work
Slowing of the rate of rise in phase 0 $\rightarrow$ ↓ conduction velocity

- They prolong muscle action potential & ventricular (ERP)
- They ↓ the slope of Phase 4 spontaneous depolarization (SA node) $\rightarrow$ decrease enhanced normal automaticity

**Mechanism of action**

- **Class IA**
  - Quinidine
  - Procainamide

They make the slope more horizontal
Class IA Drugs

- They possess intermediate rate of association and dissociation (moderate effect) with sodium channels.

**Pharmacokinetics:**

- **procainamide**
  - Good oral bioavailability
  - Used as IV to avoid hypotension

- **quinidine**
  - Good oral bioavailability
  - Metabolized in the liver

Procaainamide metabolized into N-acetylprocainamide (NAPA) (active class III) which is cleared by the kidney (avoid in renal failure)
Class IA Drugs Uses

- Supraventricular and ventricular arrhythmias
- Quinidine is rarely used for supraventricular arrhythmias
- IV procainamide used for hemodynamically stable ventricular tachycardia
Class IA Drugs Toxicity

Quinidine

AV block
- Torsades de pointes arrhythmia because it ↑ ERP (QT interval)
- Shortens A-V nodal refractoriness (↑AV conduction) by antimuscarinic like effect
- ↑ digoxin concentration by:
  1. displace from tissue binding sites
  2. ↓ renal clearance
- Ventricular tachycardia

Procainamide
- Asystole or ventricular arrhythmia
- Hypersensitivity: fever, agranulocytosis
- Systemic lupus erythematosus (SLE)-like symptoms: arthralgia, fever, pleural-pericardial inflammation.
  
  Symptoms are dose and time dependent
  
  Common in patients with slow hepatic acetylation

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Notes:

Torsades de pointes: twisting of the point. Type of tachycardia that gives special characteristics on ECG.

At large doses of quinidine → cinchonism occurs: blurred vision, tinnitus, headache, psychosis and gastrointestinal upset.

Digoxin is administered before quinidine to prevent the conversion of atrial fibrillation or flutter into paradoxical ventricular tachycardia.
Class IB Drugs

- They shorten Phase 3 repolarization
- ↓ the duration of the cardiac action potential
- They suppress arrhythmias caused by abnormal automaticity
- They show *rapid association & dissociation* (weak effect) with Na\(^+\) channels with appreciable degree of use-dependence
- No effect on conduction velocity
Agents of Class IB

**Lidocaine**
- Used IV because of extensive 1st pass metabolism
- Lidocaine is the drug of choice in emergency treatment of ventricular arrhythmias
- Has CNS effects: drowsiness, numbness, convulsion, and nystagmus

**Mexiletine**
- These are the oral analogs of lidocaine
- Mexiletine is used for chronic treatment of ventricular arrhythmias associated with previous myocardial infarction

Adverse effects:
1- neurological effects
2- negative inotropic activity

**Uses**
- They are used in the treatment of ventricular arrhythmias arising during myocardial ischemia or due to digoxin toxicity
- They have little effect on atrial or AV junction arrhythmias (because they don’t act on conduction velocity)
Class IC Drugs

- They *markedly slow Phase 0* fast depolarization.
- They markedly slow conduction in the myocardial tissue.
- They possess *slow rate of association and dissociation (strong effect)* with sodium channels.
- They only have *minor effects on the duration of action potential and refractoriness*.
- They reduce automaticity by increasing the threshold potential rather than decreasing the slope of Phase 4 spontaneous depolarization.
Uses:

- Refractory ventricular arrhythmias.
- Flecainide is a particularly potent suppressant of premature ventricular contractions (beats)

Toxicity and Cautions for Class IC Drugs:

- They are severe proarrhythmogenic drugs causing:
  1. severe worsening of a preexisting arrhythmia
  2. occurrence of life-threatening ventricular tachycardia
- In patients with frequent premature ventricular contraction (PVC) following MI, flecainide increased mortality compared to placebo.

Notice: Class 1C drugs are particularly of low safety and have shown even increase mortality when used chronically after MI
Compare between class IA, IB, and IC drugs as regards effect on Na\(^+\) channel & ERP

- **Sodium channel blockade:**
  - IC > IA > IB

- **Increasing the ERP:**
  - IA > IC > IB (lowered)

Because of K\(^+\) blockade

- **Class IA:** e.g., quinidine
  - Moderate Na\(^+\)-channel blockade
  - ↑ ERP

- **Class IB:** e.g., lidocaine
  - Weak Na\(^+\)-channel blockade
  - ↓ ERP

- **Class IC:** e.g., flecainide
  - Strong Na\(^+\)-channel blockade
  - → ERP
Class II ANTIARRHYTHMIC DRUGS
(β-adrenergic blockers)

Mechanism of action

- Negative inotropic and chronotropic action.
- Prolong AV conduction (delay)
- Diminish phase 4 depolarization → suppressing automaticity (of ectopic focus)

Uses

- Treatment of increased sympathetic activity-induced arrhythmias such as stress- and exercise-induced arrhythmias
- Atrial flutter and fibrillation.
- AV nodal tachycardia.
- Reduce mortality in post-myocardial infarction patients.
- Protection against sudden cardiac death.
Class II ANTIARRHYTHMIC DRUGS

- **Propranolol (nonselective):** was proved to reduce the incidence of sudden arrhythmic death after myocardial infarction
- **Metoprolol**
  - reduce the risk of bronchospasm
- **Esmolol:**
  - Esmolol is a very short-acting $\beta_1$-adrenergic blocker that is used by intravenous route in acute arrhythmias occurring during surgery or emergencies
Class III ANTIARRHYTHMIC DRUGS

K+ blockers

- Prolongation of phase 3 repolarization without altering phase 0 or the resting membrane potential
- They prolong both the duration of the action potential and ERP
- Their mechanism of action is still not clear but it is thought that they block potassium channels
Uses:

- Ventricular arrhythmias, especially ventricular fibrillation or tachycardia
- Supra-ventricular tachycardia
- Amiodarone usage is limited due to its wide range of side effects
Sotalol (Sotacor)

- Sotalol also prolongs the duration of action potential and refractoriness in all cardiac tissues (by action of $K^+$ blockade)
- Sotalol suppresses Phase 4 spontaneous depolarization and possibly producing severe sinus bradycardia (by $\beta$ blockade action)
- The $\beta$-adrenergic blockade combined with prolonged action potential duration may be of special efficacy in prevention of sustained ventricular tachycardia
- It may induce the polymorphic torsades de pointes ventricular tachycardia (because it increases ERP)

Ibutilide

- Used in atrial fibrillation or flutter
- IV administration
- May lead to torsade de pointes
- **Only drug in class three that possess pure $K^+$ blockade**
Amiodarone (Cordarone)

- Amiodarone is a drug of multiple actions and is still not well understood
- It is extensively taken up by tissues, especially fatty tissues (extensive distribution)
- $t_{1/2} = 60$ days
- Potent P450 inhibitor
- **Amiodarone antiarrhythmic effect** is complex comprising class I, II, III, and IV actions
  - Dominant effect: Prolongation of action potential duration and refractoriness
  - It slows cardiac conduction, works as Ca$^{2+}$ channel blocker, and as a weak β-adrenergic blocker

**Toxicity**

- Most common include GI intolerance, tremors, ataxia, dizziness, and hyper- or hypothyroidism
- Corneal microdeposits may be accompanied with disturbed night vision
- Others: liver toxicity, photosensitivity, gray facial discoloration, neuropathy, muscle weakness, and weight loss
- The most dangerous side effect is **pulmonary fibrosis** which occurs in 2-5% of the patients
Class IV ANTIARRHYTHMIC DRUGS (Calcium Channel Blockers)

- Calcium channel blockers decrease inward Ca$^{2+}$ currents resulting in a decrease of phase 4 spontaneous depolarization (SA node).
- They slow conductance in Ca$^{2+}$ current-dependent tissues like AV node.
- Examples: verapamil & diltiazem
- Because they act on the heart only and not on blood vessels.
- Dihydropyridine family are not used because they only act on blood vessels.
Mechanism of action

- They bind only to depolarized (open) channels $\rightarrow$ prevention of repolarization

So they act only in cases of arrhythmia because many Ca$^{2+}$ channels are depolarized while in normal rhythm many of them are at rest

- They prolong ERP of AV node $\rightarrow$ ↓conduction of impulses from the atria to the ventricles

Uses

- More effective in treatment of atrial than ventricular arrhythmias.
- Treatment of supra-ventricular tachycardia preventing the occurrence of ventricular arrhythmias.
- Treatment of atrial flutter and fibrillation.
Contraindication

- Contraindicated in patients with pre-existing depressed heart function because of their negative inotropic activity

Adverse effects

- Cause bradycardia, and asystole especially when given in combination with β-adrenergic blockers
Miscellaneous Antiarrhythmic Drugs

**Adenosine**

- Adenosine purinergic receptors decreasing the SA nodal firing and automaticity, reducing conduction velocity, prolonging effective refractory period, and depressing AV nodal conductivity.
- It is the drug of choice in the treatment of paroxysmal supra-ventricular tachycardia.
- It is used only by slow intravenous bolus.
- It only has a low-profile toxicity (lead to bronchospasm) being extremely short acting for 15 seconds only.
The effects of adenosine are antagonized by methylxanthines

Theophylline ➤
Caffeine ➤
Miscellaneous Drugs

**Magnesium sulfate:**
- Works on Na+/K+ ATPase, Na+ channels, certain K+ channels and Ca++ channels.
- Effective IV in refractory digitalis-induced ventricular arrhythmias only in hypomagnesemic patients.

**Potassium salts:**
- For digitalis-induced arrhythmias with hypokalemia.
- Depress ectopic pacemakers and slow conduction.
Miscellaneous Drugs

**Digoxin:**
- Old fashioned agent for atrial arrhythmias.
- Direct Actions.
- Vagotonic Effects.
- ↑ AV refractoriness.