Anti-arrhythmic drugs
Arrhythmias

- Arrhythmias consist in occasional or persistent alterations in the regular sequence of depolarization and repolarization in the heart conduction system.

- Arrhythmias are usually classified according:
  - to the site of origin (atrial, junctional or ventricular arrhythmias);
  - to the heart rate (tachyarrhythmias or bradyarrhythmias).

- The most common test used to diagnose an arrhythmia is the electrocardiogram (ECG).
Electrical system of the heart

Electrocardiogram (ECG)
Types of Arrhythmias

a) Paroxysmal supraventricular tachycardia (PSVT)

b) Atrial fibrillation

c) Atrial flutter

d) Extrasystoles

e) Monomorphically ventricular tachycardia

f) Torsades de Pointes
**Arrhythmias**

Certain factors can precipitate arrhythmias:
- ischemia,
- hypoxia,
- acidosis or alkalosis,
- electrolyte abnormalities,
- excessive catecholamine exposure,
- autonomic influences,
- drug toxicity (eg, digitalis or antiarrhythmic drugs),
- overstretching of cardiac fibers,
- presence of scarred or otherwise diseased tissue.

**Sex, Rhythm & Death: The effect of sexual activity on cardiac arrhythmias and sudden cardiac death**

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### Pro-arrhythmic effects of anti-arrhythmic drugs

| Effect                                      | Drug                          | Incidence                                      |
|---------------------------------------------|-------------------------------|------------------------------------------------|
| Marked sinus bradycardia, sino-atrial blocks| Class IA, Class IC            | Rare, except when latent sinus node disease is present |
| High-grade AV block                         | Class IA, Class IC            | Rare                                           |
| Conversion of AF to atrial flutter with higher ventricular rate | Quinidine and other Class IA | Rare with current dosages                      |
| Conversion of AF to atrial flutter with 1:1 AV conduction and wide QRS | Flecainide and propafenone | 3.5–5%                                         |
| Torsade de pointe                           | Quinidine and Class IA        | 1–8%                                           |
|                                             | Ibutilide, dofetilide, sotalol| Up to 8%                                       |
|                                             | Amiodarone                    | 0.7%                                           |
| Ventricular tachycardia or ventricular fibrillation | Potentially all AADs | Rare, except when LV dysfunction or heart failure are present |

AAD, antiarrhythmic drugs; AF, atrial fibrillation; AV, atroventricular; LV, left ventricular.
The cardiac action potential

Phase 4 - Phase 0 - Phase 1 - Phase 2 - Phase 3

- ECF: Na+
- ICF: K+

1. Transient K+ channels open and K+ efflux returns TMP to 0mV
2. Influx of Ca2+ through L-type Ca2+ channels is electrically balanced by K+ efflux through delayed rectifier K+ channels
3. Ca2+ channels close but delayed rectifier K+ channels remain open and return TMP to -90mV
4. Na+, Ca2+ channels closed, open K+ rectifier channels keep TMP stable at -90mV
### Vaughan-Williams classes of anti-arrhythmic drugs

| Class | Actions | Drugs |
|-------|---------|-------|
| I     | Sodium channel blockade | quinidine, procainamide, disopyramide |
| IA    | prolong repolarization   | lidocaine, mexiletine, tocainide, phenytoin |
| IB    | shorten repolarization   | flecainide, encainide, propafenone |
| IC    | little effect on repolarization | |
| II    | Beta-adrenergic blockade | propanolol, esmolol |
| III   | Prolong repolarization potassium channel blockade | sotalol, amiodarone |
| IV    | Calcium channel blockade | verapamil, diltiazem |
# I. Classes of anti-arrhythmic drugs

| Class | Most Efficacious For | Channels Affected | Representative Drugs |
|-------|----------------------|-------------------|----------------------|
| IA    | Atrial fibrillation  | Na\(^+\) also prolong repolarization (prolong QT) | Quinidine, procainamide, disopyramide |
|       | Ventricular arrhythmias |                   |                      |
| IB    | Ventricular arrhythmias | Na\(^+\) Also shorten repolarization (shorten QT) | Lidocaine, mexiletine |
| IC    | AV nodal reentry     | Na\(^+\) No significant effect on repolarization | Flecainide, propafenone |
|       | WPW-related arrhythmias |                   |                      |
|       | Ventricular arrhythmias ( ? mortality) |                   |                      |
| II    | Atrial fibrillation/flutter (Ventricular arrhythmias) | Directly block beta adrenergic receptors; small Na\(^+\) blocking effect | Propranolol, esmolol, acebutolol |
| III   | Atrial fibrillation/flutter Ventricular arrhythmias | Prolong QT with little effect on repolarization (block either fast K\(^+\) or slow Na\(^+\) currents) | Amiodarone, sotalol, ibutilide, dofetilide |
| IV    | Atrial fibrillation/flutter Atrial automaticities AV nodal reentry | Block AV Node Ca\(^+\) channels | Verapamil, diltiazem |
| Adenosine | AV nodal reentry Orthodromic tachycardia | Complete blockade of AV node conduction |                      |
| Digitalis | AV nodal reentry Atrial fibrillation/flutter | Reduces AV nodal conduction by blocking Na\(^+\) - K\(^+\) ATPase |                      |
| Magnesium | Torsades de pointes | Suppression of early afterdepolarizations through blockade of calcium or sodium channels |                      |
II. Classes of anti-arrhythmic drugs

| Vaughn-Williams Class | DRUG                          | ECG Changes | CHANNELS | RECEPTORS | Clinical Effects |
|-----------------------|-------------------------------|-------------|----------|-----------|-----------------|
| A                     | Quinidine                     | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Procainamide                  | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Disopyramide (Norpace)        | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
| B                     | Lidocaine (Xylocaine)         | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Mexiletine (Mexitil)          | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
| C                     | Propafenone (Rythmol)         | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Flecaïnide (Tambocor)         | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
| II                    | β-Adrenergic antagonists      | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Dronedarone (Multaq)          | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Amiodarone (Cordarone)        | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Sotalol (Betapace)            | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Ibutilide (Convert)           | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Dofetilide (Tikosyn)          | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
| III                   | Verapamil (Calan, Isoptin)    | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
|                       | Diltiazem (Cardizem)          | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |
| Misc                  | Adenosine (Adenocard)         | ☢           | ☢ ☢ ☢    | ☢ ☢ ☢ ☢ ☢ | ☢ ☢ ☢ ☢ ☢ |

Legend:
- Antagonist relative potency:
  - L = Low
  - M = Moderate
  - H = High

- Agonist: △
- ECG Changes related to Ca^{2+} channel block: ☢
- ECG Changes related to Na⁺ channel block: ☢
- ECG Changes related to K⁺ channel block: ☢
Anti-arrhythmic drugs I sub-classes

An easy way to remember…

- **IA** Disopyramide Quinidine Procainamide (**Double Quarter Pounder**)

- **IB** Lidocaine Mexiletine (**Letuce Mayo**)

- **IC** Flecainide Propafenone (**Fries Please**)

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*I* Anti-arrhythmic drugs I sub-classes
Anti-arrhythmic drugs in Class I

- Anti-arrhythmic drugs included in the class I bind to and block the fast Na\(^+\) channels that are responsible for the rapid depolarization (phase 0) of the cardiac action potential, although with differences in the efficacy. Sub-class IC has the greatest effect on phase 0, IB drugs has the smallest, sub-class IA is intermediate in its effect on phase 0.

IC > IA > IB

- Some anti-arrhythmic drugs included in the class I can also block the K\(^+\) channels responsible for phase 3, affecting the effective refractory period (ERP).

IA (increase ERP) > IC > IB (decrease ERP)

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
Anti-arrhythmic drugs: sub-class IA

- Anti-arrhythmic drugs included in the sub-class IA **moderately** block the open rapid Na\(^+\) channels;

- Anti-arrhythmic drugs included in the sub-class IA also block the K\(^+\) channels, **increasing** the effective refractory period.

- These electrophysiological effects are manifested in both atrial and ventricular tissue, and therefore Class IA drugs have the potential of treating both atrial and ventricular tachyarrhythmias.
Disopyramide is an oral agent.

Disopyramide is prescribed in order to maintain the sinus rhythm in presence of atrial flutter or atrial fibrillation and to prevent recurrence of ventricular tachycardia or fibrillation.

Marked pro-arrhythmic effects (especially in patients with a history of congestive heart failure) and several drug-drug interactions.
Quinidine

- Quinidine is a stereoisomer of quinine, originally derived from the bark of the cinchona tree.

- Quinidine is administered orally as one of three salts (sulfate, gluconate, or polygalacturonate).

- Quinidine, combined with verapamil, is effective in treating atrial fibrillation.

- The most common side effects are gastrointestinal, mainly diarrhea (30-50% of patients). Cinchonism, also after the first administration. Pro-arrhythmic effects.
Procainamide is a derivative of the local anesthetic agent procaine.

Because procainamide is available for relatively rapid intravenous loading, it has often been used to treat atrial fibrillation or slow incessant ventricular tachycardias.

The most common acute side effects are gastrointestinal (especially nausea, vomiting, and diarrhea), and hypotension (when the drug is administered intravenously). Chronic administration of procainamide can induce agranulocytosis (rare but mortality in 25% of patients) and lupus (frequent, 20% of patients). Several drug-drug interactions (cimetidine).
Anti-arrhythmic drugs: subclass IB

- Anti-arrhythmic drugs included in the sub-class IB **weakly** block Na\(^+\) channels.

- Anti-arrhythmic drugs included in the sub-class IB **decrease** the effective refractory period. This effect is more visible in fibers that have a longer action potential duration, like Purkinje fibers.

- Anti-arrhythmic drugs included in the sub-class IB have profound effects on conduction velocity in damaged myocardium, but they do not prolong conduction velocity in healthy cardiac tissue.
Lidocaine is a local anesthetic first introduced as an anti-arrhythmic drug in the 1950s.

Lidocaine is administered intravenously with a plasma half-life of 1–2 hours. For this trait, lidocaine is considered the drug of choice for emergency therapy of arrhythmias.

Lidocaine is one of the least cardiotoxic Na⁺ channel blockers. The predominant side effects relate to the CNS: paresthesias, tremor, nausea of central origin, lightheadedness, hearing disturbances, slurred speech, and convulsions. These occur most commonly in elderly or otherwise vulnerable patients or when a bolus of the drug is given too rapidly. Nevertheless, lidocaine may be ineffective in hypokalemic patients.
Mexiletine is a structural analog of lidocaine, is resistant to first-pass hepatic metabolism and effective by the oral route.

The electrophysiological effects of mexiletine are virtually identical to those of lidocaine and it is frequently combined with quinidine to increase efficacy while decreasing the risk of pro-arrhythmia.

Mexiletine is approved for treatment of ventricular arrhythmias.

A very narrow therapeutic window limits mexiletine use. Tremor, dizziness, memory loss.
Anti-arrhythmic drugs: subclass IC

- Anti-arrhythmic drugs included in the sub-class IC produce a **potent and selective** blockade of the open rapid Na⁺ channels.

- Anti-arrhythmic drugs included in the sub-class IC have **no effect** on the effective refractory period.

- Flecainide and propafenone are first-line drugs for most of the arrhythmias.
Flecainide was synthesized in 1972 and approved by the FDA in 1984.

Flecainide is recommended as one of the first line therapies for pharmacological conversion as well as maintenance of sinus rhythm in patients with atrial fibrillation and/or supraventricular tachycardias.

Flecainide may cause severe exacerbation of arrhythmia. Flecainide may interact with cimetidine, fluconazole, certain HIV protease inhibitors (such as ritonavir, tipranavir), anticonvulsant drugs (such as phenytoin, phenobarbital), among others.

*Br. J. clin. Pharmac.* (1986), 22, 108–110

Altered pharmacokinetics of oral flecainide by cimetidine

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Propafenone has some structural similarities to propranolol and possesses weak β-blocking activity. Its spectrum of action is very similar to that of quinidine.

Propafenone is useful for the treatment of supraventricular arrhythmias and life-threatening ventricular arrhythmias in the absence of structural heart disease.

Propafenone has pro-arrhythmic effects. The other side effects (neurological and gastrointestinal mainly) are usually well tolerated and often resolve with continued therapy or dosage reduction. Propafenone can cause a lupus-like facial rash, and also a condition called exanthematous pustulosis, which is a nasty rash accompanied by fever and a high white-blood-cell count. Numerous drug-drug interactions have been reported with propafenone.

*Br. J. clin. Pharmac.* (1987), 24, 213–220

Drug interaction between propafenone and metoprolol

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Interaction between warfarin and propafenone in healthy volunteer subjects

Interaction Between Propranolol and Propafenone in Healthy Volunteers

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Interaction between warfarin and propafenone in healthy volunteer subjects

The effect of propafenone on the pharmacokinetic and pharmacologic effects of warfarin was studied in healthy normal male volunteer subjects. Each drug was administered alone for 1 week followed by a combined administration for an additional week. Blood samples were analyzed for propafenone and warfarin concentrations and the effect of each treatment on the prothrombin time was assessed. The concurrent administration of warfarin did not produce any changes in the absorption or disposition kinetics of propafenone. Concurrent propafenone administration did lead to a reduction in the clearance of warfarin, resulting in an average increase of 38% in the mean steady-state plasma warfarin concentration. During the combined therapy phase, the prothrombin time increased significantly (P < 0.01) from the "warfarin alone" phase. We conclude from this study that the concomitant administration of propafenone and warfarin may lead to an enhanced anticoagulant effect that may require a reduction in the warfarin dose. (C)lin Pharmacol Ther 1987;42:306-11.)

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# Anti-arrhythmic drugs class II: β-blockers

| Agent             | Mechanism of Action                                                                 | Therapeutic use                                                                 |
|-------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| **Non-selective β-adrenergic antagonists (first generation):** |                                                                                      |                                                                                  |
| Propranolol       | Equal affinity for β1 and β2. Membrane stabilizing effect.                              | Used for: hypertension, angina, supraventricular arrhythmia, ventricular arrhythmia, MI. |
| Nadolol           | Equal affinity for β1 and β2. No sympathomimetic or membrane stabilizing activity.     | Used for: Hypertension, angina, LQTS.                                            |
| Timolol           | Equal affinity for β1 and β2. No sympathomimetic or membrane stabilizing activity.     | Hypertension, congestive HF, acute MI.                                            |
| **β1-selective adrenergic antagonists (second generation):** |                                                                                      |                                                                                  |
| Metoprolol        | No sympathomimetic or membrane stabilizing activity.                                   | Used for: essential hypertension, angina, tachycardia, HF, vasovagal syncope, secondary prevention after MI |
| Atenolol          | No sympathomimetic or membrane stabilizing activity.                                   | Used for: hypertension, coronary heart disease, arrhythmias, angina, reduces risk of complications after MI |
| Esmolol           | Little sympathomimetic activity, no membrane-stabilizing activity.                     | Used when short duration is desired or in critically ill patients where rapid withdrawal may be necessary. |
| Acebutolol        | Some sympathomimetic and membrane stabilizing activity.                                | Used for hypertension, atrial and ventricular arrhythmias, acute MI in high-risk patients |
| Bisoprolol        | No sympathomimetic or membrane stabilizing activity. Higher degree of β1 selectivity than metoprolol or atenol. | Used for: HF, hypertension, MI, arrhythmias                                        |
| **β-adrenergic antagonists with additional cardiovascular effects (third generation - also possess vasodilatory actions):** |                                                                                      |                                                                                  |
| Labetalol         | Competitive antagonist to α1 and β receptors (β1 and β2). Partial agonist activity at β2 and also inhibits neuronal uptake of NE (cocaine-like). | Used for chronic hypertension or hypertensive emergencies                           |
| Carvedilol        | Blocks α1, β1, and β2 similar to labetalol, but also has antioxidant and anti-inflammatory properties. Has membrane-stabilizing action, but no sympathomimetic activity. | Produces vasodilation and anti-inflammatory effects may help treatment of hypertension, congestive HF, and LV dysfunction after MI |
| Celliprolol       | β1 antagonist. β2 partial agonist. Also α2 antagonist and promotes NO production.       | Reduces HR and blood pressure. Used to treat hypertension and angina               |
| Nebivolol         | β1 antagonist with endothelial NO-mediated vasodilatory action.                        | Also has antioxidant action and neutral or favorable effects on carbohydrate and lipid metabolism. Approved for the treatment of hypertension |
Features of β-blockers

- In both the SA and AV nodes, β-blockers slow the spontaneous firing rate by decreasing the slope of phase 4 and increasing the effective refractory period of the cardiac action potential;

- β-blockers have little effect on SA nodal conduction in normal individuals but they can markedly prolong SA nodal conduction in patients with intrinsic SA nodal disease;

- β-blockers can help to prevent the formation of reentrant arrhythmias in myocardium that has been damaged by ischemia;

- β-blockers depress the catecholamine-stimulated automaticity.
Anti-arrhythmic drugs class III: Agents that block $K^+$ channels and prolong repolarization

- Anti-arrhythmic drugs included in the class III block the $K^+$ channels that mediate repolarization, and thus increase the effective refractory period.

- Dronedarone and sotalol are first-line drugs for most of the arrhythmias.
Amiodarone is an iodine-containing benzofuran derivative.

Intravenous amiodarone has been used to treat a wide range of arrhythmias, particularly in the post-operative period. Oral amiodarone is effective in most forms of supraventricular and ventricular tachycardia with its use limited by the frequency and severity of its adverse effects.

The most significant adverse effects include thyroid dysfunction (hypo or hyper), chemical hepatitis, worsening sinus node dysfunction, and pulmonary fibrosis.

Amiodarone inhibits hepatic metabolism, but it can also affect the bioavailability, protein binding and renal excretion of several clinically important coadministered drugs.

**Drug interactions with amiodarone**

There are a number of important drug interactions with amiodarone. This agent appears to have a marked effect on the kinetics of some commonly used cardiovascular drugs, such as warfarin, digoxin, quinidine, and procainamide, and has dynamic interactions with others, such as the beta blockers and some calcium antagonists. Bleeding has been reported, apparently caused by a potentiation of the anticoagulant effect of warfarin by amiodarone. Torsades de pointes has been observed when quinidine, propafenone, or mexiletine is given together with amiodarone. Furthermore, amiodarone may interact with beta-blocking agents and some of the calcium antagonists to produce symptomatic sinus bradycardia and sinus arrest, especially in a latent or overt sick sinus syndrome. During surgery, amiodarone may induce hypotension and an atropine-resistant bradycardia, possibly by interacting with anesthetic agents. A knowledge of the time of onset, extent, duration, and possible mechanisms of the interactions of amiodarone with other cardioactive drugs is still incomplete, but further studies are of great therapeutic importance. (Am Heart J 106:924, 1983.)

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Dronedarone is a close analogue of amiodarone, but since it lacks the iodine moieties, dronedarone has fewer toxic effects on the thyroid and other organs. For these reasons, dronedarone is a first-line drug for several arrhythmias.

Dronedarone was developed to treat atrial fibrillation and then started to be used as an antiarrhythmic drug.

The most common side effects of dronedarone are gastrointestinal (diarrhea, nausea, abdominal pain, vomiting) and weakness.

Dronedarone has fewer drug interactions comparing with amiodarone. Concomitant use with CYP3A4 inhibitors should be avoided (ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, nefazodone, verapamil, diltiazem & grapefruit juice).
Sotalol is formulated as a racemic mixture of d- and l-sotalol, because the l-isomer has β-blocking activity, whereas both the d- and l-isomers share action potential prolonging effects.

Sotalol is approved for the treatment of significant ventricular and supraventricular arrhythmias but can be useful for treating all types of tachyarrhythmias. Sotalol can be usefull for the maintenance of sinus rhythm in patients with atrial fibrillation. It is also approved for treatment of supraventricular and ventricular arrhythmias in the pediatric age group. The drug is generally considered more effective than Class IA drugs but not as effective as amiodarone, although considered a first-line drug.

Side effects include those attributed to both noncardioselective β-blockade and pro-arrhythmia. Other adverse effects of sotalol include, in decreasing order of frequency, fatigue, dyspnea, chest pain, headache, gastrointestinal disturbances (nausea and vomiting).

Sotalol may interact with IA and other class III antiarrhythmic drugs, antacids, clonidine, diuretics, drugs prolonging the QT interval.
Ibutilide is a new Class III antiarrhythmic agent, structurally analog of sotalol.

Ibutilide is approved for intravenous chemical cardioversion of recent onset atrial fibrillation and atrial flutter in adults.

The major adverse effect of ibutilide is its propensity to cause Torsades de pointes due to QT prolongation occurring in approximately 4% of adult patients, usually within 40 minutes of initiating the infusion.

No specific drug interaction studies have been performed. Concomitant β-receptor or calcium channel antagonists apparently do not interact, although data are limited (Clinical Pharmacology of Antiarrhythmic Drugs. Raymond L. Woosley, Farshad Shirazi, in Cardiovascular Therapeutics (Third Edition), 2007).
Dofetilide is a “pure” class III drug.

Dofetilide is approved for the maintenance/restoration of normal sinus rhythm in patients with atrial fibrillation.

The principal cardiac adverse effect is the risk of Torsades de pointes due to QT prolongation, which is approximately 3% in adult trials. Most pro-arrhythmic events are observed in the first 3 days. Dofetilide has been reported to cause occasional noncardiac symptoms, including headache, gastrointestinal disturbances, sleep disorders, and flulike symptoms.

Concomitant use with CYP3A4 inhibitors should be avoided (ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, nefazodone, verapamil, diltiazem, and grapefruit juice).
Anti-arrhythmic drugs class IV: Agents that block the slow inward \( \text{Ca}^{++} \) current

- Many \( \text{Ca}^{++} \)-blocking agents have been developed, but only two are commonly used (and have been approved) for the treatment of cardiac arrhythmias: **verapamil and diltiazem**.

- Verapamil and diltiazem both block the slow inward \( \text{Ca}^{++} \) current (L-type calcium channel). The administration of class IV drugs slows conduction velocity and increases the effective refractory period.
Verapamil has a structure similar to that of papaverine.

Verapamil is useful for slowing the ventricular response to atrial tachyarrhythmias. Verapamil is also effective in ectopic atrial tachycardia and supraventricular tachycardia. Finally, verapamil causes peripheral vasodilation, which may be beneficial in hypertension and peripheral vasospastic disorders.

Orally administered verapamil is well tolerated by the majority of patients. Most complaints are with respect to gastrointestinal side effects (constipation and gastric discomfort). Other complaints include vertigo, headache, nervousness, and pruritus.

Concomitant use with CYP3A4 inhibitors should be avoided (ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, nefazodone, diltiazem, and grapefruit juice).
Diltiazem

- Diltiazem is a benzothiazepine derivative that shares electrophysiological effect and clinical uses of verapamil.
- Diltiazem appears to be similar in efficacy to verapamil in the management of atrial arrhythmias.
- The adverse effects are similar to verapamil with a lower incidence of ventricular depression.
- Diltiazem is extensively metabolized through the CYP450 system. For this reason, concomitant use with CYP450 inhibitors may increase diltiazem concentrations leading to adverse effects even at clinically recommended doses.
Miscellaneous anti-arrhythmic agents

- Certain agents used for the treatment of arrhythmias do not fit the conventional class 1–4 organization. These include:

  1) Digoxin,
  2) adenosine,
  3) magnesium.
Digoxin

- Digitalis glycosides, especially digoxin, have been used in clinical medicine since the 1700s.

- The clinical utility of digoxin is twofold. First, it increases intracellular Ca\(^{++}\) during muscle contraction, thus increasing inotropy. Second, digoxin inhibits the membrane-bound Na\(^{+}\)-K\(^{+}\)ATPase enzyme.

- Since digoxin slows the conduction through the AV node, it can be administered for significant ventricular arrhythmias.

- Digoxin has a narrow therapeutical window and potentially life-threatening cardiac adverse effects. Gastrointestinal disorders (nausea, vomiting, anorexia, diarrhea, and cramps), neuropsychological disorders (visual disturbances, restlessness, and delirium), and bradycardia are warning signs. Some drug combinations can aggravate the cardiac adverse effects of digoxin, or reduce its efficacy (cholestyramine, antacid gels, kaolin-pectate, certain antimicrobial drugs and cancer chemotherapeutic agents).
The nucleoside adenosine can activate the inward rectifier $K^+$ current and inhibit the $Ca^{++}$ current.

Intravenous adenosine is useful for the acute termination of supraventricular tachycardia that utilizes the AV node. Adenosine is also helpful for the diagnosis of narrow complex tachycardias by unmasking, such as atrial flutter and ectopic atrial tachycardia.

Adverse reactions to the administration of adenosine are not uncommon; however, the short half-life of the drug limits the duration of such events.

There are a few significant drug interactions with adenosine, in particular with dipyridamole (including combination preparations with aspirin), carbamazepine (which increases the action of adenosine), methylxanthine compounds (theophylline and caffeine).
Magnesium Sulfate

- Originally used for patients with digitalis-induced arrhythmias who were hypomagnesemic, magnesium infusion has been found to have antiarrhythmic effects in some patients with normal serum magnesium levels.

- The precise mechanism by which magnesium can ameliorate arrhythmias has not been established. Functionally, magnesium is required for the membrane-bound Na+/K+ ATPase, which is the principal enzyme that maintains normal intracellular potassium concentration.

- Magnesium sulfate can be administered orally, intramuscularly, or intravenously, when a rapid response is needed.

- The most well-established use of magnesium is in the therapy of Torsades de pointes.

- For the acute treatment of cardiac arrhythmias, the administration of intravenous magnesium has proven very safe. There is some potential of pushing magnesium levels into the toxic range in the presence of severe renal failure, but the overall risk of doing so is low.