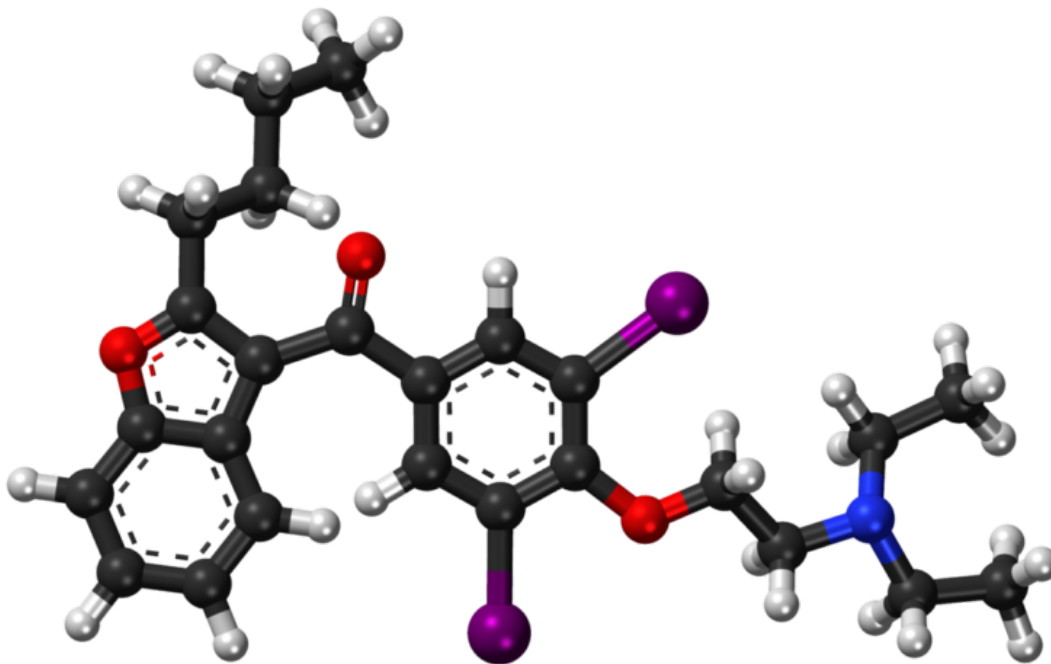


Class 3: Potassium Channel Blockers – Antiarrhythmic Drugs

[See online here](#)

The main role of antiarrhythmic agents is to prevent the occurrence of arrhythmia and, in the case of those patients in which abnormal rhythm has occurred; it helps in the termination of the arrhythmia. Antiarrhythmics are classified in various types by means of many classifications. The Vaughan-Williams classification is one of the widely accepted among those. Class 3 drugs constitute potassium channel blockers. These will be discussed in this article.



Antiarrhythmic Drugs

Antiarrhythmic drugs can be classified according to their mechanism of action. Therefore, the **Vaughan-William classification** lists five groups:

Class 1 constitutes the **sodium channel blockers** and is, in turn, divided into three groups (1A, 1B, and 1C), based on the action potential duration, the amount of reduction of the phase 0 slope, and effective refractory period.

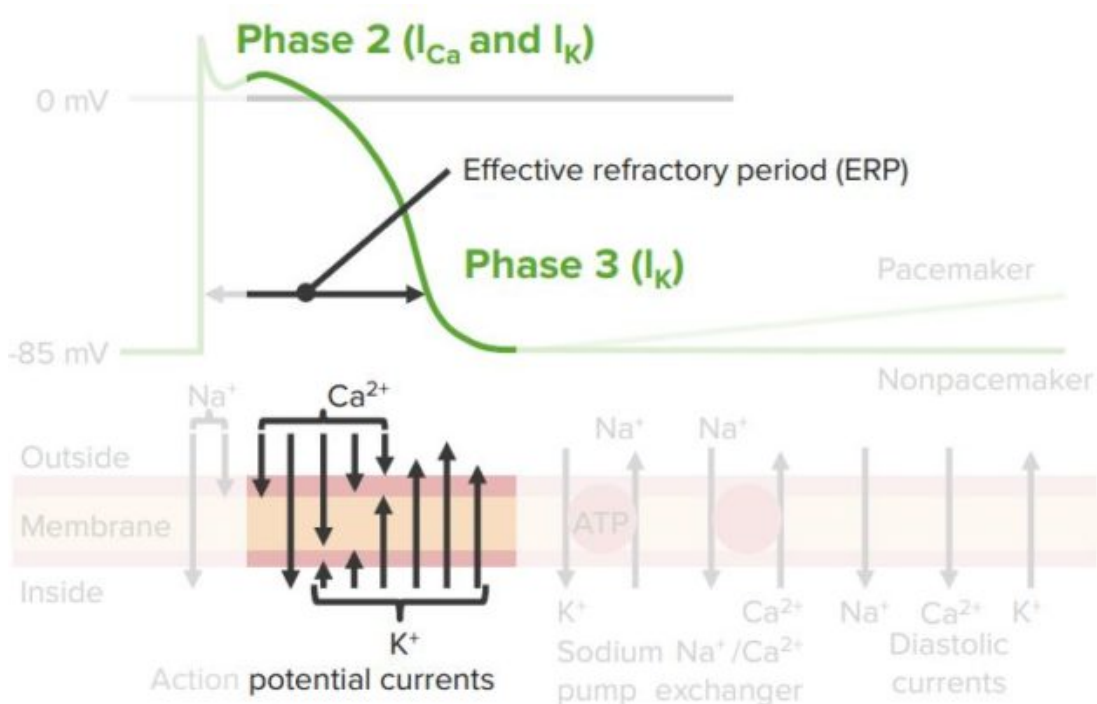
Class 2 drugs constitute of **beta-blockers**.

Class 3 are **potassium channel blockers** – amiodarone, dronedarone, bretylium, sotalol, ibutilide, and dofetilide. These will be discussed in this article.

Calcium channel blockers are classified as **class 4** and **miscellaneous drugs** are **class 5**.

Mechanism of Action of Potassium Channel Blockers

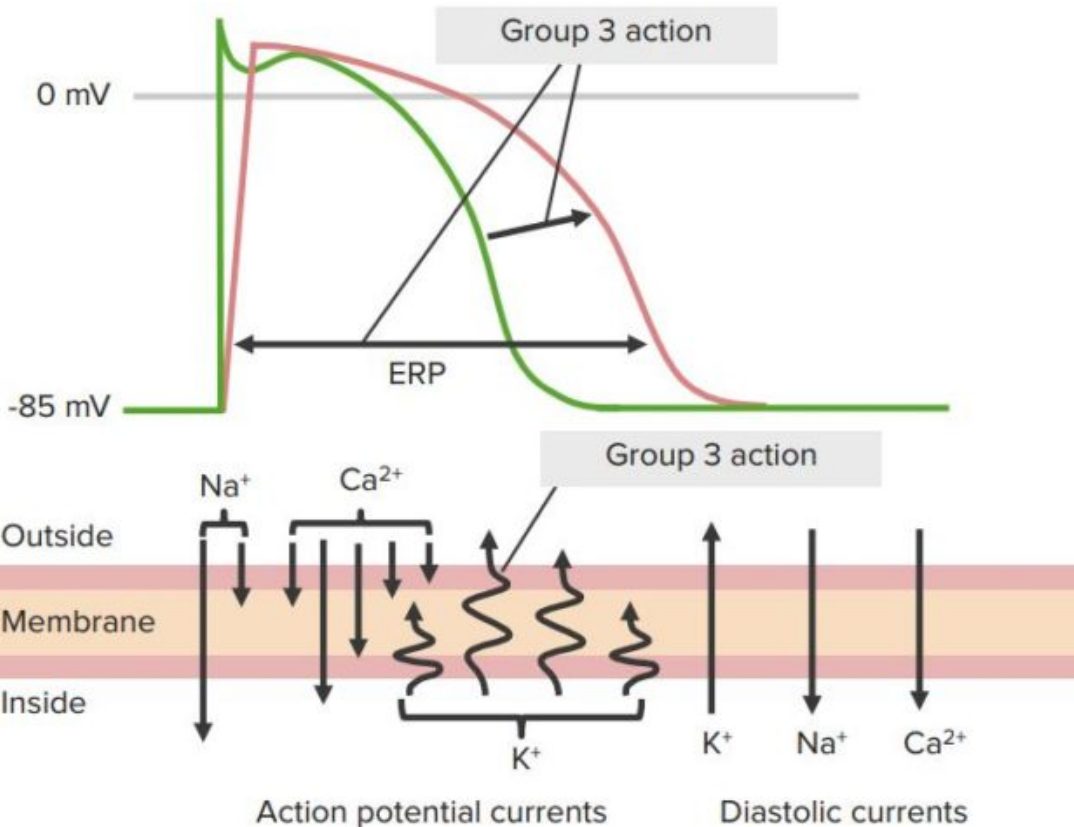
Potassium is the chief ion in the **repolarization**. At the end of depolarization, potassium efflux occurs following the opening of the potassium channels. These drugs bind to and block the potassium channels that are responsible for phase 3 repolarization. Therefore, blocking these channels slows (delays) repolarization, which leads to an increase in action potential duration and an increase in the effective refractory period (ERP).



"Group 3 Antiarrhythmics. Effective refractory period" Image created by Lecturio

This group of drugs binds to the channel which is responsible for the potassium movement and blocks it (**rapid component of the delayed rectifier current (IKr)**). Once the blocking has happened, the refractory period increases.

The refractory period is the time interval in which no stimulus can induce the occurrence of a new action potential, which in turn leads to no propagation of myocardial contraction. The refractory period is further divided into two types, named **relative and absolute refractory period**. The potassium channel blocker increases the duration of the absolute refractory period of both the atria and the ventricles; thus the action potential widens, slowing the frequency of depolarizations.



"Antiarrhythmics-Group-3" Image created by Lecturio

One of the important mechanisms which cause continuous tachyarrhythmia is the **circuit of excitatory impulse** which excites the ventricle again and again. Potassium channel blockers block these re-entry circuits by means of inhibition of the effect of the impulse by making the tissue refractory at the time the impulse arrives.

It is worth to note that **amiodarone** is said to have an **electrophysiological property** in addition to its potassium channel blocking property. It also acts as a sodium channel blocker, anti-adrenergic and L-type calcium channel blocker (note that these are the property of class 1, class 3 and class 4 drugs according to the Vaughan-Williams classification).

All these are the reasons behind the therapeutic efficacy of amiodarone.

Amiodarone

Amiodarone has shown efficacy in the management of both supraventricular and ventricular **arrhythmias**, but its approved usage is limited by its long time of onset of action and its array of side effects.

Pros & Cons and the Main Indication of Amiodarone

Atrial Arrhythmia



Image: "ECG of atrial fibrillation (top) and normal sinus rhythm (bottom). The purple arrow indicates a P wave, which is lost in atrial fibrillation." by J. Heuser. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Amiodarone, both IV and oral, is given as a maintenance treatment, restoration treatment and for the prophylaxis of **atrial fibrillation**, ventricular tachycardia, including ventricular fibrillation; atrial fibrillation and atrial flutter (off-label use).

Maintenance Treatment

Though not FDA approved, oral amiodarone is widely used for the maintenance treatment of **sinus arrhythmia** in patients with atrial fibrillation. Though oral amiodarone is not a recommended therapy for the cardioversion in active atrial fibrillation (this is because the oral amiodarone takes time for its action to occur), it can be given in some cases.

Oral amiodarone is also used for the **prevention of paroxysmal atrial fibrillation**. Intravenous amiodarone is used mainly in severe cases and the indications include the maintenance of sinus rhythm in AF patients who are unstable hemodynamically.

Restoration Treatment

Though convincing evidence is not available, amiodarone is used for the **restoration of sinus rhythm** in patients with unstable atrial fibrillation. Critically ill patients form the main treatment group (in this group of patients, ventricular fibrillation occurs along with atrial fibrillation contributing to the instability).

Given as a Prophylaxis

Amiodarone (both oral and intravenous) is used as **prophylaxis before cardiac surgery** in order to prevent atrial fibrillation in high-risk patients. The drug is also given to those patients who have a high risk of atrial fibrillation during **electrical cardioversion**. The treatment, in this case, should start long before (2-6 weeks before the planned cardioversion).

Ventricular Arrhythmia

Oral amiodarone has shown efficacy in preventing the occurrence of VT in patients with **myocardial infarction** and **congestive heart failure**.

Ventricular Refractory Arrhythmia and Pulseless VT and VF (Sudden Cardiac Death)

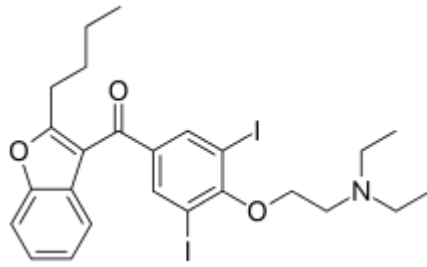


Image: "Skeletal formula of amiodarone—a class III antiarrhythmic. Created with ChemDoodle and Adobe Illustrator." by Vaccinationist - PubChem. License: [Public Domain](#)

A recent RCT (2016) published in NEJM, where lidocaine, amiodarone, and placebo are compared for pulseless VT or VF in those patients in whom initial defibrillation or vasopressor therapy has shown refraction, has shown that there is no difference in survival (primary outcome of the trial).

There occurred a **mild non-significant survival benefit** on both the drug treatment groups when compared to the placebo in the bystander-witnessed arrest.

It has to be noted that the two most famous trials, namely the ALIVE trial and the ARREST trial, where amiodarone has been compared with lidocaine in **sudden cardiac arrest** patients having persistent VF after defibrillation, have shown the only improvement in the rate of hospital admissions after the arrest, but not survival. In the ARREST trial, **amiodarone was associated with more side effects**. Survival to hospital discharge and survival with favorable neurologic outcome, however, was not improved by amiodarone compared with placebo or amiodarone compared with lidocaine, although these studies were not powered for survival or favorable neurologic outcome.

Based on the above evidence, amiodarone is suggested by the AHA guidelines as the first-line drug for the treatment during sudden cardiac arrest, **rather than lidocaine** (this is also confirmed by a Cochrane study): 'Amiodarone may be therefore considered for VF/pVT that is unresponsive to CPR, defibrillation, and a vasopressor therapy. (Class IIb, LOE B-R)".

It should, however, be remembered that the first line of therapy to be given to a patient with VF or VT related sudden cardiac arrest is an **effective CPR along with defibrillation** if indicated.

Defibrillation (**implantable cardioverter-defibrillators (ICDs) after successful administration with automatic external defibrillators, or AED's**) is the only proven effective treatment of the VF and VT. The administration of the antiarrhythmic drugs, like amiodarone and lidocaine, is only after effective CPR and successful defibrillation.

Pharmacokinetics of Amiodarone

Oral amiodarone is lipophilic and it takes time to attain the intended concentration in the blood (due to the increase in the volume of distribution seen with the lipophilic drugs).

Amiodarone is an **inhibitor of CYP3A4**, so the interaction concerned with the drugs which are metabolized by the CYP3A4 needs to be taken care of.

The drug also significantly interacts with warfarin, this requiring dose modification. In addition to this, the alteration in **thyroid function** caused by amiodarone further affects

warfarin concentration.

Adverse and Side Effects Related to Amiodarone

Though amiodarone is almost a wonder drug in arrhythmias, it has gone into disfavor mainly because of its side effect profile. That's the reason why it is used mainly in **refractory ventricular arrhythmia**, rather than atrial fibrillation, even if it has high efficacy in AF.

The side effects are mainly seen with long term therapy, rather than short term intravenous therapy.

The exposure to low-dose oral amiodarone for a long duration has the following odds of developing side effects when compared to placebo, namely 4.2%, 3.4%, 2.0% for thyroid, ocular and skin/neurological/pulmonary toxicity respectively. The above data is according to a meta-analysis on the side effect profile.

Mnemonic: Amiodarone Side-Effects + Toxicity are a 'BITCH'

Bradycardia/**B**lue man

Interstitial Lung Disease

Thyroid (hyper and hypo)

Corneal (ocular)/**C**utaneous (skin)

Hepatic/**H**ypotension when IV (due to solvents)

The side effect profile of intravenous amiodarone is different. The most common adverse effect with intravenous preparations is **hypotension**, and this is significantly reduced by the latest pharmaceutical preparation (containing aqueous base).

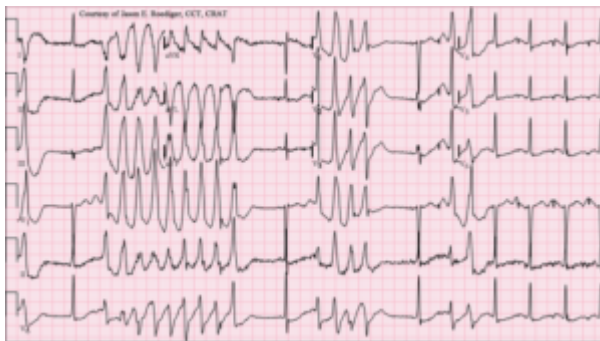


Image: "Prolonged QT Interval; Torsades de pointes (TdP)." by Jer5150 - Own Work. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

It should be noted that although amiodarone is more potent compared to other groups of antiarrhythmic agents, it has fewer pro-arrhythmic effects. When the arrhythmia occurs with amiodarone, the most commonly seen is the **Torsades de pointes**. The risk increases in women and with the presence of other co-electrolyte abnormalities.

The most common cause of death with a patient on amiodarone therapy is **pulmonary toxicity** with the most important predictor being the cumulative dose given. The most common type of pulmonary toxicity involves **chronic interstitial pneumonitis** and the presence of an **increased number of foamy macrophages in the lungs' air spaces**.

This warrants **immediate stoppage of the drug** and treatment with **corticosteroids**.

The **other side effects** include gastrointestinal disturbances, liver function abnormalities, bradycardia, asystole, localized phlebitis, non-productive cough, acute respiratory distress syndrome (rare), and bluish-slate gray discoloration of the skin (see above), along with the presence of photosensitivity.

In addition, **neurological toxicity**, like peripheral neuropathy, paresthesia, abnormal walking, and alteration in the blood lipid levels are seen.

Hypothyroidism or **hyperthyroidism**, are not uncommon.

Reversible corneal deposits can be seen in patients treated with amiodarone. As the vision remains still intact, the corneal micro-deposits are not an indication for stopping the amiodarone therapy. The mechanism behind the formation is due to the secretion of amiodarone through the lacrimal gland. There is also a **risk of optic nerve injury** causing blindness.

Regarding the liver function abnormality, it is recommended to monitor the liver function every 6 months. The drug needs to be discontinued if the elevation in the liver enzymes is more than the two-fold.

The two proposed mechanisms are **phospholipidosis** (the phospholipids of the liver interact with the amiodarone) and **metabolic idiosyncrasy** (potential in some individuals to produce more toxic metabolites from a given drug).

Reverse Use Dependence

Except for amiodarone, all the other members of class 3 antiarrhythmic drugs, like sotalol, exert the property of reverse use dependence. This means that, as the heart rate decreases, there occurs an increased risk of **prolongation of QT interval**. This increases the risk of **Torsades de pointes** and also decreases the efficacy of the drug.

There are also other proposed mechanisms on why the incidence of Torsades de pointes is less with amiodarone; they include the properties of amiodarone like concurrent inhibition of L type calcium channels, but the mechanism is not fully understood.

Dronedarone

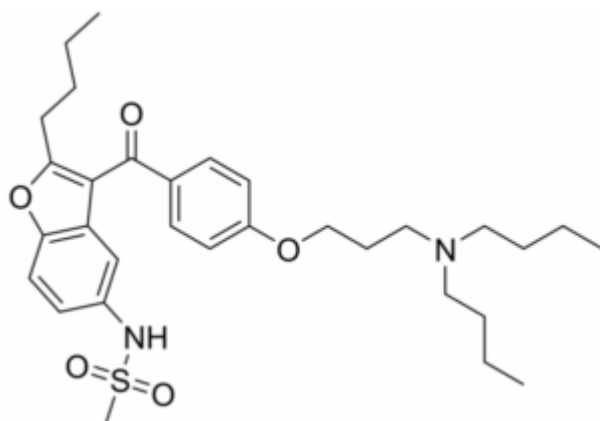


Image: "2D-Structure of Dronedarone" by Harbinary - Own work.
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The mechanism of action is the same as the whole group. It acts on all the 4 channels (sodium, potassium, calcium and the alpha 1 and it antagonizes all these receptors).

Indication

The drug is used in patients with persistent AF who need to reduce the risk of hospitalization for AF (note, in these patients the rhythm can still be reverted back). The drug is also used for the treatment of AF in patients of Hypertrophic Obstructive Cardiomyopathy (HOCM).

Contraindications

The drug is contraindicated in patients with **NYHA class 4 symptomatic heart failure**. Dronedarone is also shown to increase the risk of death in those patients with refractory atrial fibrillation.

Adverse Effect

Prolonged QT is the most common adverse effect seen with this drug. Along with that, there occurs an increase in the renal parameters, dermatologic manifestation like allergic dermatitis, neuromuscular weakness, and bradycardia.

Sotalol

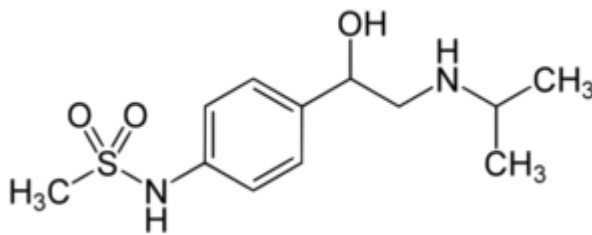


Image: "Chemical Structure of Sotalol" by Yikrazuul - Own work.
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Mechanism

The drug is a **racemic mixture of d and l isomers**. The concentrations of both isomers is approx. 1:1 and have different mechanisms of action.

The d isomer has the blocking property of delayed potassium channel-induced depolarization (similar to other drugs in the class 3 antiarrhythmics); the l isomer in addition to this property also has a beta-blocking property.

It should be noted that although the name sotalol sounds like a beta-blocker, it is classified under the class 3 anti-arrhythmic agent based on its functional properties.

Indication

Oral sotalol is used for the treatment of sustained VT which is potentially life-threatening and in sinus rhythm patients at risk of developing [atrial fibrillation](#).

Adverse Effects

The drug should not be given in patients with **congenital QT prolongation** and its common side effects are a decrease in heart rate, difficulty breathing, a dizzy feeling,

fatigue and lack of energy.

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