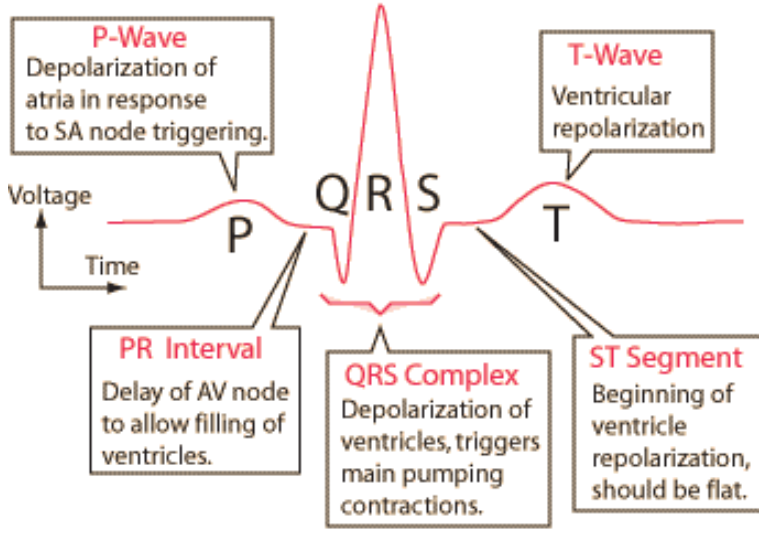
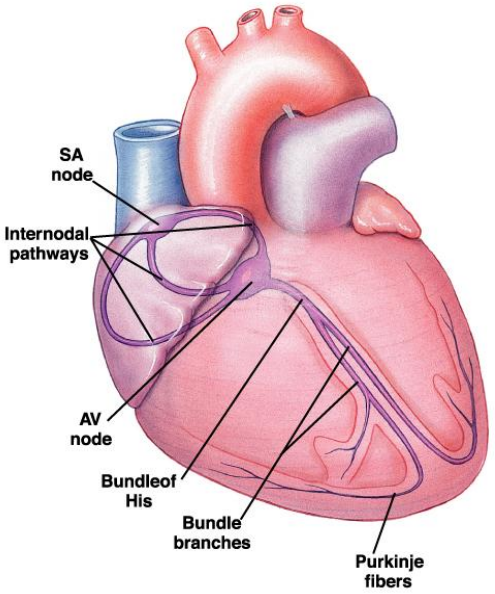
ELECTRICAL SIGNALS CONTROL THE CARDIAC ACTIVITY

- The heart beat begins when an electrical impulse from the sinoatrial node (SA node or sinus node) moves through it.
- The normal electrical sequence begins in the right atrium and spreads throughout the atria to the atrioventricular (AV) node. From the AV node, electrical impulses travel down a group of specialized fibers called the His-Purkinje system to all parts of the ventricles.



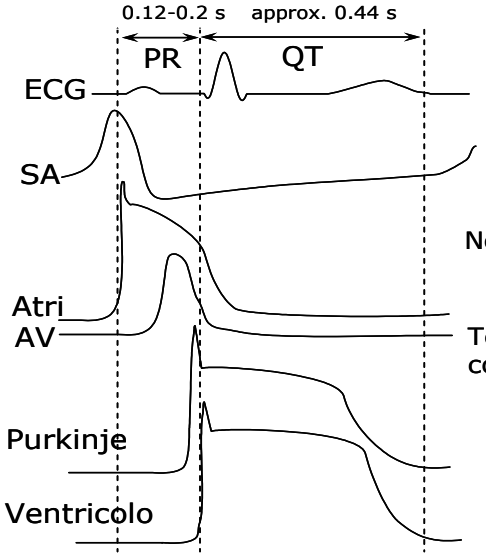


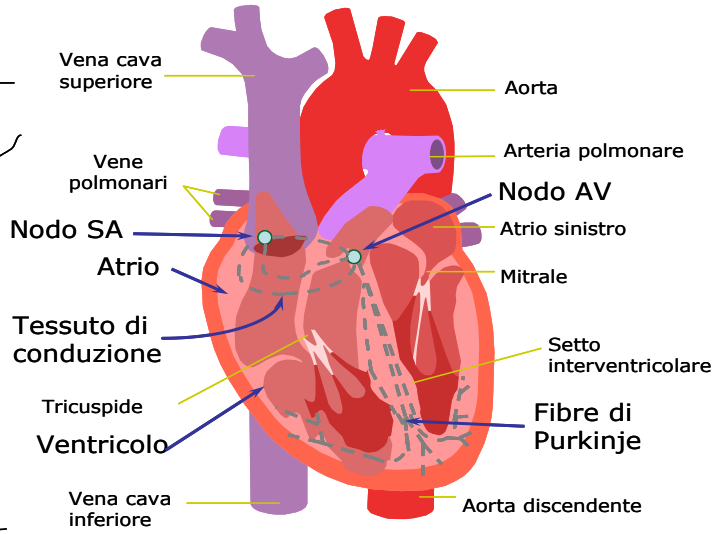
- Electrocardiography (ECG or EKG) records the heart's electrical activity

ARRHYTHMIA

• The term "arrhythmia" refers to any change from the normal sequence of electrical impulses. The electrical impulses may happen too fast, too slowly, or erratically – causing the heart to beat irregularly.

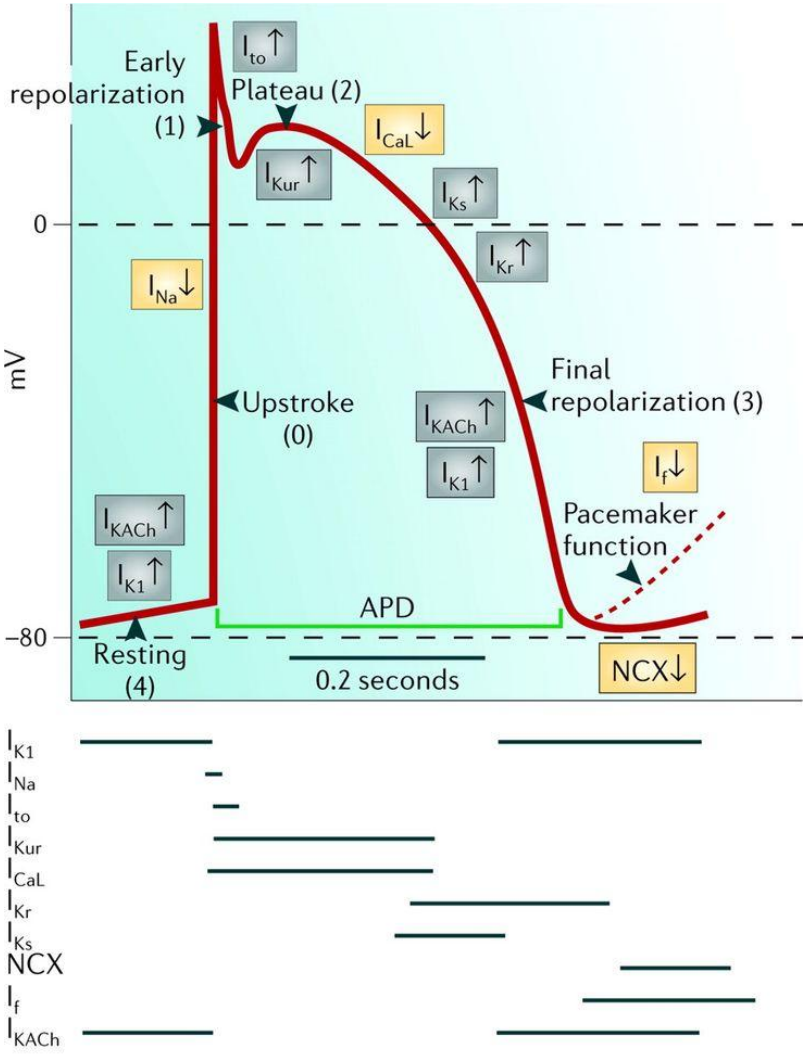
• When this happens, the heart can't pump blood effectively, and therefore the lungs, brain and all other organs can't work properly and may be damaged.





• Direct antiarrhythmic therapy, including antiarrhythmic drugs, cardioversion-defibrillation, implantable cardioverter-defibrillators (ICDs), pacemakers (and a special form of pacing, cardiac resynchronization therapy), or a combination, is used.

CAUSES OF DYSRHYTHMIAS



Arrhythmisa/Dysrhythmias arise because:

- **Delayed after-depolarization, which triggers ectopic beats**

Delayed after-depolarization is caused by an inward current associated with abnormally raised intracellular Ca

- **Re-entry, resulting from partial conducting block**

Re-entry is facilitated when parts of the myocardium are depolarized as a result of disease

- **Ectopic pace-maker activity**

Ectopic pacemaker activity is encouraged by sympathetic activity

- **Heart block**

Heart block results from disease in the conducting system, expecially in the atrioventricular node

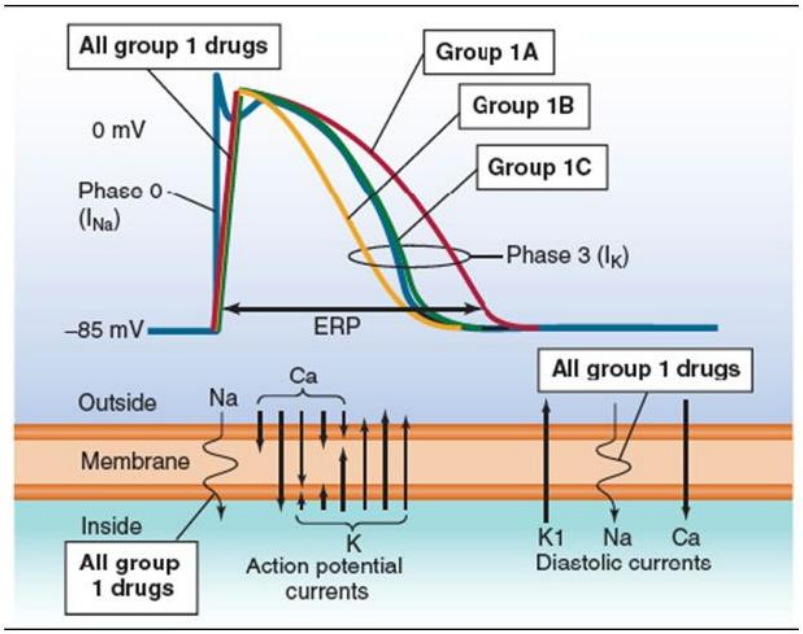
ANTI-DYSRHYTHMIC DRUGS

Vaughan Williams Classification

Class	Drug	Channel	Mechanism	ECG Effect
I	1a: Quinidine, Procainamide, Disopyramide	Sodium	Slow depolarization 1c > 1a > 1b	1a: ↑ QT, QRS, and PR 1b: usually no change 1c: ↑ PR and QRS
	1b: Lidocaine, Mexiletine			
	1c: Propafenone, Flecainide			
II	Beta Blockers		AV Nodal Blockade	↓ HR and ↑PR
III	Amiodarone Ibutilide Dofetilide Dronedarone Sotalol	Potassium	Slow Repolarization	↑QT
IV	Calcium Channel Blockers (nondihydropyridine)	Calcium	AV Nodal Blockade	↓ HR and ↑PR

CLASS I – Sodium Channel Blockers

Class I antiarrhythmic drugs are traditionally divided into three **subclasses--Ia, Ib, and Ic--**on the grounds of ***differences in kinetics of interaction with the sodium channel and different effects on the duration of the action potential.***



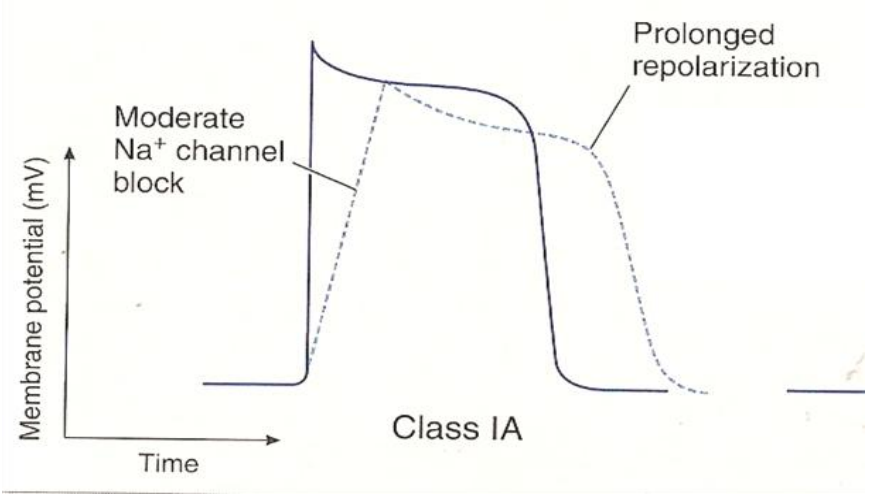
These drugs block the fast sodium channels responsible for the rapid depolarization (phase 0). Because the slope of phase 0 depends on the activation of fast sodium-channels and the rapid entry of sodium ions into the cell, blocking these channels decreases the slope of phase 0, which also leads to a decrease in the amplitude of the action potential.

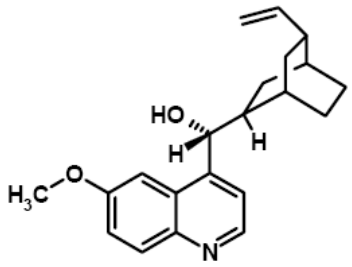
The principal effect of reducing the rate and magnitude of depolarization by blocking sodium channels is a ***decrease in conduction velocity in non-nodal tissue*** (atrial and ventricular muscle, purkinje conducting system). Therefore, blocking sodium channels reduces the velocity of action potential transmission within the heart (reduced conduction velocity; negative dromotropy).

CLASS Ia – Sodium Channel Blockers

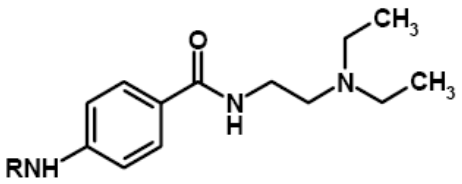
This class of sodium channel blocking antiarrhythmic drugs are classified as **use-dependent** in that they **bind to <u>open</u> sodium channels**. Their effectiveness is therefore dependent upon the frequency of channel opening. In general, they ***prolong the action potential***

Class Ia

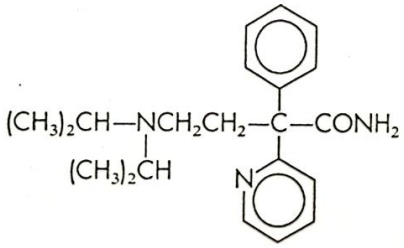




QUINIDINE

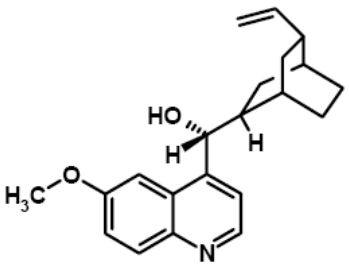


PROCAINAMIDE



DISOPIRAMIDE

Class Ia



QUINIDINE

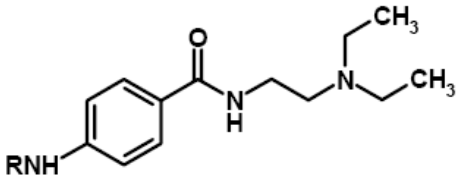
PHARMACOKINETICS

Rapid oral absorption; rapid attainment of peak blood levels (60-90 minutes)
Elimination half-life: 5-12 hours
IM injection possible but not recommended (injection site discomfort)
IV administration limited due to myocardial depression and peripheral vasodilation
80%-90%: bound to plasma albumin
Hepatic metabolism: hydroxylation to inactive metabolites, followed by renal excretion. 20% excreted unchanged in urine. Impaired hepatic/renal function results in accumulation of quinidine and metabolites. Quinidine is a potent INHIBITOR of **P450- CYP2D6 cytochrome**

ADVERSE REACTIONS

The anticholinergic effects can produce tachycardia, dry mouth, urinary retention, blurred vision and constipation.
Diarrhea, nausea, headache and dizziness are also common side effects of many Class I drugs.
Quinidine enhances digitalis toxicity, especially if hypokalemia is present.
Quinidine, by delaying repolarization, can precipitate torsades de pointes (especially in patients with long-QT syndrome), a ventricular tachyarrhythmia caused by afterdepolarizations.

Class Ia



PROCAINAMIDE

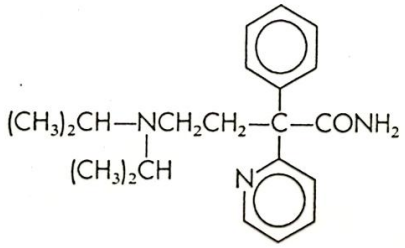
PHARMACOKINETICS

Local anesthetic (procaine) analog. Long-term use avoided because of lupus-related side effect. Hepatic metabolism: cardioactive metabolite N-acetylprocainamide (NAPA); NAPA accumulation may lead to Torsades de pointes. By contrast to procaine, procainamide is highly resistant to hydrolysis by plasma esterases. 40%-60% excreted unchanged (renal) Renal dysfunction requires procainamide dosage reduction

ADVERSE EFFECTS

Most important difference compared quinidine: procainamide does not exhibit vagolytic (antimuscarinic) activity. It is less likely to produce hypotension, unless following rapid IV infusion.

DISOPIRAMIDE



PHARMACOKINETICS

Very similar to quinidine, it has a greater antimuscarinic effects. Hepatic metabolism, with dealkylated metabolite less anticholinergic. 50% - excreted unchanged, renal

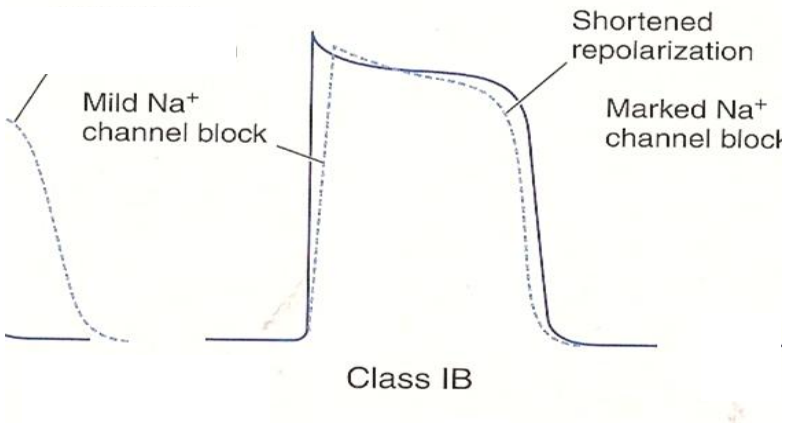
ADVERSE EFFECTS

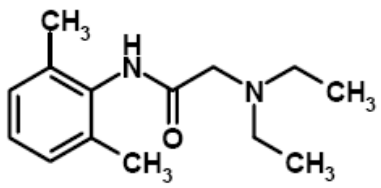
Different from qunidine's in that disopyramide is not an alpha-adrenergic receptor blocker but is anti-vagal. Dry mouth, urinary hesitancy, blurred vision, nausea. QT interval prolongation (ECG) with potential paradoxical ventricular tachycardia (quinidine-like). Can cause torsades de pointes, a ventricular arrhythmia

CLASS Ib – Sodium Channel Blockers

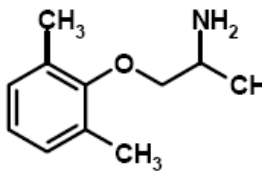
The drugs of the Ib class, in addition to their effect on the sodium voltage-gated channels, ***accelerate cellular repolarization by increasing potassium efflux,*** and ***decrease the duration of the action potential and the refractory period.*** Type Ib agents exhibit rapid association and dissociation from the ***NA channel in the inactivated state***

Class Ib

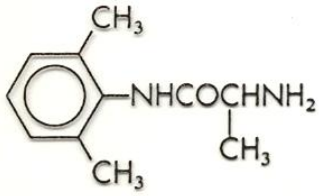




LIDOCAINE



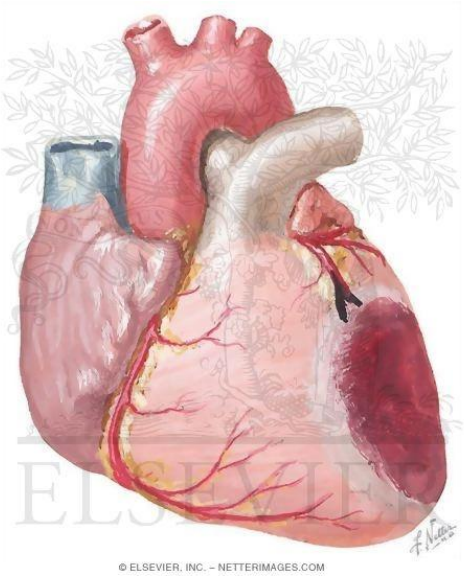
MEXILETINE



TOCAINIDE

CLASS Ib – Sodium Channel Blockers

RATIONALE FOR THEIR USE in POST-ISCHEMIC HEART



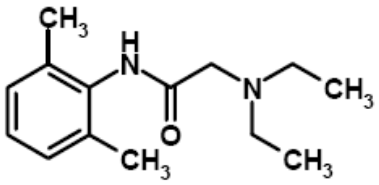
Hypoxic tissues lack ATP to operate the Na/K ATPase pump. So without this pump the cell cannot reset the membrane potential back to normal or does it very slowly compared to normal cells hence the hypoxic cells stay longer in the refractory state.

During diastole, in ischemic tissue, the membrane potential does not return to normal resting levels but remains partially depolarized and class Ib drugs remain bound (higher affinity, longer time constant for unblocking that at less negative resting potentials).

Therefore, these drugs are more effective in suppressing activity in depolarized, arrhythmogenic cardiac tissue but have little effect on normal cardiac tissue.

For this effect, they may reduce incidence of ventricular fibrillation during the initial time frame following acute myocardial infarction.

Class Ib



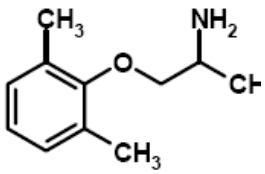
LIDOCAINE

PHARMACOKINETICS

LIDOCAINE is a local anesthetic administered by i.v. for therapy of ventricular arrhythmias. Extensive first-pass effect requires IV administration. Half-life: two hours. Hepatic Metabolism

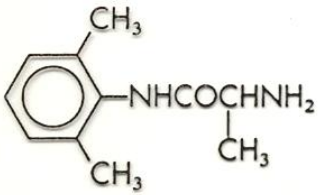
ADVERSE EFFECTS

Major side effect – neurological. Large doses, rapidly administered can result in seizure. Factors that reduce seizure threshold for lidocaine include hypoxemia, hyperkalemia, acidosis. Otherwise: CNS depression, apnea.



MEXILETINE

MEXILETINE is an analog of lidocaine, but with reduced first-pass metabolism. Suitable for oral administration



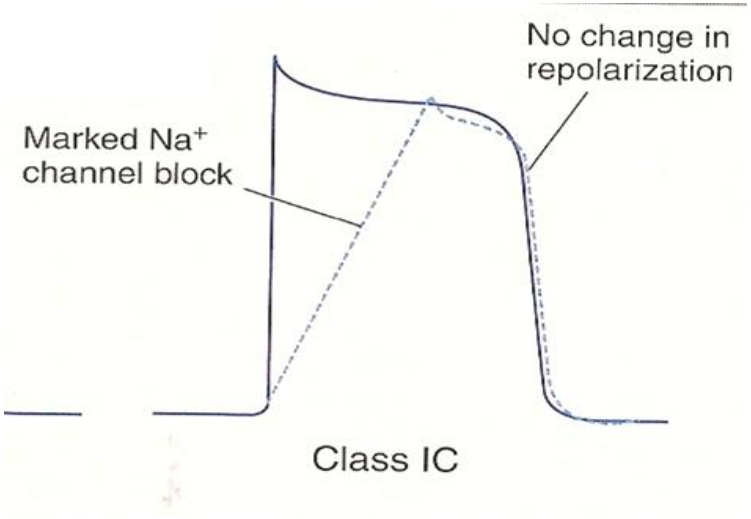
TOCAINIDE

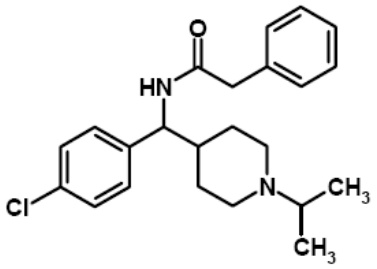
TOCAINIDE is similar to mexiletine. Suitable for oral administration, but RARELY USED due to possibly fatal bone marrow aplasia and pulmonary fibrosis. Tremor and nausea are major dose-related adverse side effects

CLASS Ic – Sodium Channel Blockers

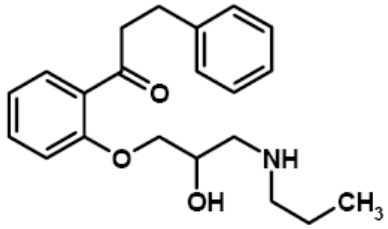
Type Ic drugs slowly dissociate from resting sodium channels. They **prolong the depolarisation phase**, have little effect on the repolarization phase, overall **reducing duration of action potentials**

Class Ic

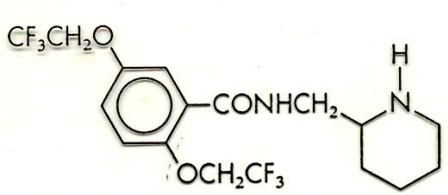




LORCAINIDE

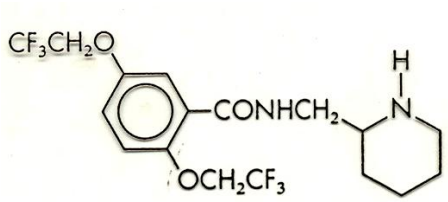


PROPAFENONE



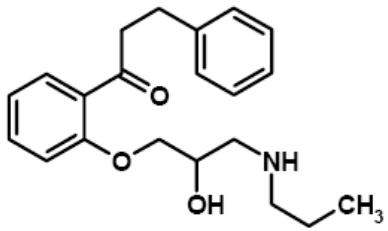
FLECAINIDE

PHARMACOKINETICS



FLECAINIDE

FLECAINIDE is a fluorinated local anesthetic analog of procainamide more effective than quinidine or disopyramide in suppressing ventricular tachycardia and ventricular premature contractions.
Oral absorption: excellent
Long elimination half-time (approximately 20 hours)
25% flecainide: excreted unchanged (kidneys)
Hepatic metabolism: weakly active metabolites



PROPAFENONE

PROPAFENONE can be administered as immediate release or sustained release formulation.
It reaches peak plasma levels in 2-3 hours, with half-life of 12-24 hours.

ADVERSE EFFECTS

They include nausea, constipation, dizziness and ataxia.

CLASS I – Sodium Channel Blockers

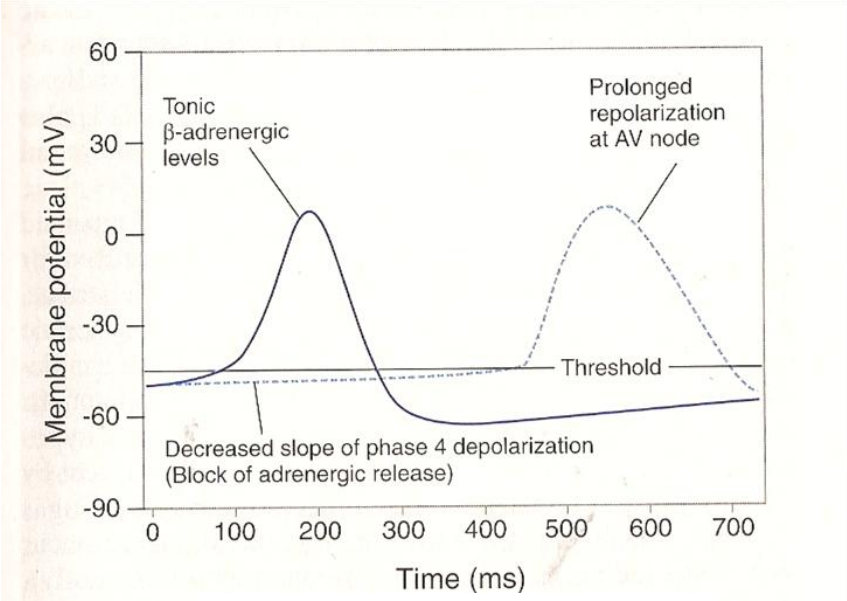
CLASS IA: **ATRIAL FIBRILLATION, FLUTTER; SUPRAVENTRICULAR & VENTRICULAR TACHYARRHYTHMIAS**		
QUINIDINE*	anticholinergic (moderate)	cinchonism (blurred vision, tinnitus, headache, psychosis); cramping and nausea; enhances digitalis toxicity
PROCAINAMIDE	anticholinergic (weak); relatively short half-life	lupus-like syndrome in 25-30% of patients
DISOPRYAMIDE	anticholinergic (strong)	negative inotropic effect
CLASS IB: **VENTRICULAR TACHYARRHYTHMIAS (VT)**		
LIDOCAINE*	IV only; VT and PVCs	good efficacy in ischemic myocardium
TOCAINIDE	orally active lidocaine analog	can cause pulmonary fibrosis
MEXILETINE	orally active lidocaine analog	good efficacy in ischemic myocardium
CLASS IC: **LIFE-THREATENING SUPRAVENTRICULAR (SVT) & VENTRICULAR TACHYARRHYTHMIAS (VT)**		
FLECAINIDE*	SVT	can induce life-threatening VT
PROPAFENONE	SVT & VT;	β-blocking and Ca^{++}-channel blocking activity can worsen heart failure
MORICIZINE	VT; IB activity	

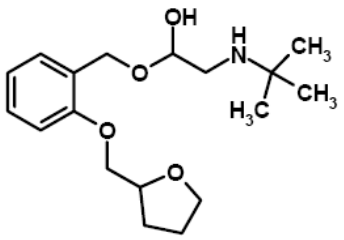
* prototypical drug

CLASS II – BETA ADRENERGIC RECEPTOR BLOCKERS

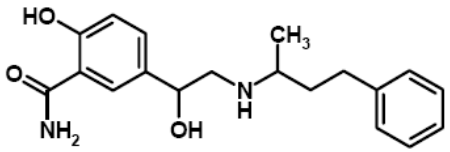
They depress phase 4 spontaneous depolarization (expecially at ***SA nodus***) and prolong repolarization (expecially at ***AV nodus***).

They produce both negative inotropic and chronotropic effects. They are particularly effective in catecholamine-induced cardiac stimulation

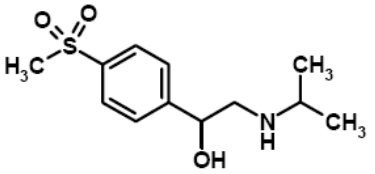




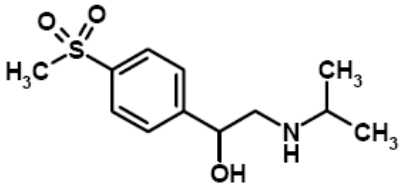
BUFETOLOL



LABETALOL



SOTALOL



SOTALOL

PHARMACOKINETICS

• **SOTALOL** is a racemic compound. While both D and L sotalol act as potassium channel blockers, the L-sotalol displays β-blocking activity. Due to its dual action, it is often used preferentially to other beta blockers as treatment for both ventricular fibrillation and ventricular tachycardia.

Since sotalol is removed from the body through the kidneys, it should not be used in people with a creatinine clearance rate below 40 mL/min. It is also excreted in breast milk, so mothers should not breastfeed while taking sotalol.

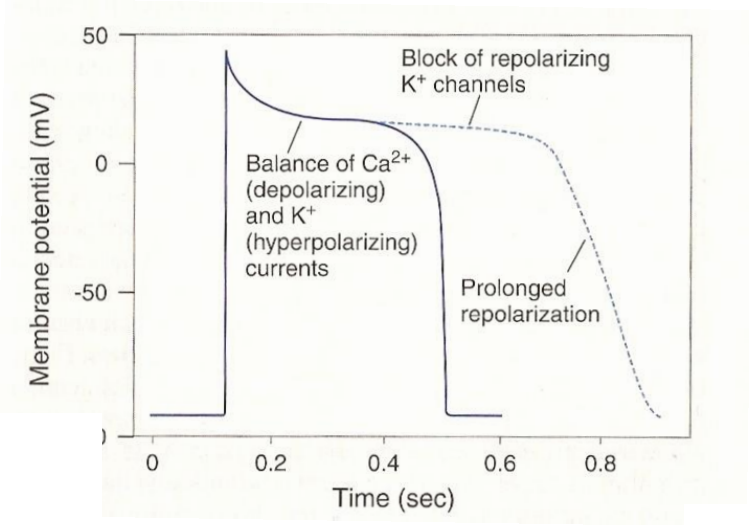
ADVERSE EFFECTS

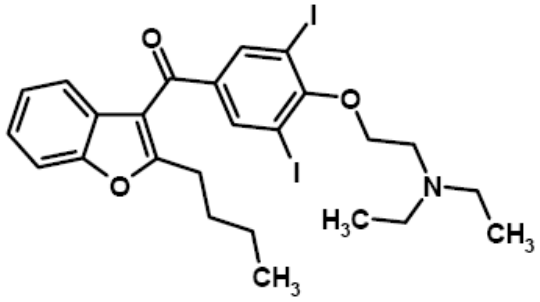
Most common side effects include **fatigue, dizziness, lightheadedness, headache, weakness, nausea, shortness of breath, bradycardia, palpitations, or chest pain**. Risk for all of these effects increases with dosage.

In rare cases, the QT prolongation caused by sotalol can lead to the development of life-threatening **torsade de pointes (TdP)** ventricular tachycardia.

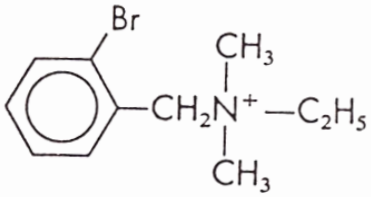
CLASS III – POTASSIUM CHANNEL BLOCKERS

By ***reducing amplitude of repolarizing K currents*** during phase II, they ***prolong ventricular action potential***. Since these drugs do not affect the sodium channel, conduction velocity is not decreased. The prolongation of the action potential duration and refractory period, combined with the maintenance of normal conduction velocity, prevent re-entrant arrhythmias.

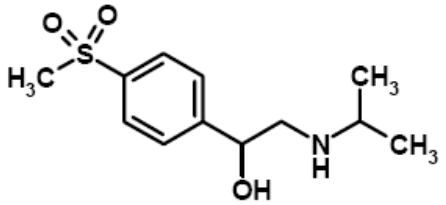




AMIODARONE

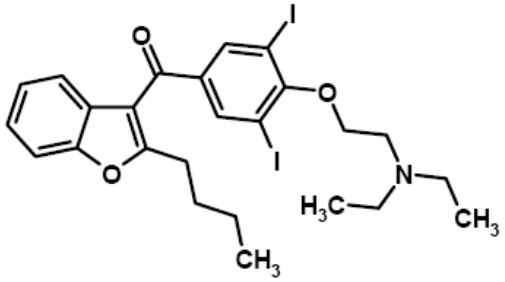


BRETILIUM



SOTALOL

AMIODARONE



•**AMIODARONE** is categorized as a class III antiarrhythmic agent, but it has numerous other effects however, including actions that are similar to those of antiarrhythmic classes Ia, II, and IV.
In addition, amiodarone resembles thyroid hormone, and its binding to the nuclear thyroid receptor might contribute to some of its pharmacologic and toxic actions

PHARMACOKINETICS

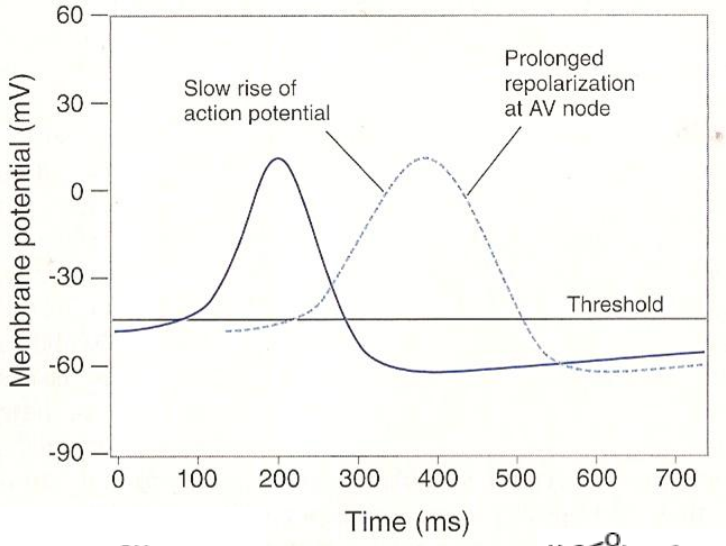
• Amiodarone takes weeks to achieve its maximum effectiveness. This is because it is stored in most of the tissues of the body, and to "load" the body with the drug, all the tissues need to be saturated.
• Amiodarone leaves the body very, very slowly. It is not excreted by the liver or the kidneys, but it is lost when amiodarone-containing human cells are lost. Thus, the "half life" of the drug, in contrast to most other drugs, is measured in weeks.
•Because amiodarone is stored in many different kinds of tissues, it can produce side effects affecting many different organs. In addition, some of these side effects take months or years to develop.

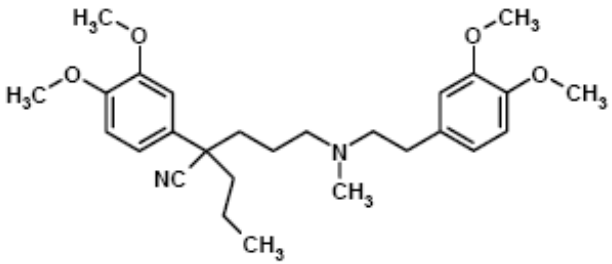
ADVERSE EFFECTS

LUNG - the most serious reaction is interstitial lung disease.
THYROID (hypo-hyperthyroidism) both under- and overactivity of the thyroid may occur.
EYE (optic neuritis-corneal deposits) Corneal micro-deposits are almost universally present in patients taking amiodarone for at least 6 months. These deposits typically do not cause any symptoms.
GI AND LIVER Abnormal liver enzyme common. Much rarer jaundice, hepatomegaly and hepatitis.
SKIN necrosis. More common discoloration
CARDIOVASCULAR - Thrombophlebitis of peripheral vein is a well recognised complication of intravenous amiodarone use in high doses (300–1200 mg) or prolonged infusion

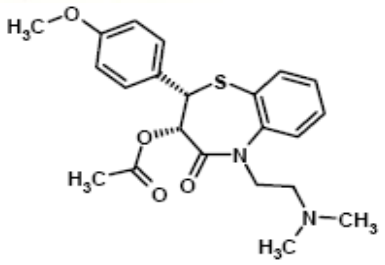
CLASS IV – CALCIUM CHANNEL BLOCKERS

Their antiarrhythmic properties are related to the ability to decrease the firing rate of aberrant pacemaker sites within the heart, and to their ability to **decrease conduction through the AV node**, and **shorten phase II** (the plateau) of the cardiac action potential. This action at the atrioventricular node helps to block reentry mechanisms, which can cause supraventricular tachycardia.

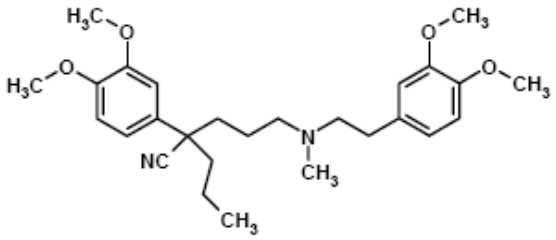




VERAPAMIL



DILTIAZEM



VERAPAMIL

Verapamil blocks both activated and inactivated L-type calcium channels. AV nodal conduction time and effective refractory period are prolonged. Slows the SA node by its direct action Extracardiac Effects. Peripheral vasodilation (Less than nifedipine)

PHARMACOKINETICS

Absorbed orally. It is extensively metabolized by the liver. Excreted by kidneys.

ADVERSE EFFECTS

Verapamil and diltiazem have negative inotropic properties and, therefore, may be contraindicated in patients with preexisting depressed cardiac function.
Both drugs can also produce a decrease in blood pressure because of peripheral vasodilation an effect that is actually beneficial in treating hypertension.
Other side effects – Constipation, dizziness, headache, nausea, hypotension, and peripheral edema

CONTRAINDICATIONS

Sick sinus syndrome, 2nd or 3rd degree heart block, and hypotension. Digoxin & verapamil are contraindicated in the **Wolf Parkinson White Syndrome** (WPW), an abnormal band of atrial tissue connecting the atria and ventricles that can electrically bypass the normal pathways of conduction; a re-entry circuit can develop causing paroxysms of tachycardia.

SUMMARY - MAIN PK FEATURES OF ANTIARRHYTHMIC DRUGS

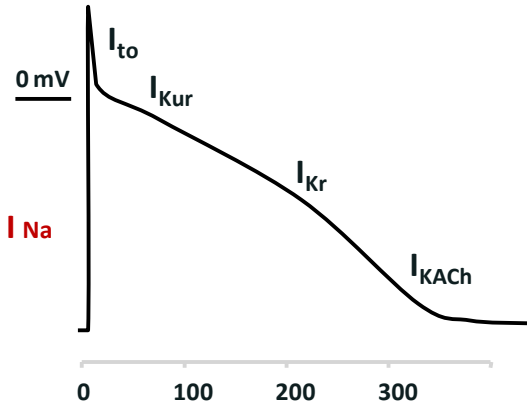
	BIO (%)	PP binding (%)	T½ (h)	Interv. Therap. Range (mg/ml)	Elimination route
PROCAINAMIDE 1A	90-95	15-20	3-5	4-12	Liver/kidney
DISOPIRAMIDE 1A	85	Variab	4-8	2-5	Liver/kidney
QUINIDINE 1A	70-85	70-95	6-8	2-5	Liver
LIDOCAINE 1B	-	50-80	1-4	1.5-5	Liver
TOCAINIDE 1B	>90	10-50	11	5-12	Liver/kidney
PROPAFENONE 1C	5-50	95	2-4	0.2-1.0	Liver
FLECAINIDE 1C	95	30-40	12-27	0.2-1.0	Liver/kidney
SOTALOL 3	100	0	7-18	2.5	Kidney
AMIODARONE 3	35-65	96	30-100 DAYS	1-2.5	ALL TISSUES

NEWER ANTIARRHYTHMIC DRUGS

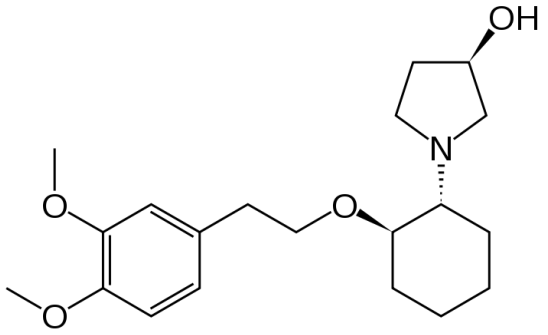
VERNAKALANT

Vernakalant is an atrial-selective, multiple ion channel blocker being investigated for use in AF. It acts as an atrial repolarization-delaying agent with its major target I Kur, but also blocks I to and INa, although there is little effect on I Kr or Iks. As I kur is present in higher density in the atria, vernakalant is relatively atrial selective.

Vernakalant infusion dose-dependently prolongs atrial ERP but has no significant effect on ventricular ERP or QT interval The I Na inhibition is rate- and voltage-dependent. Vernakalant has, therefore, a much greater effect in fibrillating atria than in the ventricle and is less likely to be proarrhythmic. Most common side effects are hypotension , dysgeusia, sneezing, paresthesias, nausea.



Current	IC_{50} (μM)
I_{to}	5-30
I_{Kur}	3-13
I_{KACh}	10
I_{Kr}	7-21
I_{Ks}	> 100
I_{K1}	> 100



VERNAKALANT

Fedida et al. J Cardiovasc Electrophysiol 2005

VERNAKALANT CLINICAL STUDIES IN ATRIAL FIBRILLATION

Vernakalant Hydrochloride for Rapid Conversion of Atrial Fibrillation

A Phase 3, Randomized, Placebo-Controlled Trial

Denis Roy, MD; Craig M. Pratt, MD; Christian Torp-Pedersen, MD; D. George Wyse, MD, PhD; Egon Toft, MD; Steen Juul-Moller, MD; Tonny Nielsen, MD; S. Lind Rasmussen, MD; Ian G. Stiell, MD; Benoit Coutu, MD; John H. Ip, MD; Edward L.C. Pritchett, MD; A. John Camm, MD; for the Atrial Arrhythmia Conversion Trial Investigators

Circulation. 2008; 117:1518

Usefulness of Vernakalant Hydrochloride Injection for Rapid Conversion of Atrial Fibrillation

Craig M. Pratt, MD[a,*], Denis Roy, MD[b], Christian Torp-Pedersen, MD[c], D. George Wyse, MD, PhD[d], Egon Toft, MD[e], Steen Juul-Moller, MD[f], Enrique Retyk, MD[g], and David Humphrey Drenning, MD[h]; Atrial Arrhythmia Conversion Trial (ACT-III) Investigators[i]

(Am J Cardiol 2010;106:1277–1283)

Electrophysiology

A multicenter, open-label study of vernakalant for the conversion of atrial fibrillation to sinus rhythm

Ian G. Stiell, MD,[a] Johan S. Roos, MD,[b] Katherine M. Kavanagh, MD,[c] and Garth Dickinson, MD[a,d]
Ottawa, Calgary and Vancouver, Canada; and Somerset West, South Africa

Am Heart J 2010;159:1095-101.

DRONEDARONE/CELIVARONE/BUDIODARONE

Noniodinated benzofuran derivatives with effects similar to amiodarone

DRONEDARONE:

Rate-dependent inhibition of the rapid Na+ current (class I), α- and β-adrenergic receptor inhibition (class II), blockade of K+ outward currents as the main mechanism of action (class III), and blockade of slow Ca2+ inward currents (class IV)

BUDIODARONE:

Unlike dronedarone, budiodarone retains 2 iodine atoms in its molecular structure. It has electrophysiological properties similar to amiodarone and has a shorter half-life .Ester modification of the compound changes its metabolic pathways such that budiodarone undergoes rapid degradation by plasma and tissue esterases to an inactive compound.

There are as yet no published data on long-term exposure to budiodarone, so its potential for chronic toxicity is unknown

DRONEDARONE : SIDE EFFECTS

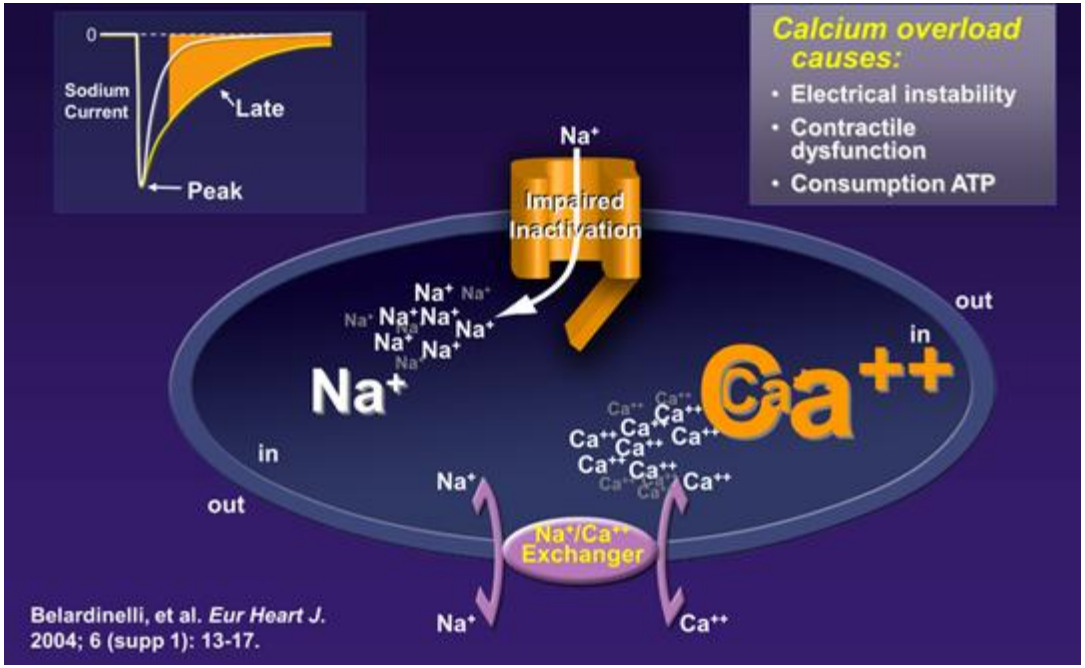
Table 2 Side effects of dronedarone*

Adverse effects	Percentage reported
Diarrhea	9%
Nausea	5%
Rash	5%
Bradycardia	3%
Laboratory/ECG effects	
QT prolongation	28%
Serum creatinine increase	51%

Notes: *These data are based on a 400 mg twice daily dose of dronedarone in ATHENA, EURIDES, ADONIS, ERATO, and DAFNE studies.[13–15,18]

RANOLAZINE

Ranolazine inhibits persistent or late ***inward sodium current (I_{Na})*** in heart muscle in a variety of voltage-gated sodium channels.



Inhibiting this current leads to ***reductions in elevated intracellular calcium levels.*** This in turn leads to reduced tension in the heart wall, leading to reduced oxygen requirements for the muscle.

The QT prolongation effect of ranolazine on the surface electrocardiogram is the result of inhibition of I_{Kr}, which prolongs the ventricular action potential.

RANOLAZINE AS POTENTIAL ANTIDYSRHYTHMIC DRUG

Table 2. Rate of Tachyarrhythmias Detected on cECG Monitoring After Non–ST-Segment Elevation MI

	Ranolazine, n (%)	Placebo, n (%)	RR (95% CI)	*P*
Ventricular arrhythmias				
VT ≥3 beats ≥100 bpm	1646 (52.1)	1933 (60.6)	0.86 (0.82, 0.90)	<0.001
VT ≥4 beats ≥100 bpm	662 (20.9)	941 (29.5)	0.71 (0.6, 0.78)	<0.001
VT ≥8 beats (lasting <30 s)	166 (5.3)	265 (8.3)	0.63 (0.52, 0.76)	<0.001
Polymorphic VT ≥8 beats	38 (1.2)	46 (1.4)	0.83 (0.54, 1.28)	0.40
Sustained VT (≥30 s)	14 (0.44)	14 (0.44)	1.01 (0.48, 2.13)	0.98
Monomorphic	4 (0.13)	7 (0.22)	0.59 (0.17, 2.06)	0.37
Polymorphic	10 (0.32)	7 (0.22)	1.41 (0.52, 3.78)	0.46
Supraventricular arrhythmias				
New-onset atrial fibrillation	55 (1.7)	75 (2.4)	0.74 (0.52, 1.05)	0.08
Other SVT ≥120 bpm lasting at least 4 beats	1413 (44.7)	1752 (55.0)	0.81 (0.77, 0.85)	<0.001