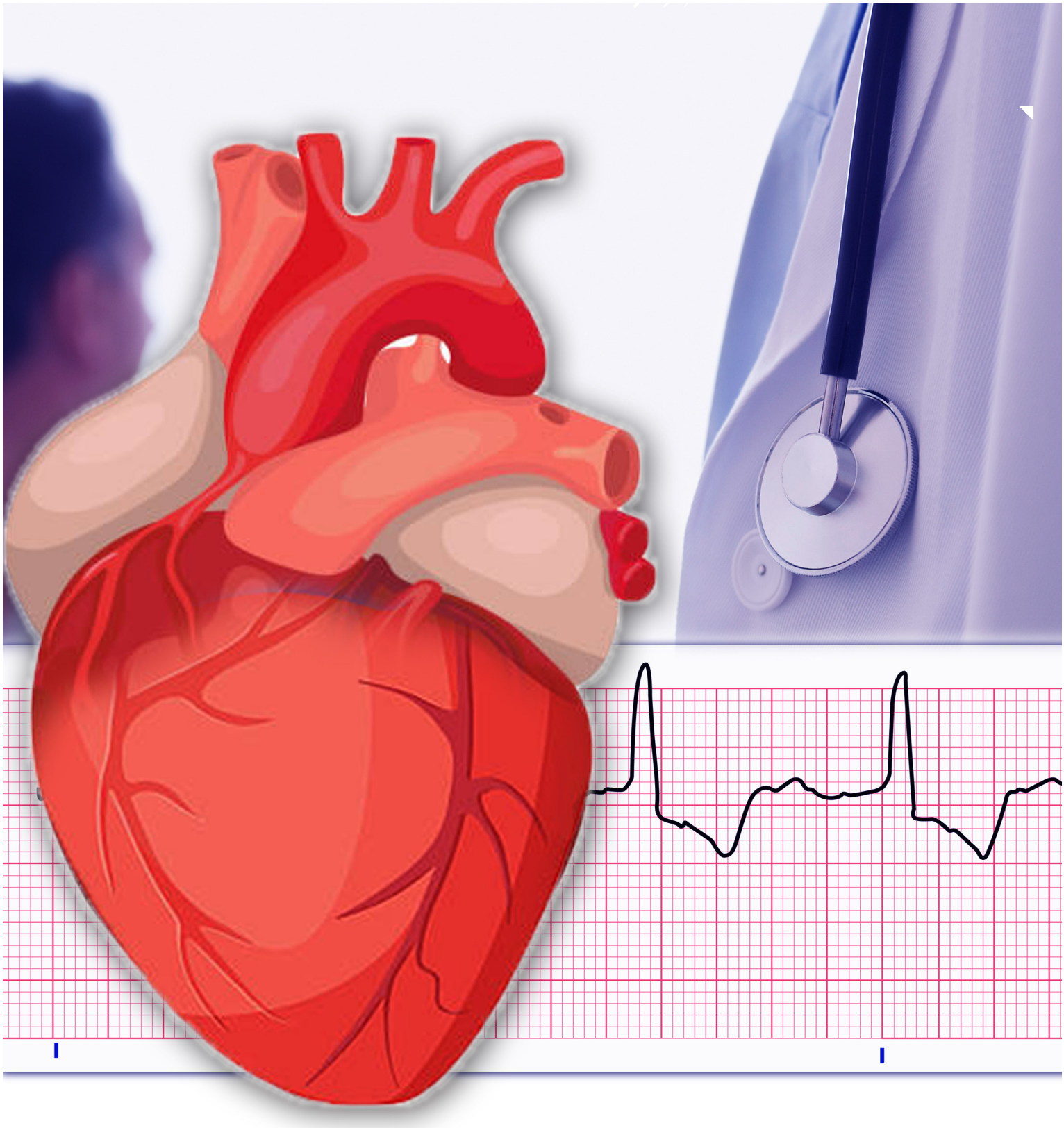
# ANTIARRHYTHMIC AGENTS :

## Overview



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# Antiarrhythmic Agents - Overview

**ANCC Accredited NCPD Hours: 2 hrs**

**Target Audience: RN/APRN**

## Need Assessment

Cardiac arrhythmias constitute a major public health problem. Pharmacological intervention remains mainstay to their clinical management. Most antiarrhythmic drugs are potent compounds with a relatively narrow therapeutic index. When prescribed judiciously, they can have a key role in enhancing or prolonging the lives of patients with most common arrhythmias. Ultimately the optimal use of antiarrhythmic drug therapy depends in large part on understanding the pharmacodynamics and pharmacokinetics of each antiarrhythmic drug. Numerous antiarrhythmic drugs are available, each of which has a unique pharmacological profile. Understanding the different pharmacodynamic properties of these drugs is important to predict the antiarrhythmic effects in a patient.

## Objectives

- Describe the mechanism of arrhythmogenesis
- Identify two limitations for current antiarrhythmic therapy for ventricular tachycardia
- Describe the action of beta blockers as antiarrhythmics
- Discuss the action of amiodarone
- Understand the action of Class I antiarrhythmic agents

## Goal

The goal of this article is to assess the impact of various antiarrhythmic agents and emerging pharmacotherapy for arrhythmia

## Introduction

Ventricular arrhythmias, including ventricular fibrillation (VF) and sustained ventricular tachycardia (VT), are the principal causes of sudden cardiac death in patients with structural heart disease. While coronary artery disease is the predominant substrate associated with the development of ventricular tachycardia, these arrhythmias are known to occur in a variety of disorders, including dilated cardiomyopathy, valvular and congenital heart disease and cardiac ion channelopathies such as the long QT syndrome. In a minority of patients, ventricular tachycardia occurs in the absence of structural heart disease. Despite the established mortality benefit of the implantable cardioverter defibrillator (ICD) in patients at risk of lethal arrhythmias, recurrent ventricular tachycardia/ ventricular fibrillation events continue to be a source of morbidity and impaired quality of life in such patients.

Antiarrythmic agents, also known as cardiac dysrhythmia medications, are a group of drugs that suppress abnormal rhythms of the heart. Antiarrhythmic therapy is indicated in selected patients to treat symptomatic ventricular tachycardia episodes, to reduce the incidence of implantable cardioverter defibrillator shocks and potentially to improve quality of life and reduce hospitalizations related to cardiac arrhythmia. The ultimate goal of antiarrhythmic drug therapy is to restore normal rhythm and conduction. Antiarrhythmic drugs are used to:

- Decrease or increase conduction velocity
- Alter the excitability of cardiac cells by changing the duration of the effective refractory period
- Suppress abnormal automaticity

All antiarrhythmic drugs directly or indirectly alter membrane ion conductance, which in turn alters the physical characteristics of cardiac action potentials. The primary adverse effects of antiarrhythmic medications are related to both cardiac and extracardiac toxicity, including the risk of proarrhythmia. [1, Rank 4]

## Indications of antiarrhythmic therapy

Cardiac arrhythmias are a frequent problem in clinical practice. Not all arrhythmias require treatment with potentially toxic antiarrhythmic drugs. Arrhythmias that typically require treatment fall into 3 basic categories (as shown in figure 1):

- Arrhythmias that decrease cardiac output (e.g. severe bradycardia, ventricular tachycardia or fibrillation)
- Arrhythmias that are likely to precipi-

tate more serious arrhythmias (e.g. atrial flutter may lead to sustained ventricular tachycardia)

➤ Arrhythmias that are likely to precipitate an embolism due to creation of vascular stasis (e.g.chronic atrial fibrillation)

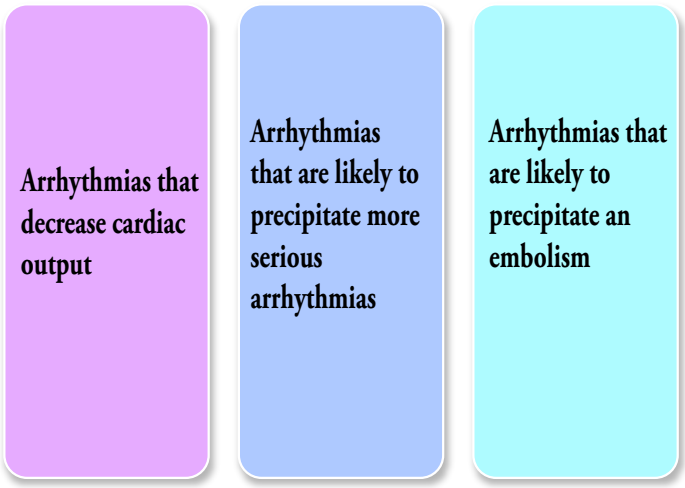


Figure 1: Indications of antiarrhythmic therapy

## Mechanisms of Arrhythmogenesis

Ventricular arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF), are the leading cause of sudden cardiac death (SCD), which in turn represents about half of all cardiovascular mortality and accounts for over 350,000 deaths annually in the United States. Ventricular tachycardia can be either sustained (lasting >30 s) or non- sustained and can have a uniform QRS morphology (monomorphic) or a variable morphology (polymorphic). The vast majority of ventricular tachycardia is related to myocardial pathologic processes that promote cardiac fibrosis or inflammation, most commonly from coronary artery disease (CAD) in over 80% of patients. However, myocarditis, dilated cardiomyopathy, congenital heart disease, cardiac infiltrative diseases, arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy are also known to contribute to an arrhythmogenic substrate (as shown in figure 2). In about 10% of patients, ventricular tachycardia occurs in the absence of structural heart disease. This subset of ventricular tachycardia is thought to be either idiopathic or related to primary electrical disease, such as the long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), or other cardiac ion channelopathies. [2, Rank 5]

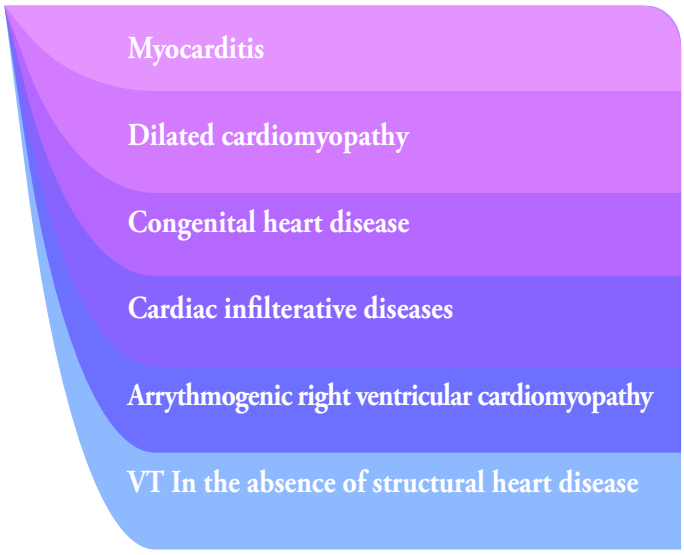


Figure 2: Factors contributing to arrythmogenic substrate

The mechanisms responsible for cardiac arrhythmias are generally divided into (as shown in figure 3)

- Disorders of impulse formation
- Disorders if impulse conduction
- Combinations of both

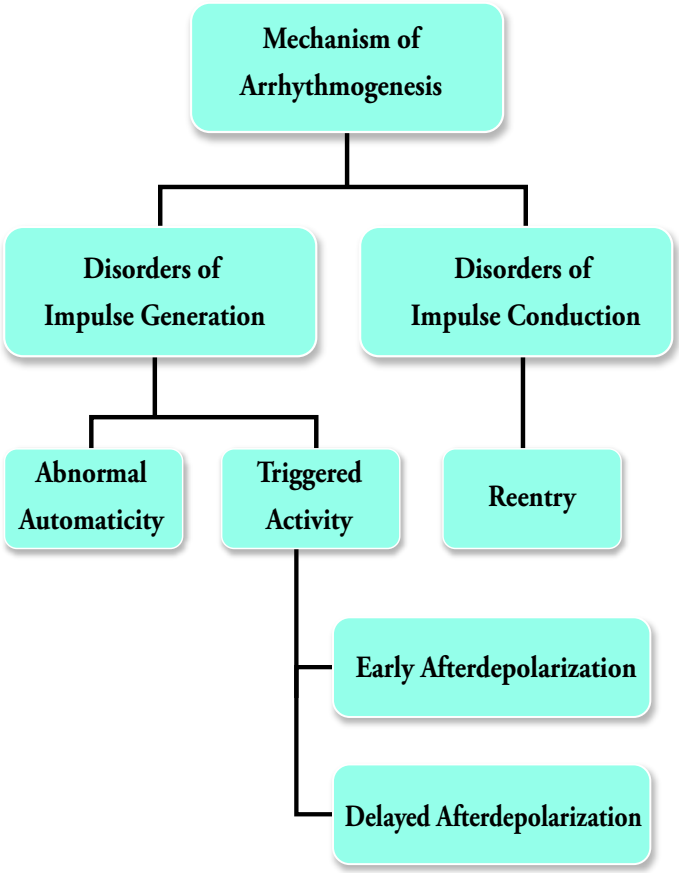


Figure 3: Mechanism of arrhythmogenesis

Disorders of impulse formation can be disorder in automaticity or trigger activity. Automaticity is the property of a fiber to initiate an impulse spontaneously without need for prior stimulation. Triggered activity is initiated by after depolarizations, which are depolarizing oscillations in membrane voltage induced by one or more preceding action potentials. This can be categorized to early after depolarization (EADs) and late or delayed after-depolarization's (DADs). Disorder of impulse conduction can be conduction block or re-entry. Re-entrant rhythms include (as shown in figure 4)

- Atrioventricular nodal re-entrant tachycardia(AVNRT)
- Atrioventricular re-entrant tachycardia (AVRT)
- Atrial flutter
- Atrial fibrillation
- Ventricular tachycardia

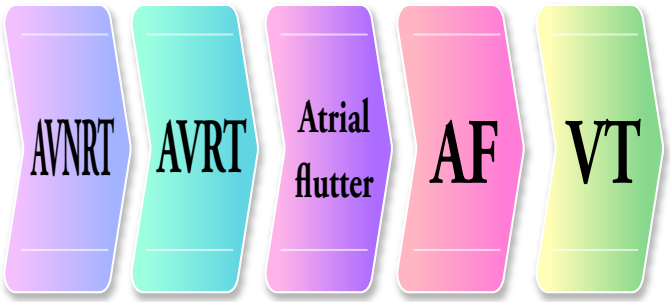


Figure 4: Re-entrant rhythms

Atrial fibrillation occurs when structural and/or electrophysiological abnormalities alter atrial tissue to promote abnormal impulse formation and /or propagation (as shown in figure 5).

The only intervention demonstrated to improve survival in patients at risk of sudden cardiac death from ventricular arrhythmias is the implantable cardioverter defibrillator (ICD). It is indicated for secondary prevention in patients with a history

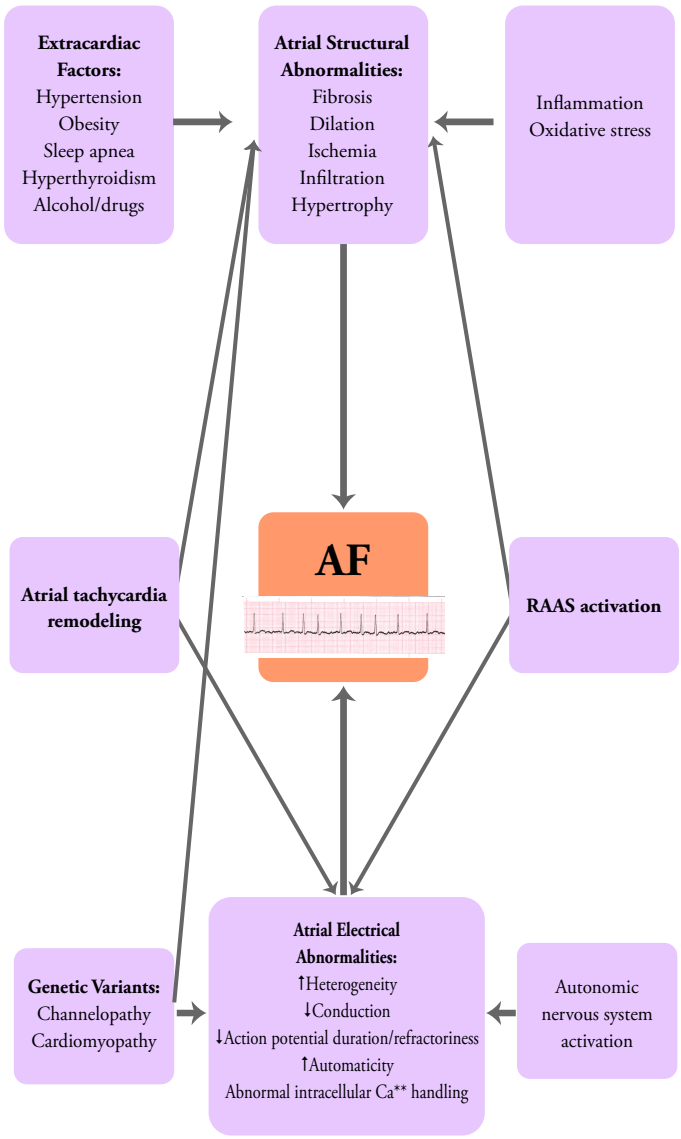


Figure 5: Mechanism of AF

of sustained ventricular tachycardia/ ventricular fibrillation and for primary prevention in patients with a history of heart failure or previous myocardial infarction and left ventricular ejection fraction (LVEF) of 35% or less. There are several limitations, however, with the implantable cardioverter defibrillator as primary therapy for ventricular tachycardia/ventricular fibrillation.

➤ First, and most important, is that although the implantable cardioverter defibrillator effectively terminates ventricular arrhythmias, it does not prevent them.

➤ Second is the morbidity associated with both appropriate and inappropriate implantable cardioverter defibrillator shocks.

➤ Third, the current selection criteria for implantable cardioverter defibrillator candidacy are imperfect, as many implantable cardioverter defibrillator recipients never receive appropriate implantable cardioverter defibrillator therapy for ventricular tachycardia/ventricular fibrillation, whereas many other patients with left ventricular ejection fraction greater than 35% who are not eligible for the implantable cardioverter defibrillator go on to experience sudden cardiac death.

➤ In addition, the benefit of the implantable cardioverter defibrillator is not established in the early post-myocardial infarction period; despite an increased risk of arrhythmic death in this population, there was no difference in total mortality in patients within 6 and 40 days of acute myocardial infarction treated with the implantable cardioverter defibrillator vs. medical therapy in a randomized trial.

In the Antiarrhythmic Versus Implantable Defibrillator (AVID) trial of secondary prevention implantable cardioverter

defibrillator therapy, the 1-year arrhythmia event rate was 90% in the implantable cardioverter defibrillator arm and was reduced to 64% with concurrent antiarrhythmic therapy. Overall, up to 70% of patients with an implantable cardioverter defibrillator receive adjuvant antiarrhythmic drug therapy, even though there is no medication formally approved for this indication.

The indications for adjunctive antiarrhythmic therapy are (as shown in figure 6):

- To reduce the incidence of appropriate and inappropriate implantable cardioverter defibrillator shocks
- To slow the rate of spontaneous ventricular tachycardia episodes to improve their hemodynamic tolerance
- To facilitate pace termination by the implantable cardioverter defibrillator

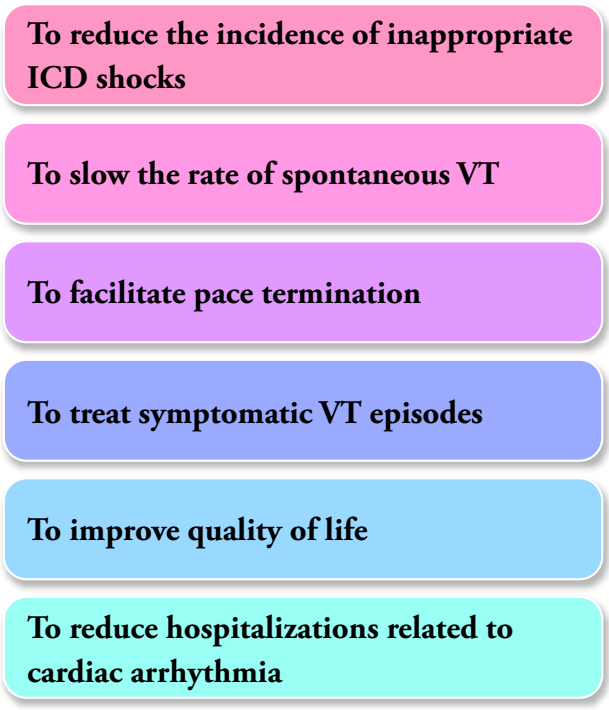


Figure 6: Indications of adjunctive antiarrhythmic therapy

- To treat symptomatic ventricular tachycardia episodes
- To improve quality of life
- Potentially to reduce hospitalizations related to cardiac arrhythmia. [4, rank 4]

Current antiarrhythmic therapy for ventricular tachycardia is limited by its potential for both cardiac and extracardiac toxicity, including the risk of proarrhythmia and by its limited efficacy (as shown in figure 7).


Figure 7: Limitations of antiarrhythmic therapy

In the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial, amiodarone and sotalol were each significantly more effective in preventing implantable cardioverter defibrillator shocks compared to beta-blockers alone, but 1-year shock rates were still 10% in the amiodarone arm and 24% in the sotalol arm, with drug-related adverse effects leading to discontinuation in one in five patients. No new antiarrhythmic agents have yet been approved for the treatment

for ventricular tachycardia in the past decade; however, novel concepts in the understanding of ventricular arrhythmogenesis have the potential to deliver new therapeutic targets for ventricular tachycardia that balance antiarrhythmic efficacy against the risks of organ toxicity, negative inotropy and proarrhythmic effects seen with contemporary drug therapy. Several clinical trials have evaluated the efficacy and safety of various antiarrhythmic medications used for the treatment of ventricular tachycardia in patients with established cardiovascular disease. [5, Rank 4]

## Mechanisms of Arrhythmogenesis

## Classification of Antiarrhythmic Agents

| | | | |
|---|---|---|---|
| Class I agents | Sodium channel blocker | Class IA | Quinidine Procainamide Dispyramide |
| | | Class IB | Lidocaine Mexiletine |
| | | Class IC | Flecainide Propafenone |
| Class II agents | Adrenergic receptor blockers | | Propranolol Metoprolol Carvedilol |
| Class III agents | Potassium channel blockers | | Amiodarone Satalol Dofetilide Dronedarone |
| Class IV agents | Calcium channel blockers | | Verapamil |
| Other antiarrhythmics | | | Adenosine Digoxin Dronedarone |

Table 1: Vaughan Williams classification

The most common classification scheme for antiarrhythmic agents is the Vaughan Williams classification (as shown in table 1), which characterizes drugs based on their ability to block specific ion currents or cell receptors.

### *Class I agents*

Class I agents are sodium channel blockers, further divided into (as shown in figure 8) Class IA (quinidine, procainamide and disopyramide). It is the largest class of antiarrhyhmic drugs. Class I antiarrhythmic drugs acts by blocking voltage sensitive sodium channels. These drugs bind to sodium channels when the channels are open and in activated state and dissociate when the channels are in resting phase. Inhibition of sodium channel decrease rate of rise of phase 0 of cardiac membrane action potential and slows down conduction velocity.

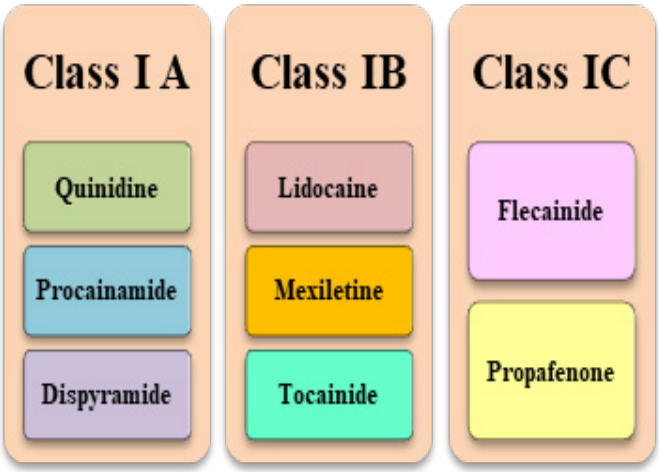


Figure 8: Class I antiarrhythmic agents

Class IB (lidocaine, mexiletine): These drugs have minimal effect on rate of depolarization. These drugs interact with sodium channels in both the open and inactivated state.

Class IC (flecainide, propafenone): These drugs are very potent blockers of open sodium channels and dissociate very slowly and incompletely from sodium channels in between heart beats.

The Cardiac Arrhythmia Suppression Trial (CAST) compared Class IC agents to placebo in post-myocardial infarction patients with impaired left ventricular ejection fraction (40% or less) for the suppression of ventricular ectopy and was terminated prematurely due to excess mortality in the antiarrhythmic arm. Both all-cause mortality and arrhythmic death were increased with both encainide and flecainide treatment. As such, Class IC antiarrhythmic agents are no longer recommended therapy for patients with ischemic heart disease or left ventricular dysfunction from any cause. Conversely, the risk of ventricular proarrhythmia with Class IC agents in the absence of structural heart disease is low; however, in patients with atrial arrhythmias, flecainide or propafenone may promote 1:1 atrioventricular nodal conduction with acceleration of the ventricular rate and a wide QRS tachycardia.

**Procainamide**

- **Most atrial and ventricular arrhythmias in patients without a history of ischemic heart disease**
- **2 nd drug of choice for treatment of sustained ventricular arrhythmias following MI ( amiodarone or lignocaine are preferred)**

**Lidocaine**

- **2 nd drug of choice to terminate VTach and prevent VFib after DC conversion**

**Flecainide / Propafenone Lidocaine**

- **Supraventricular arrhythmias in patients without a history of ischemic heart disease.**

Figure 9: Clinical indications of class I drugs

Earlier studies that examined Class I agents for secondary ventricular tachycardia / ventricular fibrillation prevention in post-myocardial infarction patients showed they were inferior in efficacy to both amiodarone and sotalol. The most commonly used Class I agent in this setting is mexiletine, used in 20% of patients who received adjuvant antiarrhythmic treatment in the implantable cardioverter defibrillator arm of the AVID trial. As a Class IB antiarrhythmic agent, it does not seem to carry the increased mortality risk associated with the Class IC drugs, based on observational

data with the Class IB drug lidocaine from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I and GUSTO-IIb) trials. [12, Rank 2]

Quinidine, procainamide, and disopyramide are Class IA antiarrhythmic agents that have intermediate sodium channel blocker activity (compared to Class IC agents) and also prolong action potential duration via potassium channel blockade. They are indicated in the treatment of supraventricular arrhythmias and ventricular tachycardia (as shown in figure 9).

While the lower efficacy and poor tolerability of the Class I agents has relegated them to third-line therapy for the prevention and treatment of ventricular arrhythmia, there is evidence that combination therapy with a Class I and a Class III agent may be more effective than monotherapy with either agent [13, Rank 3]

## *Class II agents*

Class II agents are beta-adrenergic receptor blockers, such as propranolol. Beta blockers prevent or terminate tachyarrhythmia's caused by increased sympathetic tone, excessively high levels of circulating plasma catecholamines or tissue super sensitivity to catecholamines. By reducing the effects of catecholamines they may act to:

- Reduce pacemaker automaticity

> **" Beta-blockers are considered first-line therapy for patients with systolic heart failure "**

- Reduce delayed after depolarizations (DAD's)

### Beta-Blockers

Beta-blockers (as shown in figure 10) are considered first-line therapy for patients with systolic heart failure and following acute myocardial infarction for their established survival benefit in these populations. In addition, beta-blockers are indicated in the treatment of certain ion channelopathies, such as congenital long QT syndrome and CPVT. Beta blockers may stop the arrhythmia from occurring, but more often, are useful for slowing down the heart rate

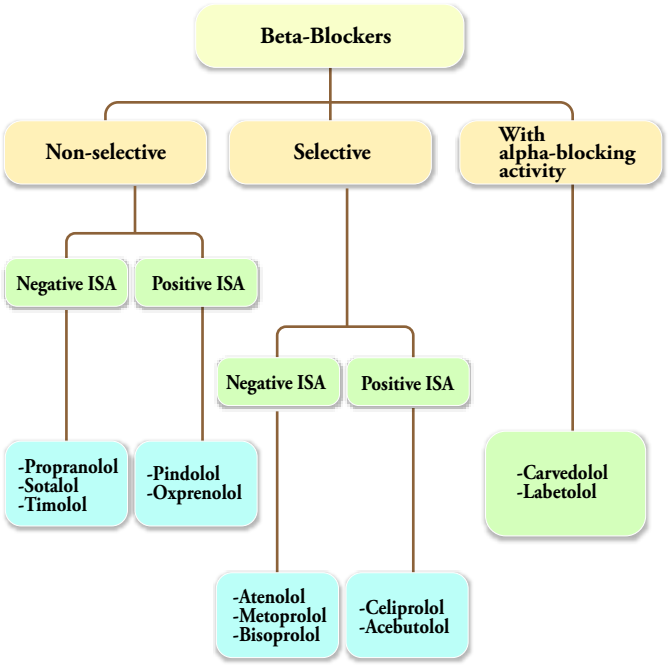


Figure 10: Types of beta blockers

during the arrhythmia without actually terminating it.

In the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), bisoprolol reduced all-cause mortality by 34% and sudden cardiac death by 44% in patients with heart failure. The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) randomly assigned over 45,000 patients to either a combination of intravenous and oral metoprolol or placebo within 24 h of acute myocardial infaction and showed that the use of early beta-blocker therapy reduced the risk of ventricular fibrillation development, although this was counterbalanced by an increase in cardiogenic shock, especially during the first day after admission. Overall, a meta-analysis of beta-blocker studies in post-myocardial infarction patients suggests a significant relative benefit in preventing sudden cardiac death and all-cause mortality. [7, Rank 5]

Beta blockers are indicated in (as shown in figure 11)

- Supraventricular arrhythmias:-sinus tachycardia, supraventricular tachycardias, Wolff-Parkinson-White syndrome (WPW) with orthodromicAVRTs
- Rate control for :- Atrial Flutter, Atrial fibrillation
- Ventricular arrhythmias
- Conditions predisposing towards arrhythmias and sudden cardiac death:- acute myocardial infarction, Long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia

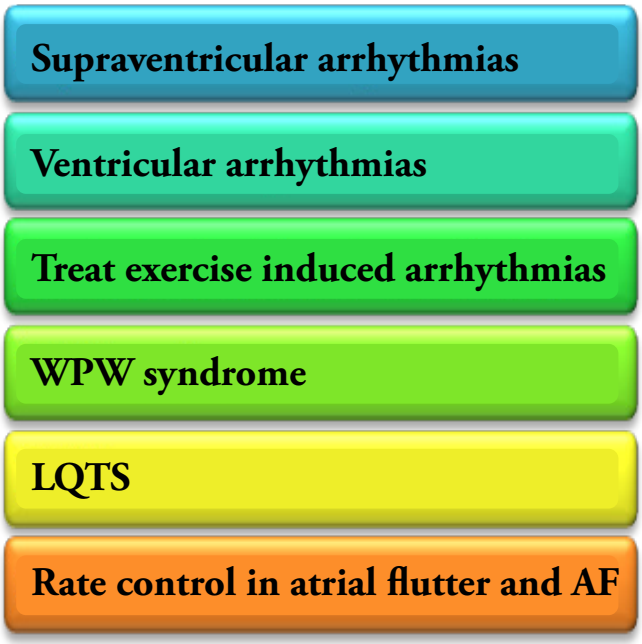


Figure 11: Clinical indication of Class II drugs

## *Class III*

Class III agents are potassium channel blockers (as shown in figure 12), such as amiodarone, sotalol, dofetilide and dronedarone. These drugs bind to and block the potassium channels that are responsible for


Figure 12: Class III Antiarrhythmic drugs

phase 3 depolarization, which leads to an increase in action potential duration and an increase in the effective refractory period.

**Amiodarone**

It is one of the most commonly used drugs for chronic treatments of arrhythmias. It is effective against both ventricular and atrial arrhythmias. Amiodarone has some unusual characteristics including a very long half life of several weeks and a relatively lack of selectivity between multiple antiarrhythmic targets. At therapeutic doses it blocks sodium, potassium and calcium channels, as well as α and β adrenergic receptors. It is in essence a non selective antiarrhythmic shotgun.

Amiodarone has a low risk of proarrhythmia, despite causing prolongation of the action potential duration and QT interval, probably because it reduces heterogeneity of depolarization. Torsade de pointes occurred in less than 1% in the EMIAT and CAMIAT trials. Extra cardiac toxicity (as shown in figure 13), however, is well described, and is related to both a daily and cumulative dose effect of amiodarone. Clinical hypothyroidism occurs in up to 32% of patients and may require thyroxin supplementation even after drug discontinuation. Hyperthyroidism can also occur, but is less common in the western world where dietary iodine intake is adequate. Pulmonary toxicity is less common but is among the most serious adverse drug reactions, presenting as chronic interstitial pneumonitis, bronchiolitis obliterans with organizing pneumonia, or the acute respiratory distress syndrome. Corneal deposits, skin photosensitivity, neuropathy, and gastrointestinal side effects have also been reported. [9, Rank 5]

**"Amiodarone is known to have multichannel blocking properties.**

**Amiadarone shows beta blocker like and potassium channel blocker like actions on the SA and AV nodes, increases the refractory period via sodium and potassium channel effects and slows intra-cardiac conduction of the cardiac action potential via sodium channel effects."**


Figure 13: Side effects of Amiodarone

Sotalol is a potassium channel blocker that prolongs action potential duration and is a Vaughan Williams Class III agent. It is a racemic mixture of D-sotalol, which has pure Class III antiarrhythmic activity and L-sotalol, which has Class III and beta-blocker effects. Doses less than 120 mg twice daily appear to have a primary beta-blocker effect, with higher doses producing significant Class III activity.

**" Sotalol is a non-selective competitive beta adrenergic receptor blocker that also exhibits class III antiarrhythmic properties by its inhibition of potassium channels.**

**Because of its dual action, satolal prolongs both the PR interval and the QT interval. "**

A placebo-controlled trial in 302 implantable cardioverter defibrillator recipients showed that treatment with racemic sotalol significantly reduced the risk of death or implantable cardioverter defibrillator shock (34% incidence with sotalol vs. 54% with placebo) at 1 year. However, the rate of drug discontinuation in the sotalol arm was 27%. A similar finding was noted in the OPTIC trial, with nearly a quarter of patients discontinuing sotalol therapy due to drug intolerance. The most common adverse reactions in these trials were related to the beta-blocking effects of the drug; symptomatic bradycardia and torsade de pointes were rare. Of note, in the Survival With Oral D-Sotalol (SWORD) trial, D-sotalol, which does not have significant beta-blocking effects, was associated with increased mortality and proarrhythmia in patients with post-MI left ventricular dysfunction. [10, Rank 3]

The most significant adverse reaction associated with sotalol is torsade de pointes, seen in 2–3% of patients; especially at risk are women and patients with heart failure or chronic kidney disease (because of its significant renal drug elimination). For this reason, it is common practice to initiate sotalol therapy in the inpatient setting with continuous electrocardiograph monitoring during the loading phase for five doses in patients at higher risk. QT interval prolongation and bradycardia can presage the development of proarrhythmia and may warrant a reduction of the sotalol dose. Other adverse effects include fatigue, bronchospasm, dyspnea and heart failure (as shown in figure 14). Unlike amiodarone, these effects are related to the daily dose but not the cumulative dose, making sotalol a more attractive first-line therapy for younger patients or those for whom longer-term treatment is anticipated. [11, Rank 5]

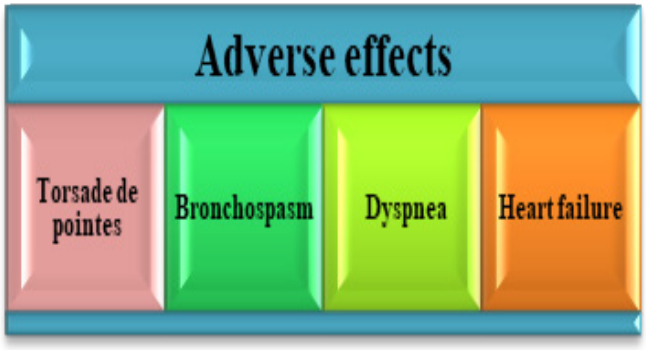


Figure 14: Adverse effects of Sotalol

## *Class IV agents*

Class IV agents are calcium channel blockers, such as verapamil. They decrease the inward current carried by calcium resulting in a decreased rate of phase 4 spontaneous depolarization. It also slows conduction in tissues that depend on calcium currents such as AV node. Therefore, by blocking calcium entry into the cell, calcium channel blockers cause vascular smooth muscle relaxation (vasodilation), decreased myocardial force generation (negative inotrophy), decreased heart rate (negative chronotrophy) and decreased conduction velocity within the heart (negative dromotrophy), particularly at the atrioventricular node (as shown in figure 15).

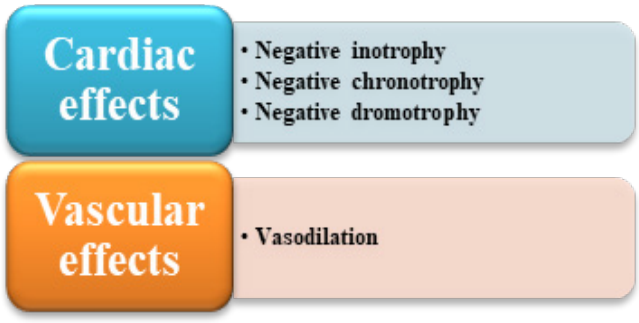


Figure 15: Action of Class IV antiarrythythmics

The antiarrhythmic properties of calcium channel blockers are related to their ability to decrease the firing rate of aberrant pacemaker site within the heart, but more importantly are related to their ability to decrease conduction velocity and prolong repolarization, especially at the atrioventricular node (as shown in figure 16).

**Verapamil/ Diltiazem**

- **Prophylaxis against re occurance of paroxysmal supraventricular tachycardia**
- **Control of ventricular rate in patients with chronic atrial fibrillation or flutter**

Figure 16: Clinical indication of class IV antiarrhythmics

The Vaughan Williams classification does not, however, account for the complex actions of certain antiarrhythmics, such as amiodarone, which is known to have multichannel blocking properties. [6 Rank 3]. Antiarrhythmic drugs can also be used depending on the underlying heart conditions (as shown in table 2). Drugs used for supraventricular arrhythmias- adenosine, verapamil, diltizem. Drugs commonly used for ventricular arrhythmias are lignocaine, mexelitine, bretylium. Drugs used for

supraventricular as well as ventricular arrhythmias include amiodarone, beta blockers, disopyramide, procainamide.

| Arrythmia | Drug |
|---|---|
| Sinus tachycardia | Propranol |
| Atrial extrasystole | Propranol |
| AF/Atrial Flutter | Esmolol, Verapamil, Digoxin |
| PSVT | Adenosine, Esmolol |
| Ventricular tachycardia | Lignocaine, amiodarone |
| Ventricular fibrillation | Lignocaine Amidarone |
| A-V block | Atropine, Isoprenaline |

Table 2: Antiarrhythmics based on dysrhythmias

## Antiarrhythmic Agents and Survival Agents

Therapeutic options for atrial fibrillation have evolved with the development of pulmonary vein ablation over the past decade. However, a meta-analysis showed that single pulmonary vein isolation procedures achieve successful rhythm control off of antiarrhythmic drugs (AADs) in only 57% of patients, and multiple pulmonary vein ablations were successful in71% of patients off of antiarrhythmic drugs; therefore adjunctive use of antiarrhythmic drugs remain an important option for many patients with symptomatic atrial fibrillation in the post ablation period, as well as remaining a primary therapeutic option for many other patients. The choice of antiarrhythmic drugs is often limited and based on co-morbid conditions (as shown in figure 17).

One of these co morbid conditions is the presence of left ventricular hypertrophy. Left ventricular hypertrophy has long been associated with increased risk of sudden cardiac death. It has been proposed that patients with hypertension and left ventricular hypertrophy are at increased risk of torsades de pointes because of a predisposition to the development of early after depolarizations. Prior animal models with cardiac hypertrophy have also demonstrated that left ventricular hypertrophy has pronounced effects on dispersion of refractoriness and repolarisation, increasing vulnerability to fibrillation. [14, Rank 4]

Although atrial fibrillation guidelines have recommended amiodarone as a drug of choice in patients with atrial fibrillation and substantial left ventricular hypertrophy, this recommendation poses a significant challenge in many patients with left ventricular hypertrophy who might be at risk for long term toxic effects of amiodarone. A

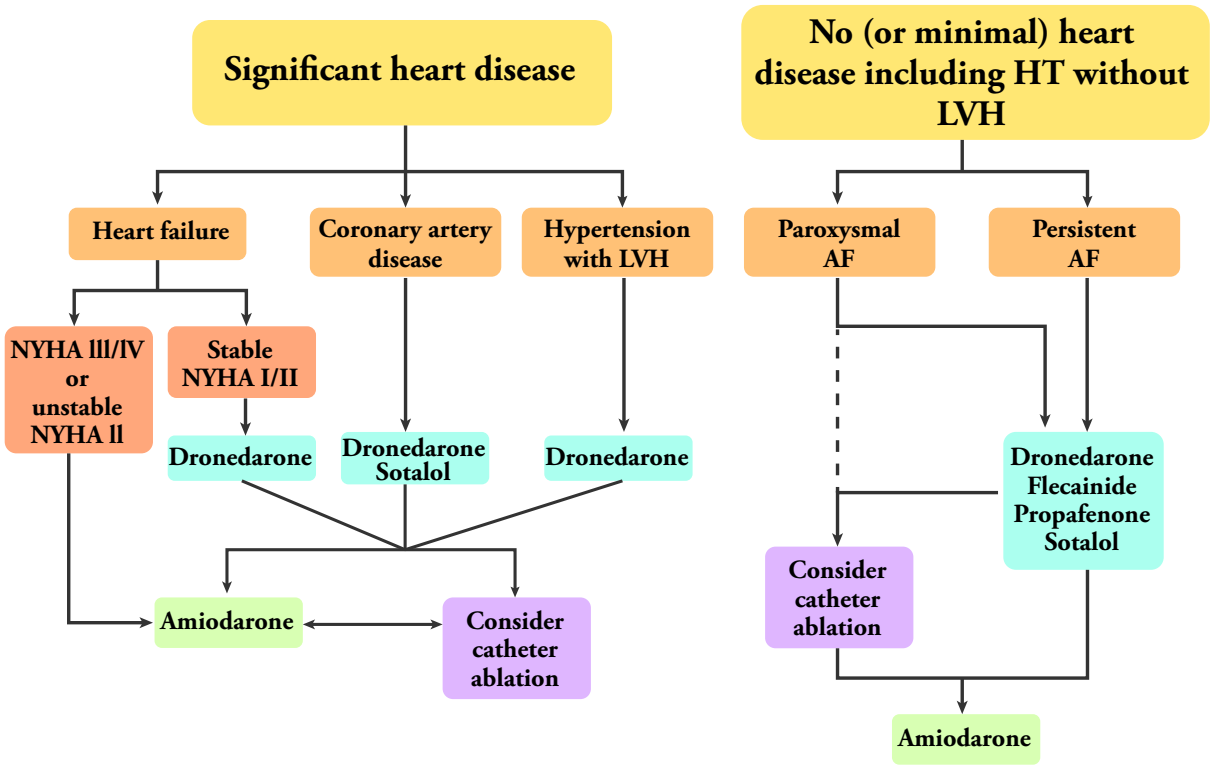


Figure 17: Choice of antiarrhythmic drug according to underlying pathology.

rationale for amiodarone may be in its perceived lower risk of proarrhythmia. Although amiodarone may prolong QT interval, its propensity for torsades de pointes is exceedingly low, possibly due to multiple ion channel blockade that may reduce early after depolarizations and/or reduced transmural dispersion of repolarization. [15, Rank 2]

There is limited clinical data in humans to guide antiarrhythmic drug recommendations in patients with atrial fibrillation and left ventricular hypertrophy, as there has been no clinical study of safety or survival outcomes comparing the use of antiarrhythmic drugs in the presence of left ventricular hypertrophy and atrial fibrillation, including prior pivotal atrial fibrillation trials such as AFFIRM and the Canadian Trial of Atrial Fibrillation. The AFFIRM AAD sub study noted more deaths in patients who were randomly assigned to Class 1 antiarrhythmic drugs compared to amiodarone, although most of the deaths occurred after change of the initial antiarrhythmic drug assignment, amiodarone was often the replacing drug and left ventricular hypertrophy was not addressed. In another sub-analysis of AFFIRM, amiodarone, sotalol or class 1C antiarrhythmic drugs were compared to propensity-score matched rate control patients. The composite outcome of mortality and first cardiovascular hospitalization was significantly higher in the amiodarone and sotalol groups, but not significantly different in the

Class 1C group. In this study the antiarrhythmic drug groups were not compared against one another nor were any analysis done specific to LVH. [16, Rank 4]

## Effect of Drug Concentration on QT Interval and Arrhythmia Risk

The QT interval is the length of time required for the heart to repolarize following the onset of depolarization. Ventricular depolarization, expressed as the QRS complex on an electrocardiogram, is the rapid movement of ions (sodium, potassium and calcium) across the cellular membrane, creating electrical impulses that lead to ventricular contraction. When the outflow of potassium from the myocardium exceeds the inflow of sodium and calcium, repolarization occurs and is expressed as T wave in electrocardiogram.


Figure 18: Antiarrhythmic Drugs commonly associated with QT prolongation

Antiarrhythmic agents were the first drug associated with QT prolongation (as shown in figure 18) and ventricular arrhythmias. Class I antiarrhythmic agents (e.g. quinidine, disopyramide and procainamide) have frequently been linked to inducing arrhythmia and Torsades de pointes. Sotalol and amiodarone, class III antiarrhythmics are known to prolong the QT interval by blocking the IKr. The treatment of arrhythmias with traditional antiarrhythmics has long been known to be beneficial, but also to carry proarrhythimic and pro-torsadogenic side effects. Blockade of the KCNH2 channel, specifically IKr, and subsequent QT prolongation as observed on surface electrocardiogram can predict torsade de pointes. However, QTc prolongation alone could not be attributed to either pure IKr-blockade from multichannel blockade. In order to differentiate the effects, in a prospective, randomized controlled trial with 22 patients (mean age of 26.9±5.5 years, 11 females) researchers administered dofetilide (pure IKr-blocker) along with three other antiarrhythmics - quinidine (Na+ channel blockade), ranolazine (Na+channel blockade; commonly used as an anti-anginal), and verapamil (cardiac specific L-type Ca2+ channel blockade), each exhibiting varying degree of IKr-channel blockade as well. Direct blockade of the K+channel by class III antiar-

rhythmic dofetilide prolonged both early (J–Tpeak) and late (Tpeak – Tend) repolarization currents, while multichannel blockade from the other antiarrhythmic classes primarily resulted in shortening of early repolarization (J–Tpeak) segment. This observation allowed differentiation of the effects of antiarrhythmics during repolarization. This has clinical significance of course; the ability to track changes in J–Tpeak and Tpeak – Tend offers more precise observations in cardiac drug safety evaluation. Specifically, in understanding the triggers for arrhythmias and Torsades de pointes, it has been shown that blockade of IKr can potentiate Torsades de pointes due to increased Na+ and Ca2+ inward current, EAD. Thus, inhibition of this inward ion flux through multichannel blockade may minimize EADs and reduce the risk of arrhythmogenesis and subsequent Torsades de pointes. While the direct IKr-blockade by the class III antiarrhythmic dofetilide has been shown to prolong both early and late repolarization currents, the effect of drugs from other classes on IKr channels (in addition to their respective target channel) appear to alter either the Ca2+and/or Na+ inward currents, resulting in prolongation of early repolarization. [17, Rank 3]

Studies examined 13 cases of drug-induced TdP secondary to administration of either dofetilide (5 cases, 80% female) or sotalol (8 cases, 75% female), both known to affect cardiac K+ channels with pro-arrhythmogenic and pro-torsadogenic properties. QTc in lead V6 and the T wave right wave slope in aVR were most prominent T wave parameters contributing to a strong correlation with Torsades de pointes (QTc in V6, mean case vs. control: 500±44 vs. 410±38 msec, $p<0.001$, $r=0.77$; T wave right wave slope in aVR, mean case vs. control: –682.88±38 vs. –1509.53±44 mV/s, $p<0.001$, $r=0.56$). ECG analysis showed comparable correlations with QTc in lead V3 and T wave right slope in lead I. Of the parameters, this analysis showed that T wave right slope in Lead I possessed high correlation to risk of arrhythmias and allowed delineation of Torsades de pointes risk from the control groups. Specifically, the characteristics of the slope of the T wave in Lead I was of focus, amplitude and duration of the terminal portion of the wave. The results suggest that the Torsades de pointes cases (13/39) presented with shallower right slopes, possibly implicating substantial dispersion of the refractoriness in both the transmural and apicobasal gradients. In cases with T wave abnormalities, particularly the amplitude and duration, COGx interpretations have the potential to predict those most likely at risk for arrhythmogenesis and Torsades de pointes. [18, Rank 5]

Although QT prolongation has been linked to the use of certain drugs, it remains difficult to predict the relative risk associated with their administration. Drugs that have QT prolonging effects should not exceed recommended dosing range, as drug induced arrhythmia is often a result of high drug concentrations. In addition these medications should be prescribed with caution in patients who have underlying risk factors, such as cardiac disorders. Screening for potential drug interactions and electrolyte abnormalities may also help lead to safer therapies, potentially preventing the development of ventricular arrhythmias.

## Antiarrhythmic Drug Therapy in Patients with atrial fibrillation

Antiarrhythmic drugs are the first line of therapy for maintenance of sinus rhythm in patients with atrial fibrillation (as shown in figure 19). The goal of antiarrhythmic drug therapy is to reduce the duration and frequency of atrial fibrillation episodes, thus improving the patient quality of life and symptoms. The majority of these drugs act by reducing the likelihood of re-entry by prolonging the atrial effective refractory period through the inhibition of K+ currents or reduction of atrial excitability via inhibition of Na+ currents. However, most of these drugs affect multiple other ion channels as well as adrenergic receptors. Drugs that affect multiple channels are more effective for maintenance of sinus rhythm than selective ion channel blockers. Stabilization of Ca2+ handling abnormalities and normalization of gap junction physiology have been other targets for treatment of atrial fibrillation.

> **"Antiarrhythmic drugs are the first line of therapy for maintenance of sinus rhythm in patients with atrial fibrillation.**
>
> **Amiodarone is the most potent antiarrhythmic drug available to maintain sinus rhythm and prolong recurrence of atrial fibrillation."**

Each of these drugs varies in its efficacy for maintaining sinus rhythm and possesses unique adverse effect profiles. Disopyramide and quinidine, class IA agents that are effective in atrial fibrillation, have fallen out of favor due to their adverse effect profiles, including worsening of heart failure and increased mortality. Due to its anticholinergic activity, long-acting disopyramide does have a role in vagally mediated atrial fibrillation. [19, Rank 3]

Flecainide and propafenone are Class IC arrhythmic agents recommended for the management of atrial fibrillation in patients

without structural heart disease. When compared with placebo, both are effective for maintenance of sinus rhythm and for prolongation of the time to recurrence of atrial fibrillation. Since both of these drugs may have a propensity to promote 1:1 atrioventricular (AV) conduction during atrial flutter, an atrioventricular nodal blocking agent is routinely co-administered. In addition to its Na+ channel-blocking effect, propafenone has some additional beta-adrenergic-blocking effects.

Class III drugs used to maintain sinus rhythm include amiodarone, dronedarone, sotalol and dofetilide. Amiodarone is not approved by the US Food and Drug Administration for rhythm control of atrial fibrillation; however, it is one of the most commonly prescribed antiarrhythmic drugs for this condition. In addition to inhibition of the outward potassium currents (Class III effect), amiodarone also has class I (Na+ channel blocking), Class II (anti-adrenergic), and Class IV (Ca2+ channel blocking) effects. From the efficacy standpoint, amiodarone is the most potent antiarrhythmic drug available to maintain sinus rhythm and prolong recurrence of atrial fibrillation. Limited data are available to directly compare its efficacy with other antiarrhythmic drugs, although studies that compared it with sotalol and propafenone found amiodarone to be superior. The use of amiodarone may be limited by significant cardiovascular and non-cardiovascular adverse effects. The use of amiodarone requires surveillance for lung, liver and thyroid toxicity, which involves evaluation at baseline and then follow-up evaluations every 6 months or yearly. [20, Rank 2]

Dronedarone is a non-iodinated congener of amiodarone developed with the hypothesis that deletion of the iodine moiety would lead to fewer adverse effects while retaining the antiarrhythmic properties of amiodarone. Randomized trials evaluating dronedarone reported its efficacy in maintaining sinus rhythm, reduction in hospitalization and cardiovascular mortality. However, in patients with advanced heart failure, its use was associated with increased mortality. Dronedarone is now considered reasonable to reduce hospitalization for cardiovascular events in patients with paroxysmal atrial fibrillation. Its use should be reserved for selected low-risk individuals who may have failed other antiarrhythmic drugs.

Sotalol is a K+ ion channel blocker effective at preventing recurrences of atrial fibrillation in comparison with placebo at doses ranging from 80 to 160 mg twice daily. In addition to its antiarrhythmic activity, sotalol also has non-selective beta-adrenergic-blocking properties and is known to provide efficient rate control in

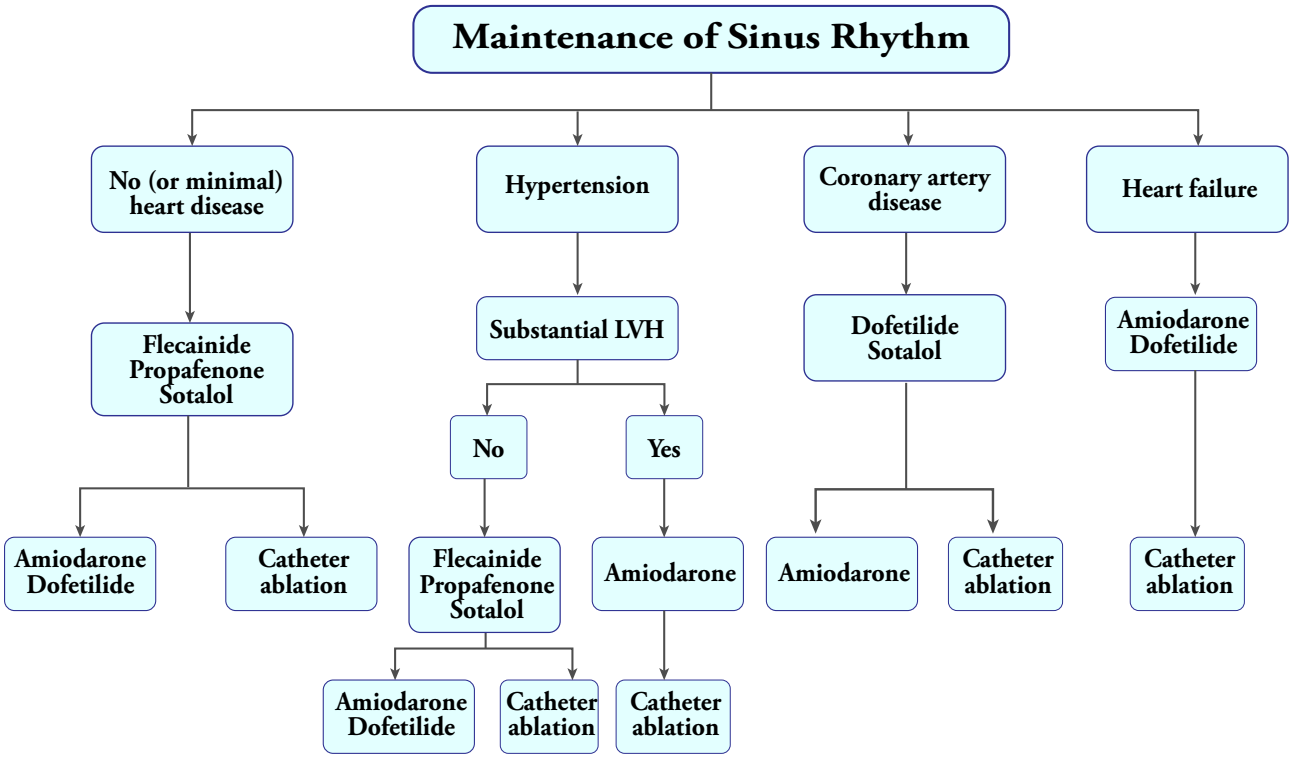


Figure 19: Antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation.

cases of atrial fibrillation recurrence. Sotalol may cause bradycardia and proarrhythmia due to QT prolongation. Thus, it is usually recommended that patients be hospitalized for close cardiac rhythm monitoring upon initiation of the drug as well as with each upward dose adjustment. [21, Rank 1]

**" Disopyramide does have a role in vagally mediated atrial fibrillation due to its anticholinergic activity**

**Flecainide and propafenone are class Ic arrhythmic agents recommended for the management of atrial fibrillation in patients without structural heart disease. "**

Dofetilide, another Class III antiarrhythmic agent, was studied in the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study, which reported a 58% efficacy in maintaining sinus rhythm at 1 year with dofetilide in comparison with 25% in the placebo group. In the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) study involving patients with reduced left ventricular systolic function, the dofetilide group had a 79% probability of maintaining sinus rhythm in comparison with 42% with placebo at 1 year in addition to a reduced risk of all-cause or congestive heart failure-related hospitalization.In this study, torsades de pointes occurred in 1.6% patients, and half of those

occurred on day 2 of dofetilide treatment. Due to this risk of torsades, initiation of this drug requires a mandatory inpatient loading period for 3 days with titration of the dose based upon QT interval and renal function. Ibutilide, another class III antiarrhythmic available in an intravenous form, is used mostly for acute conversion to sinus rhythm and is not used as maintenance therapy to prevent atrial fibrillation recurrence.

The intravenous formulation of vernakalant has recently been approved in Europe for pharmacological cardioversion of atrial fibrillation of ≤7 days' onset, or ≤3 days for patients after cardiac surgery. It increases atrial refractoriness and causes rate dependent slowing of atrial conduction through its effects on potassium currents (Ito, IAch, IKur) and late cardiac sodium current (INa). [23, Rank 4]

## Effect of rhythm control using antiarrhythmic drug therapy on progression of atrial fibrillation

In the RECORD atrial fibrillation registry of patients with recently diagnosed atrial fibrillation, 54% of patients in the rate-control arm progressed to permanent atrial fibrillation in comparison with 13% in the rhythm-control group. Upon application of propensity scoring to account for patient co morbidities, the impact of treatment strategy with rhythm control was found to be favourable (odds ratio [OR] 0.20, 95% CI 0.17–0.25; P < 0.0001). In another prospective survey that evaluated patients worldwide, patients treated with rhythm control showed less progression of atrial fibrillation in comparison with a rate-control strategy (11% versus 26%; P < 0.001). In multivariate logistic regression, rate control (as shown in figure 20) rather than rhythm control was an independent predictor of AF progression (OR 3.2, 95% CI 2.5–4.1; P < 0.0001). As shown in animal studies, prevention of electrical remodeling of the atrium that occurs with increasing atrial fibrillation burden has been hypothesized to be responsible for delay in atrial fibrillation progression. Additionally, patients with atrial fibrillation maintained in sinus rhythm are known to have a reduction in left atrial size and improvement of left ventricular systolic function, both of which are important factors associated with atrial fibrillation progression. [24, Rank 5]

It has been argued that a rhythm-control strategy could appear to be more favorable due to its selective application in younger patients with fewer co morbidities, factors that are independently associated with atrial fibrillation progression. However, upon using propensity scoring models to correct for the influence of these variables, the overall results in the

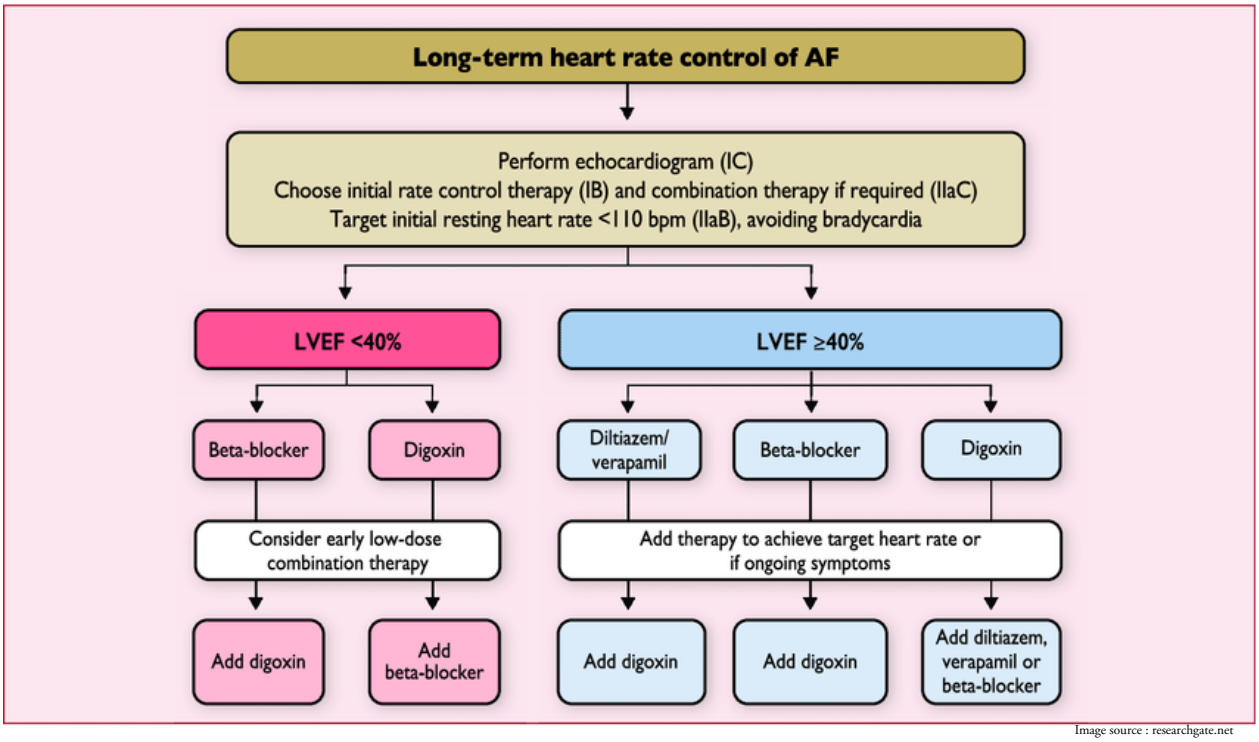


Figure 20: Long-term heart rate control in patients with atrial fibrillation

above-mentioned analyses remained unchanged and a rhythm-control strategy remained a significant deterrent for atrial fibrillation progression.

Use of antiarrhythmic drug therapy is often hampered by limited efficacy in controlling atrial fibrillation over a prolonged duration of time, coupled with an increased risk for adverse effects. In a systematic review evaluating the efficacy outcomes of all antiarrhythmic drugs, the rate of success in control of atrial fibrillation (during the follow-up periods of the included studies) was 52% (95% CI 47–57) and drug discontinuation due to adverse effects was 10.4%, along with a 2.8% overall mortality. Additionally, in the Euro Heart Survey on atrial fibrillation that examined the natural progression of atrial fibrillation, antiarrhythmic drugs were used in 50% of patients and amiodarone in approximately 25%, yet the use of these agents was not significantly associated with a reduction in atrial fibrillation progression. A limitation of this study was that patients were not randomized to a specific treatment strategy, and treatment decisions were left to attending cardiologists. [25, Rank 3]

## Comparison of catheter ablation with antiarrhythmic drug therapy

Radiofrequency catheter ablation (RFA) of atrial fibrillation when compared with the use of antiarrhythmic drug therapy has been reported to have more favourable outcomes for reducing the progression of

atrial fibrillation. In a study, 106 patients who presented to the emergency room with a first diagnosed episode of atrial fibrillation were followed prospectively for 5 years. Of these, 56 (53%) developed recurrent paroxysmal atrial fibrillation and were placed on long-term antiarrhythmic drug therapy. Atrial fibrillation became persistent in 24 of 45 patients taking antiarrhythmic drug therapy. In 11 such patients who failed antiarrhythmic drug therapy, radiofrequency ablation of atrial fibrillation was performed, and none of these patients had recurrence of atrial fibrillation. Among the persistent atrial fibrillation patients who failed drug therapy, 16 of 24 (67%) progressed to permanent atrial fibrillation, thus providing evidence for the superiority of radio frequency ablation of atrial fibrillation in preventing progression of atrial fibrillation. Similarly, in the Ablation for Paroxysmal Atrial Fibrillation (APAF) trial, 198 patients with paroxysmal atrial fibrillation were randomly assigned to radiofrequency ablation or antiarrhythmic drug therapy. At 4 years of follow-up, by intention-to-treat analysis, 72.7% of patients in the ablation arm and 56.5% in the antiarrhythmic drug therapy arm remained free of recurrent atrial fibrillation (P = 0.017). In this study, antiarrhythmic drug therapy in about 88% of patients was ineffective, requiring crossover to the radiofrequency ablation arm due to frequent recurrences and progression of atrial fibrillation. [26, Rank 4]

> **" Radiofrequency ablation is generally considered only if antiarrhythmic drugs fail in patients with persistent atrial fibrillation who remains severely symptomatic despite adequate ventricular rate control "**

The widespread acceptability of radiofrequency ablation as a first-line treatment modality for atrial fibrillation has been limited due to a lack of long-term follow-up data about the efficacy and safety profile across all patient groups, including those with underlying structural heart disease. Additionally, the procedure is invasive and is associated with a number of serious complications such as pulmonary vein stenosis, thromboembolism, atrio-esophageal fistula and pericardial tamponade. Thus, it is important to understand which patients are less likely to benefit from ablation therapy. Until such questions are answered by well conducted randomized controlled trials, the true efficacy of catheter ablation across all patient populations and whether it just delays or truly prevents progression of atrial fibrillation remains to be proven conclusively. [27, Rank 2]

## Emerging Antiarrhythmic Therapy

Emerging antiarrythmic therapies include those agents that have not yet been approved for clinical uses but have been tested in clinical investigations or early phase clinical trials (as shown in figure 21).

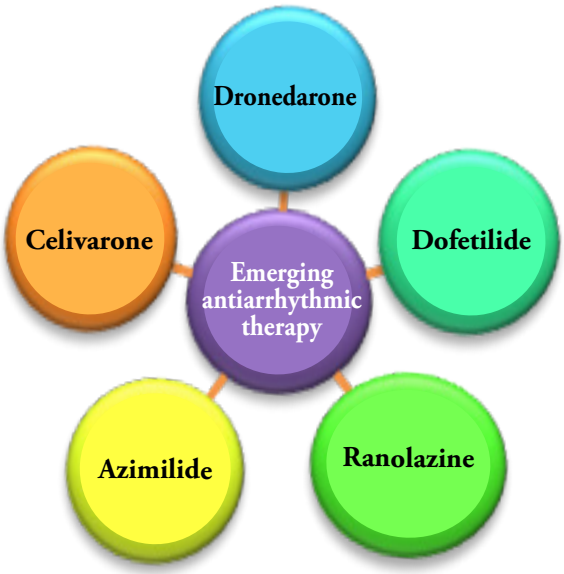


Figure 21: Emerging anti arrhythmic therapy

## Dronedarone

Dronedarone is a recent addition to the antiarrhythmic armamentarium. A Vaughan Williams Class III agent, dronedarone is a multichannel blocker similar in structure to amiodarone but non-iodinated. It was developed with the potential to achieve antiarrhythmic efficacy similar to that of amiodarone, without the extra cardiac toxicity seen with long-term amiodarone therapy. It is approved for the treatment of atrial fibrillation, largely based on results of A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation (ATHENA), a placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation or atrial flutter, which demonstrated significant reductions in the composite endpoint of all-cause mortality and cardiovascular hospitalization with dronedarone vs. placebo. In two earlier randomized trials of dronedarone in patients with atrial fibrillation or flutter, rates of pulmonary, thyroid and hepatic adverse effects were not significantly greater with dronedarone than with placebo at 1 year follow-up. After its approval in the United States, however, subsequent reports of severe liver toxicity led to a warning by the United States Food and Drug Administration, recommending that prescribing physicians follow hepatic function tests routinely. [26, Rank 2]

Although dronedarone has not been studied specifically for the treatment of ventricular tachycardia/ ventricular fibrillation, animal studies have demonstrated antiarrhythmic properties on ventricular myocardium, and subsequent reports in humans have supported its efficacy in select cases. In addition, in ATHENA, patients on dronedarone showed a reduction in arrhythmic death. The use of dronedarone in patients

with heart failure, however, is controversial in light of the Antiarrhythmic Trial with Dronedarone in Moderate to Severe congestive heart failure Evaluating Morbidity Decrease (ANDROMEDA) trial, whose results suggest dronedarone may lead to worsening heart failure symptoms and a two-fold increase in mortality in this population. As such, dronedarone is contraindicated in Class IV heart failure patients or in those who have had a recent hospitalization for decompensated heart failure. A more recent placebo-controlled trial of dronedarone in patients with permanent atrial fibrillation and major vascular risk factors (including coronary artery disease and heart failure) was stopped prematurely due to a two-fold excess in cardiovascular mortality. Stroke, hospitalization for heart failure, and arrhythmic deaths were also significantly increased in the dronedarone arm of the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS). While some of these adverse findings were unexplained, it was postulated that the negative inotropic effects of dronedarone, along with its drug–drug interactions (notably with vitamin K antagonists and with digoxin) and potential proarrhythmic effects, may have contributed.

In summary, while dronedarone has been shown to be effective in suppressing ventricular arrhythmia in animal studies and in case reports of patients with refractory ventricular tachycardia/ventricular fibrillation episodes, the results of ANDROMEDA and PALLAS have raised doubts about the safety of this medication in patients with structural heart disease. [28, Rank 5]

## Dofetilide

Dofetilide is a Class III antiarrhythmic agent and a selective blocker of the rapid delayed rectifier potassium current, IKr. It is approved in North America for the treatment of atrial fibrillation; however, it has been shown to have efficacy in the treatment of ventricular arrhythmia. A randomized trial of patients with coronary artery disease and sustained ventricular tachycardia showed that oral dofetilide was equally as effective as oral sotalol in the prevention of recurrent ventricular arrhythmias and arrhythmic death at 1 year. A more recent study in 30 implantable cardioverter defibrillator recipients with drug-refractory ventricular tachycardia/ ventricular fibrillation episodes showed a significant reduction in both monthly ventricular arrhythmia episodes (from 1.8 ± 4.5 to 1.0 ± 3.5, P = 0.006) and monthly implantable cardioverter defibrillator therapies (from 0.9 ± 1.4 to 0.4 ± 1.7, P = 0.037) after treatment with dofetilide. In addition, 83% of patients had complete suppression of ventricular tachy-

cardia/ ventricular fibrillation during their first month of treatment.

Dofetilide is very well tolerated, although inpatient monitoring for 3 days is required during the loading phase, given the risk of QT prolongation and the potential for torsade de pointes (seen in 1–3%). Dofetilide dosing is based on calculated creatinine clearance, as a result of its renal drug elimination. The safety of dofetilide has been established in patients with left ventricular dysfunction and coronary artery disease and on the basis of limited clinical experience in the treatment of ventricular arrhythmia; it may be an alternative antiarrhythmic agent for such patients with ventricular tachycardia /ventricular fibrillation events refractory to amiodarone and/or sotalol therapy. [29, Rank 3]

## Ranolazine

Ranolazine is a novel antianginal drug with multiple ion channel blocking antiarrhythmic activity. It is a piperazine derivative with a chemical structure similar to lidocaine, and its most potent ion channel blocking effect is on late sodium current. It is thus considered a Vaughan Williams Class IB agent. Ranolazine also has effects on the delayed rectifier current (IKr) and prolongs action potential duration, with corresponding QT interval prolongation on electrocardiography. It has been shown in experimental animal models to have antiarrhythmic effects in the ventricle. In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36 trial (MERLIN-TIMI 36), ranolazine was shown clinically to reduce arrhythmia episodes, including nonsustained ventricular tachycardia, on ambulatory cardiac monitoring in patients presenting with acute coronary syndrome. It has subsequently been used in the suppression of ectopic ventricular activity and for the reduction in ventricular tachycardia burden and prevention of shocks in implantable cardioverter defibrillator recipients.

Ranolazine in particular works synergistically with the Class III antiarrhythmic agents, most commonly with amiodarone. This has been demonstrated in animal models to have an antiarrhythmic effect in both the atrium and ventricle. In rabbit hearts treated with both ranolazine and a Class III agent, there was no increase in early after-depolarizations or ventricular proarrhythmia associated with the addition of ranolazine. In addition, in the MERLIN-TIMI 36 trial, despite causing modest QT prolongation, ranolazine use was not associated with an increased risk of sudden cardiac death compared with placebo. Based on limited but positive clinical expe-

riences with ranolazine, it appears to be beneficial as add-on therapy in patients with recurrent ventricular tachycardia events while on a Class III antiarrhythmic agent. [30, Rank 3]

## Azimilide

Azimilide is an investigational Class III antiarrhythmic agent that blocks both the rapid (IKr) and slow (IKs) components of the delayed rectifier cardiac potassium current. It causes prolongation of the atrial and ventricular action potential duration and refractory period. As such, azimilide has demonstrated action against both supraventricular and ventricular arrhythmias. In the Shock Inhibition Evaluation with Azimilide (SHIELD) trial, a randomized controlled trial of 633 secondary prevention implantable cardioverter defibrillator recipients, the primary endpoint of all-cause shocks plus symptomatic tachyarrhythmias terminated by antitachycardia pacing was significantly reduced in patients receiving azimilide. In addition, the secondary endpoint of appropriate implantable cardioverter defibrillator therapies for ventricular tachycardia /ventricular fibrillation episodes was reduced by 48% and 62%, with the 75 mg and 125 mg doses of azimilide, respectively.

Based on the concerning results from previous antiarrhythmic drug trials in patients with structural heart disease, such as CAST and SWORD, azimilide was studied prospectively in the Azimilide Postinfarct Survival Evaluation (ALIVE) trial, in which 3,717 patients with recent myocardial infarction and an ejection fraction between 15% and 35% were randomly assigned to receive azimilide, 100 mg daily, vs. placebo. At 1 year of follow-up, there were no significant differences in all-cause, cardiac, or arrhythmic mortality between the azimilide and placebo groups.

Overall, azimilide was well tolerated in clinical trials. In the SHIELD trial, its discontinuation rate was similar to the placebo arm. Adverse events with azimilide include neutropenia (seen in 1% of patients) and QT prolongation leading to torsade de pointes (seen in up to 1–2% of patients). It is not currently approved for use in North America or Europe. [25, Rank 5]

## Celivarone

Celivarone is a non iodinated benzofuran derivative that is in investigational use for its action against atrial and ventricular arrhythmias. Similar to amiodarone and dronedarone, it has Class I, II, III and IV antiarrhythmic activity, but with different relative potencies for the various channels and receptors. Also, its structure and kinetics differ from those of amiodarone and lend itself to an improved side effect profile

and reduced potential for drug interactions. It was shown in a small phase 2 clinical study of implantable cardioverter defibrillator recipients to trend toward fewer ventricular tachycardia and ventricular fibrillation episodes at the higher dose of celivarone (300 mg daily), although the 46% relative risk reduction at 6 months was not statistically significant. A larger trial of 486 patients with left ventricular ejection fraction of 40% or less and at least one ventricular tachycardia /ventricular fibrillation episode within a month of enrollment, however, did not find that celivarone was any more effective for the prevention of implantable cardioverter defibrillator interventions or sudden death than placebo. In both studies, celivarone was well tolerated and had an acceptable safety profile. [26, Rank 4]

## Future Antiarrhythmic Targets

Novel targets for the treatment of ventricular arrhythmia continue to be explored and it is likely that pharmacologic agents directed at some of these targets will enter clinical trials in the next few years. The commonly used antiarrhythmic medications for ventricular tachycardia/ ventricular fibrillation primarily target sodium channels (Class I agents) or potassium channels (Class III agents), but are limited by variable efficacy and the potential for ventricular proarrhythmia. Newer therapeutic approaches to cardiac arrhythmias (as shown in figure 22) have focused on the roles of intracellular calcium, gap junctions, sodium–calcium exchange and adenosine triphosphate (ATP)-sensitive potassium channel blockade. [22, Rank 4]

### Intracellular Calcium

Altered intracellular calcium handling has been implicated in ventricular arrhythmogenesis in a number of models. Two important proteins in myocardial calcium homeostasis are the sarcoplasmic reticulum (SR) calcium ATPase (SERCA2a) and the ryanodine receptor (RyR2). The former promotes calcium reuptake into the SR and the latter is a SR calcium release channel that promotes an increase in cytosolic calcium, which in turn activates myocardial contractile proteins. Diastolic calcium leakage via RyR2 is thought to contribute to proarrhythmia, notably by promoting after-depolarizations in the cardiomyocyte. catecholaminergic polymorphic ventricular tachycardia is one cardiac electrical disorder characterized by leaky RyR2, resulting in delayed after-depolarizations and polymorphic ventricular tachycardia triggered by exercise and adrenergic stimulation. The antiarrhythmic agent flecainide targets RyR2, and was shown to prevent arrhythmias in a mouse model of catecholaminergic polymorphic ventricular tachycar-

dia, by inhibiting RyR2-mediated calcium release. Now this agent has found a role clinically to suppress ventricular tachycardia events in patients with catecholaminergic polymorphic ventricular tachycardia in conjunction with beta-blockers.

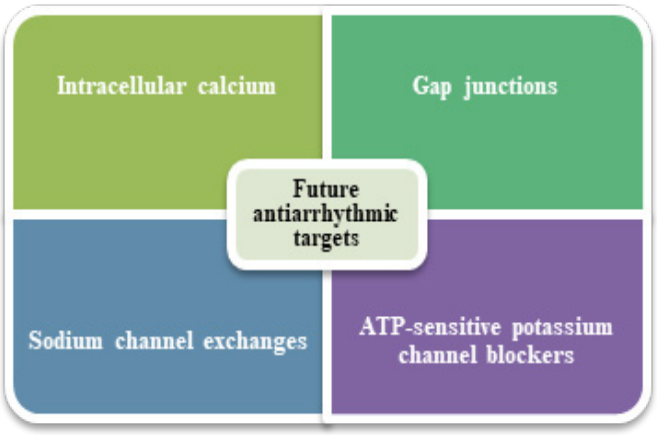


Figure 22: Future antiarrhythmic targets

Pharmacotherapies to normalize intracellular calcium handling by either stabilizing RyR2 activity or modulating associated proteins involved in diastolic SR calcium leakage in order to prevent arrhythmia may prove to be novel antiarrhythmic agents in the future. In a recent report, a pharmacologic RyR2 stabilizer was investigated in both a mouse model and in human non failing myocardium, and was found to be effective in reducing SR calcium leak. Another recent report showed that inhibition of calcium/ calmodulin-dependent kinase (CaMKII) was able to reduce cardiac arrhythmias and sudden cardiac death in a proarrhythmic mouse model similar to that seen in catecholaminergic polymorphic ventricular tachycardia (CPVT). [20, Rank 5]

## Gap Junctions

Cell–cell coupling in the heart acts to maintain synchronization of depolarization and repolarization between myocytes and disruption of this coupling is thought to contribute to arrhythmogenesis. It has been proposed that restoration or enhancement of coupling via gap junctions may be an effective antiarrhythmic target. Connexin 43 is the principal gap junction protein responsible for cell–cell coupling in ventricular myocardium, and its function is impaired during acute ischemia and acidosis. Rotigaptide an antiarrhythmic peptide that improves conduction across gap junctions has been shown in experimental animal models to suppress ischemia-induced proarrhythmia. The proposed mechanism of action of rotigaptide is prevention of the dephosphorylation of connexin 43 that accompanies acute metabolic stress. By maintaining gap junction conductance, this peptide in turn both prevents conduction slowing in the cardiomyocytes, and synchronizes the action potentials thereby reducing dispersion of refractoriness.

While the concept of normalizing gap junction conductance with an antiarrhythmic agent is a promising one, there are multiple mechanisms by which gap junction physiology can be impaired in disease states other than by dephosphorylation. The roles of myocyte fibrosis, connexin pro-

tein downregulation and trafficking in the remodeling of gap junctions have all been appreciated and may pose challenges to the development of a single pharmacotherapeutic target or agent. [21, Rank 3]

## Sodium-Calcium Exchange

The sodium–calcium exchanger (NCX) is the primary pathway for intracellular calcium removal in the cardiomyocyte. It is a cell membrane protein that removes a single calcium ion in exchange for the import of three sodium ions, while operating in the forward mode. Increased expression or activity of sodium–calcium exchanger has been associated with impaired cardiac contractility and an increased risk of arrhythmias in the setting of heart failure. Sodium–calcium exchanger also operates in the reverse mode, promoting intracellular calcium loading, during conditions of high cytosolic sodium concentration, or in the setting of digitalis use (which antagonizes the sodium/potassium ATPase). Excessive calcium loading can also be proarrhythmic, as it promotes triggered activity through delayed after-depolarizations.

NCX blockade has been considered to be a potential therapeutic strategy for cardiac arrhythmias, in particular with agents that predominantly inhibit the reverse mode over the forward mode. To date, there has been limited progress in the development of clinically useful agents. Two drugs, KBR-7943 and SEA-0400, have been shown to prevent calcium overload in models of ischemia/reperfusion injury, and appear to reduce after-depolarizations in models of vulnerable cardiac tissue. These findings are promising but await further in vivo confirmation in animal models. [20, Rank 5]

## ATP-Sensitive Potassium Channel Blockade

Myocardial ischemia is associated with increases in extracellular potassium, which is believed to contribute to ventricular proarrhythmia. The activation of cardiac cell membrane ATP-sensitive potassium channels during myocardial ischemia promotes potassium efflux and reductions in action potential duration; impaired function of the sodium/potassium ATPase may also contribute. In addition, ischemia-induced potassium accumulation is heterogeneous, which leads to dispersion of repolarisation and thereby creates a substrate for re-entrant arrhythmias.

ATP-sensitive potassium channel activity is inhibited by ATP but activated by adenosine 5 -diphosphate (ADP). Therefore, with a fall in the ATP: ADP ratio during myocardial ischemia, the ATP-sensitive potassium channel opens and potassium leaves the cell. Increases in extracellular

potassium are known to promote perturbations in cardiac electrical activity, such as increased excitability of normal ventricular tissues, leading to premature ventricular complexes, and a reduction in action potential duration. Regional dispersion of the refractory period, especially during periods of myocardial ischemia, is a major contributor to the development of ventricular fibrillation. Glibenclamide is an ATP-sensitive potassium channel inhibitor that has been shown to attenuate reductions in action potential duration in models of ischemia, and suppress extrasystoles and ventricular fibrillation.

Glibenclamide is a sulfonylurea that also provokes hypoglycemia due to its effects on noncardiac tissue. For ATP-sensitive potassium channel inhibition to become an attractive therapeutic option, cardioselective pharmaceuticals must be developed and tested. Currently, the agents HMR-1883, HMR-1098 and HMR-1402 have been developed and studied in animals, with favorable results on the reduction of ischemic cardiac arrhythmias. [22, Rank 5]

## Prevention Strategies

The best evidence of the efficacy in prevention of post operative atrial fibrillation (PoAF) has been accumulated for betablockers,sotalol and amiodarone (as shown in figure 23) which have been shown to reduce the risk of atrial fibrillation by 50-60%, with the preference given to beta blockers. The second line of treatment is amiodarone which prevents atrial fibrillation and provides an additional protection against ventricular tachyarrythmias.

## Peri-operative use of Beta Blockers

(as shown in figure 24)

The rationale for the peri-operative use of beta-blockers is to diminish myocardial oxygen demand and overall ischemic events by blunting the chronotropic and inotropic effect of catecholamine surge in the postoperative period. Slowing of the heart rate also improves diastolic filling, which allows better perfusion of the endocardium. Thus, by reducing ischemic events during surgery, beta-blockers have a beneficial effect in reducing adverse events, including the development of PoAF, as long as care is taken not to cause excessive bradycardia, hypotension or hemodynamic instability in the postoperative period. In patients on chronic beta-blockers, its abrupt discontinuation postoperatively results in a two- to fivefold increase in the incidence of PoAF. The beneficial effect of beta-blockers has been demonstrated in several clinical studies in patients undergoing coronary artery bypass graft (CABG) or valve surgery alone or in combination. [18, Rank 4]

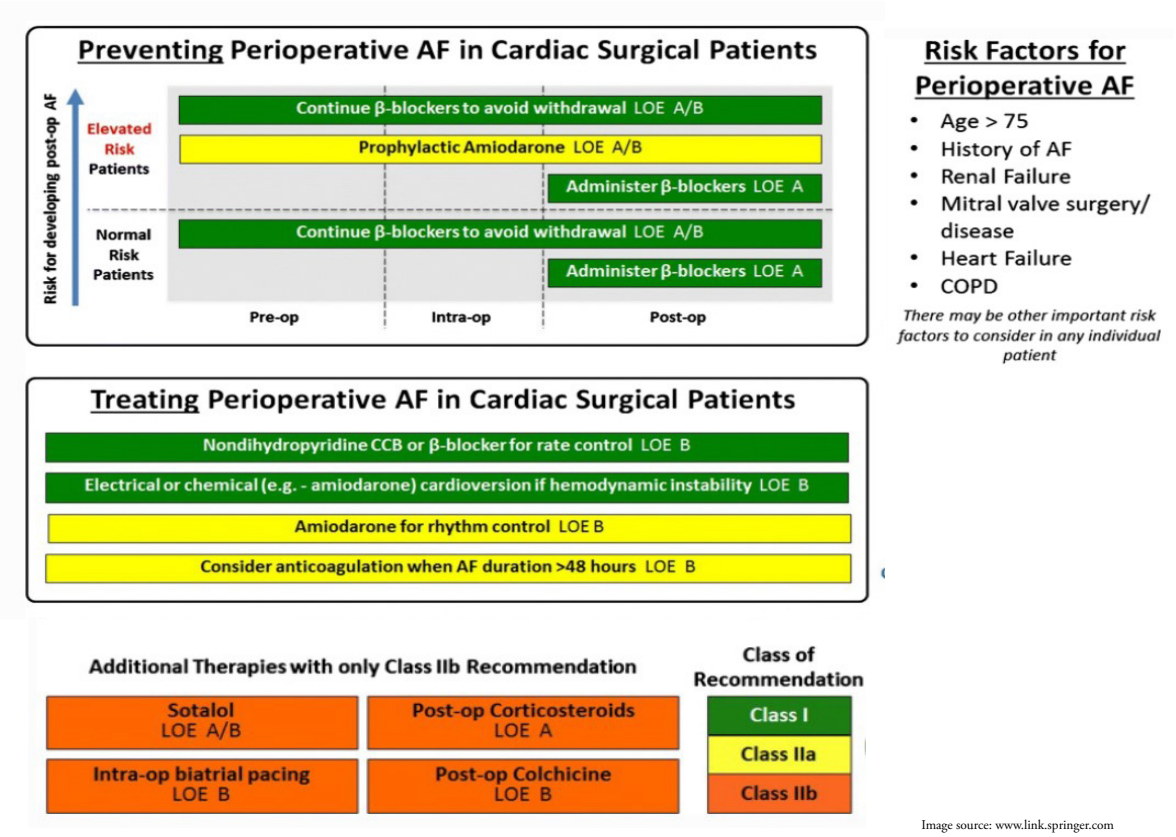


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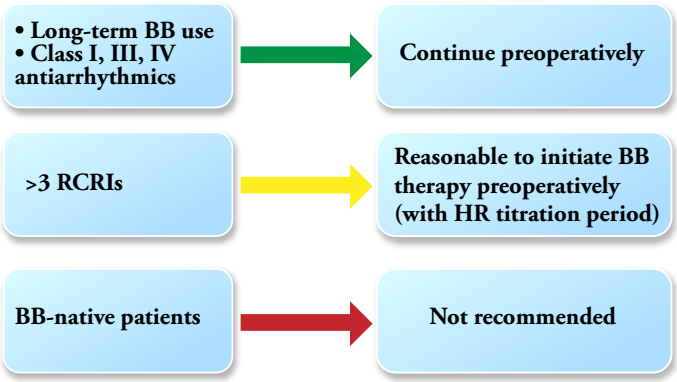
Figure 23: Perioperative administration of AADs

In a large North American observational analysis of 629,877 patients undergoing coronary artery bypass graft in the Society of Thoracic Surgeons National Adult Cardiac Surgery Database, preoperative beta-blockers were associated with a lower 30-day unadjusted mortality (2.8% vs. 3.4%; odds ratio [OR], 0.80; 95% confidence interval [CI], 0.78-0.82, p<0.001) and major procedural complications. In those with mild-to-moderate left ventricular (LV) dysfunction (ejection fraction [EF] >30-50%) there was a trend toward improved mortality, but in those with severely depressed function (left ventricular ejection fraction [LVEF] <30%), a non-significant trend toward increased 30-day mortality (OR, 1.13; 95% CI, 0.96-1.33; p=23) was present. In patients with multiple risk factors in whom a long-term beta-blocker is indicated for prevention of cardiovascular (CV) events, this should be continued, and in those not previously treated, a beta-blocker should be started at least 2-7 days before surgery. Initiation of beta-blockers in the immediate perioperative period is associated with adverse events, as recently demonstrated in the POISE (The PeriOperative Ischemia Study Evaluation) trial. In this randomized, controlled trial (RCT) enrolling 8,351 patients undergoing non-cardiac surgery, a reduction in cardiac events including ischemia and post operative atrial fibrillation was demonstrated in the beta-blocker group compared to placebo, but this was associated with an increase in

total mortality (3.1 vs. 2.3%; p=0.03) and the incidence of stroke (1.0 vs. 0.5%; p=0.005), possibly due to beta-blocker-induced hypotension (15% vs. 9.7%) and bradycardia (6.6% vs. 2.4%). This is proposed to be due to the use of metoprolol succinate at a high starting dose of 100 mg that was then titrated up to 200 mg daily.

> **"In patients in whom beta -blocker therapy is initiated, it may be reasonable to begin perioperative beta blockers long enough in advance to assess safety and tolerability**
> **Beta-blocker therapy should not be started on the day of surgery."**

This and other studies indicate that the use of beta-blockers should be individualized based on cardiovascular risk factors, especially in patients who are beta-blockers naïve, and high doses of long-acting formulation without dose titration with the potential for hypotension and bradycardia avoided. Only limited information is available about dose titration before surgery, and the best titration protocol has not been defined by RCT. However, it is prudent to titrate to a dose that will have an anti-ischemic effect and prevent excessive increase in heart rate. Abrupt withdrawal of a beta-blocker after long-term use is detrimental and should be avoided. Data about the selection of the most effective beta-blocker in reducing post operative atrial fibrillation is limited. Improved efficacy of carvedilol over metoprolol was demonstrated in two studies with 18-20% greater reduction of post operative atrial fibrillation in those on carvedilol (44-46); however, the length of hospital stay was not reduced. [16, Rank 1]




BB-β blocker
HR-Heart Rate
RCRI- Revised Cardiac Risk Index

Figure 24: Peri-operative management of β-blockers

According to the American College of Cardiology (ACC)/American Heart Association (AHA) and Heart Rhythm Society (HRS) 2014 guidelines; unless contraindicated, perioperative treatment with oral beta-blockers is recommended as a Class IA indication in patients undergoing cardiac surgery. In patients undergoing non-cardiac surgery, caution should be exercised with the use of beta-blockers. In patients already

receiving beta-blockers, their use should be continued (Class IA). In patients at high risk for cardiovascular events or with known ischemic heart disease or myocardial ischemia, preoperative initiation of beta-blockers may be considered (Class IIB). In patients at low risk for surgery, beta-blockers initiated before surgery are not recommended and high-dose beta-blockers without titration also are not recommended (Class III). Patients on beta-blockers during and after surgery must be carefully monitored if hypotension or bradycardia develops, and the dose reduced or temporarily held. [15, Rank 5]

## Prophylactic Use of Amiodarone

Amiodarone, an antiarrhythmic agent with multiple ion channel blocking properties as well as an anti-adrenergic effect, has been shown in several RCTs to be effective in reducing the occurrence of post operative atrial fibrillation by 12% to 51% when compared to placebo. In the Intravenous and Oral Amiodarone for the Prevention of post operative atrial fibrillation in Patients Undergoing Off-pump Coronary Artery Bypass Surgery trial, amiodarone infusion (5 mg/kg loading in the first postoperative hour, then 10 mg/kg for the first 24 hours) followed by oral administration (600 mg/day for 7 days and then 200 mg/day for 1 month) significantly reduced the incidence of new-onset atrial fibrillation (11.8% versus 26.5% control; p=0.025), the maximal ventricular rate response during atrial fibrillation and the duration of atrial fibrillation. Similar reduction in post operative atrial fibrillation was obtained in the Atrial Fibrillation Supression Trial II (AFIST II), with intravenous and oral amiodarone compared to the placebo or septal pacing group. The overall risk of post operative atrial fibrillation was reduced by 43% (p=0.037) and symptomatic atrial fibrillation by 68% (p=0.019) in amiodarone-treated patients vs. placebo. Intravenous amiodarone given postoperatively immediately after open heart surgery was shown to reduce the incidence of post operative atrial fibrillation (35% vs 47%; p=0.01) without significantly altering the length of stay in 300 patients undergoing standard open heart surgery randomized in a double-blind fashion to intravenous amiodarone (1 g/day for 2 days) vs. placebo.

Oral amiodarone use starting 6 days prior to surgery and continuing through six days after surgery in the PAPABEAR (Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair) trial, a double-blind, randomized, placebo-controlled trial enrolling 601 patients demonstrated a significant reduction in post operative atrial fibrillation

(16% vs. 30% in placebo group; p<.001) in both patients younger than 65 years (19% vs. 36%; P = .02) and those 65 years or older (28% vs. 54%; p<.001); in patients who had coronary artery bypass graft surgery only (22% vs. 46%; p=0.002), or valve replacement/repair surgery with or without coronary artery bypass graft surgery (25% vs. 44%; p=0.008); in patients who were on preoperative beta-blocker therapy (27% vs. 42%; p=0.03); and in those who did not receive preoperative beta-blocker therapy (20% vs. 48%; p<0.001), respectively. There were no differences in serious postoperative complications, in-hospital or 1-year mortality, or hospital readmission within 6 months of discharge. [14, Rank 5]

The dose response relationship of amiodarone and its pre- or postoperative use in reducing the incidence of post operative atrial fibrillation was assessed in a meta-analysis evaluating 14 RCTs in 2,864 patients, stratified into low (<3 g), medium (3-5 g), or high (>5 g) dosage and preoperative or postoperative timing. The incidence of PoAF was significantly reduced by amiodarone when compared to placebo (p<0.001). However, no difference in post operative atrial fibrillation outcomes was observed among the three dosing groups nor was there a difference based on pre- or postoperative administration of amiodarone. This study suggests that total amiodarone doses of 3 grams or higher may be effective in reducing the rate of post operative atrial fibrillation and that preoperative administration may not be necessary. However, this needs to be confirmed in a prospective manner. Another recent meta-analysis including 3,950 patients reported that both oral and intravenous administration, as well pre- and postoperative administration, of amiodarone was effective in prevention of post operative atrial fibrillation after cardiac surgery. Although superior to placebo in reducing the risk for post operative atrial fibrillation, no significant superiority of amiodarone over other antiarrhythmic agents, such as beta-blockers (propranolol, metoprolol and bisoprolol) and sotalol, could be established. Amiodarone has significant extracardiac (pulmonary, hepatic, visual and thyroid toxicity) and cardiac adverse effects, including significant bradycardia and QT interval prolongation, and caution should be used with its use; particularly, attention should be paid to potential drug-drug interactions with other medications. In a meta-analysis of 18 trials including 3,408 patients, an increase in the incidence of adverse reactions (bradycardia and hypotension), especially with intravenous formulation, was reported, and therefore amiodarone should not be routinely used and should be reserved for patients with a high risk of developing post operative atrial fibrillation.

In the most recent ACC/AHA/HRS guidelines published in 2014, amiodarone use is recommended as a Class IIa indication for reduction of post operative atrial fibrillation in high-risk individuals undergoing cardiac surgery or in patients unable to tolerate beta-blockers. Amiodarone also is recommended as a first-line drug in patients with heart failure who develop post operative atrial fibrillation with rapid ventricular rate response because digoxin is frequently ineffective in controlling ventricular rate with high adrenergic postoperative states and beta-blockers or non-dihydropyridine calcium channel blockers may not be tolerated due to negative inotropic effects in patients with severe ventricular systolic dysfunction. [12, Rank 5]

## Class III Antiarrhythmic Effects

The evidence for the effectiveness of Sotalol, a beta-blocker with Class III antiarrhythmic effects, in prevention of post operative atrial fibrillation comes from several small studies with reduction in the incidence of post operative atrial fibrillation between 13%-16%. In a comparative assessment of sotalol vs. conventional beta-blockers, 5 studies showed a significant decrease in the occurrence of post operative atrial fibrillation with sotalol when compared to beta-blockers. In another meta-analysis of 14 trials (five trials vs. beta-blockers; seven vs. placebo and two with both beta-blockers and placebo) including 2,583 patients, sotalol when compared to beta-blockers was more effective in reducing post operative atrial fibrillation from 25.7% vs. 13.7% (OR 0.42, 95% CI 0.26-0.65). However, the sotalol group had more side effects such as hypotension and bradycardia compared to placebo groups (6% vs. 1.9%, p=0.004). Another study reported a significantly increased risk of adverse events (10.7% vs. 2.9%) with higher sotalol dosing (240 mg) vs. low-dose sotalol (120 mg daily). Researchers similarly showed that a moderate sotalol dose of 160–240 mg daily significantly reduced post operative atrial fibrillation without appreciable side effects. The above data indicate that low-dose sotalol (<240 mg) may be better tolerated, reducing post operative atrial fibrillation without significant side effects. Despite its demonstrated effectiveness, sotalol is considered a second-line drug due to its effect on QT interval prolongation and higher incidence of proarrhythmia, including torsades de pointes, as well contraindication to its use in patients with renal insufficiency, congenital long QT syndrome or prolonged repolarization (QTc >460 ms), safety concerns in patients with advanced heart failure and the requirement for monitoring of the QTc interval. In the most recent 2014 ACC/AHA/HRS guidelines, preoperative adminis-

tration of sotalol is recommended as a Class IIb indication for patients at risk of developing post operative atrial fibrillation following cardiac surgery. [15, Rank 5]

Dofetilide, a Class III antiarrhythmic, was reported to be useful in prevention of postoperative atrial tachyarrhythmia following coronary artery bypass graft with and without valve surgery. In a double-blind, randomized, placebo-controlled study including 133 patients, dofetilide significantly reduced postoperative atrial tachycardia (18% vs. 36%; p<0.017). Interestingly, the number needed to prevent 1 patient from developing post operative atrial fibrillation was only 5.4 patients. There was no incidence of torsades de pointes in this study with a limited number of patients. Dofetilide currently is not recommended as a first-line therapy for prevention of post operative atrial fibrillation due to the need for close rhythm monitoring, side effects and increased risk of QT interval prolongation and proarrhythmia. [12, Rank 2]

## Non-dihydropyridine calcium channel blockers

Calcium channel blockers can be further classified into (as shown in figure 25) dihydropyridines and non-hydropyridines. The most smooth muscle selective class of calcium channel blockers are dihydropyridines. Because of their high vascular selectivity, these drugs are primarily used to reduce systemic vascular resistance and arterial pressure and hence used to treat hypertension. Non-hydropyridines mainly includes verapamil and diltiazem. Verapamil is relatively selective for the myocardium and is less effective as a systemic vasodilator drug. Diltiazem is intermediate between verapamil and dihydropyridines in its selectivity for vascular calcium channels.

There is some evidence regarding the usage of non-dihydropyridine calcium channel blockers (diltiazem and verapamil), which are Class IV antiarrhythmic agents, in the prevention of post operative atrial fibrillation following cardiac and non-cardiac surgery. A meta-analysis of 41 studies including 3,327 patients reported that non-dihydropyridine calcium channel blockers significantly reduced myocardial infarction (OR 0.58; 95% CI: 0.37 to 0.91; p=0.02), ischemia (OR 0.53, 95% CI 0.39 to 0.72; p<0.001) and supraventricular tachycardia (OR 0.62, 95% CI 0.41 to 0.93; p=0.02), which included patients with AF and atrial flutter. The same group in a separate systematic review of 11 studies involving 1,007 patients undergoing non-cardiac surgery reported a reduction in the occurrence of supraventricular tachycardia (SVT) (relative risk: 0.52; 95% CI: 0.37 to 0.72; p<0.0001) with the perioperative use of non-hydropyridine calcium channel

blockers. However, other meta-analyses failed to show a significant reduction in the incidence of postoperative supraventricular tachycardia with non-dihydropyridine calcium channel blockers following coronary artery bypass graft surgery. Currently, routine usage of non-dihydropyridine calcium channel blockers is not recommended by ACC/AHA/European Society of Cardiology (ESC) guidelines for the prevention of post operative atrial fibrillation. However, in patients who develop post operative atrial fibrillation, a non-dihydropyridine calcium channel blocker, is recommended as a Class I indication when a beta-blocker is inadequate to achieve rate control in both the ACC/AHA and ESC guidelines. [13, Rank 3]

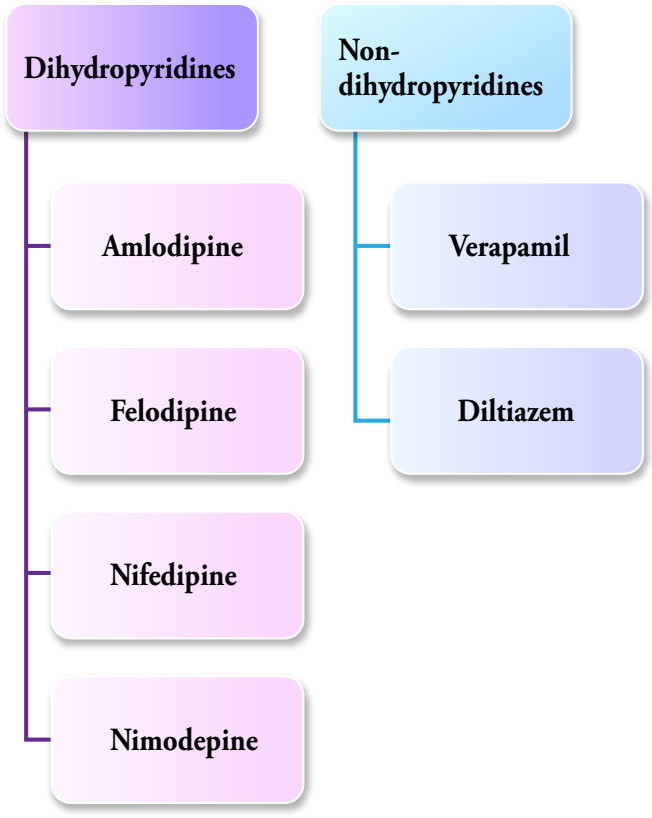



Figure 25: Calcium channel blockers

## 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)

3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins), routinely prescribed to lower low density lipoprotein cholesterol (as shown in figure 26), have been shown in multiple observational studies to reduce cardiovascular events, including post operative atrial fibrillation, by improving lipid profile and pleiotropic anti-inflammatory, antioxidative, cardioprotective, neurohumoral modulatory and coronary plaque stabilizing effects, reducing perioperative, 30-day and long-term mortality and cardiovascular events after cardiac or non-cardiac vascular surgery. In a recent meta-analysis of 15 RCTs involving 2,292 statin-naive patients undergoing cardiac or non-cardiac surgery, a reduction in the risk of PoAF was reported with the perioperative use of statins (relative risk [RR], 0.56; 95% CI, 0.45 to 0.69) along with the risk of MI (RR, 0.53; 95% CI, 0.38 to 0.74) but not death (RR, 0.62; 95% CI, 0.34 to 1.14). Overall, the duration of hospital stay was reduced in statin-treated patients but length of intensive care unit stay was unaffected. Preoperative initiation of statins (median 37 days before vascular surgery) when compared to placebo have been associated with a reduction in postoperative myocardial ischemia (hazard ratio, 0.55; CI, 0.34 to 0.88;

p=0.01), death from CV causes or MI (HR, 0.47; CI, 0.24 to 0.94; p=0.03) without any significant increase in the rate of adverse events. [11, Rank 4]

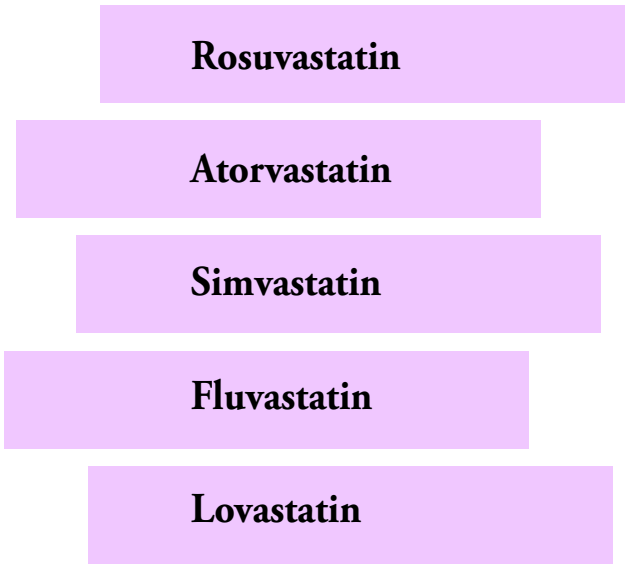



Figure 26: Lipid lowering drugs

In a recent Cochrane review of 5 RCTs of statin-naive patients undergoing elective or emergency non-cardiac arterial surgery treated with statin therapy (178 patients), started before or on the day of surgery and continuing for at least 48 hours afterward, a non-significant decrease in risk of 30-day all-cause mortality (RR 0.73, CI 0.31 to 1.75), CV mortality (RR 1.05, % CI 0.07 to 16.20) and non-fatal MI (RR 0.47, CI 0.15 to 1.52) compared to placebo was reported. The number of patients (178) included in the meta-analysis was limited. Most studies involving statins in the prevention of post operative atrial fibrillation have been promising. Atorvastatin was reported to decrease post operative atrial fibrillation following coronary artery bypass graft surgery by 14-22% when compared to placebo or usual care. The Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery study (ARMYDA-3), including 200 statin-naive patients undergoing elective cardiac surgery with cardiopulmonary bypass, reported that atorvastatin 40 mg daily starting 7 days prior to surgery when compared to placebo significantly reduced the incidence of post operative atrial fibrillation (35% versus 57%, p=0.003) and length of stay (6.3±1.2 days vs. 6.9±1.4; p=0.001). Benefits of statin pretreatment in the prevention of PoAF (24.9 vs. 29.3%; OR 0.67, 95%CI: 0.51-0.88, p<0.001) and reduction in hospital stay (weighted mean difference –0.66 days, 95% CI –1.01 to –0.30 days, p=0.0004) also was demonstrated in 2 other meta-analyses. Higher doses of statins had a more protective effect than lower doses in prevention of post operative atrial fibrillation. One retrospective study including 680 patients reported that higher-dose simvastatin (40 mg) and atorvastatin (40 mg) demonstrated the greatest benefit in reduction of post operative atrial fibrillation (15.6% and 21.2%) vs. no statins (ORs, 3.89 [p<0.0001] and 2.76 [p=0.012]) or lower doses. Similarly, it was reported that patients undergoing cardiac surgery treated

with higher-dose simvastatin (>20 mg) daily had a 36% reduction in the risk of post operative atrial fibrillation (OR 0.64, 95% CI 0.43 to 0.6; p=0.03) in comparison to those taking lower dosages. Combination of atorvastatin with a beta-blocker appears to be more effective than either drug alone, reducing the risk of post operative atrial fibrillation by 90% (OR 0.10; 95% CI 0.02-0.25) in one study. In a recent meta-analysis, statin treatment perioperatively was not associated with a significant reduction of post operative atrial fibrillation (OR 0.95; 95% CI 0.88-1.03, p=0.24) beyond 6 months follow-up in coronary artery bypass graft patients. Information on post operative atrial fibrillation prevention with preoperative statin use in patients undergoing valvular or non-coronary heart surgery is not available. The reduction in post operative atrial fibrillation with perioperative use of statins is therefore not universally reported in observational studies that do not provide precise information about the timing of initiation, the duration of statin therapy or the mechanism of benefit. Despite limited data from RCTs that enrolled only a small number of patients, the overall evidence from observational studies points toward a protective effect of perioperative statin use on cardiac complications during cardiac and non-cardiac surgery. [9, Rank 5]

## Corticosteroids

Prophylactic short-term corticosteroid usage as an anti-inflammatory agent has shown some benefit in the prevention of post operative atrial fibrillation following cardiac surgery. Researchers, in a study including 88 patients undergoing coronary artery bypass graft, demonstrated that 1 gm of intravenous methylprednisolone before surgery and 4 mg dexamethasone every 6 hours for 1 day after surgery reduced the incidence of post operative atrial fibrillation by 30% when compared to placebo. However, there was no significant difference with regard to the length of hospital stay, and the steroid group had a significant 21% increased complication rate. Similar findings were reported in a randomized, multicenter trial including 241 patients undergoing coronary artery bypass graft and aortic valve replacement. Intravenous administration of hydrocortisone (100 mg) in the evening of the operative day, then every 8 hours for the next 3 days significantly reduced the incidence of post operative atrial fibrillation with no increased risk of postoperative complications. Interestingly, both these studies also used beta-blockers in all patients. Three other recent meta-analyses also have reported that corticosteroids significantly reduced the incidence of post operative atrial fibrillation following cardiac surgery. [8, Rank 5]

## Other therapeutic modalities for treatment of arrhythmias

While drug therapy is still the most common method for treating arrhythmias, other non pharmacological therapies are also in current use (as shown in figure 27):

- DC cardioversion, implanting of a pacemaker or implantable cardioverter defibrillator
- Carotid sinus massage
- Surgical or catheter mediated ablation of an ectopic focus, coronary bypass surgery
- Lifestyle modification (avoiding events that aggravate an arrhythmia e.g. exertion, emotional stress, non-ideal diet)

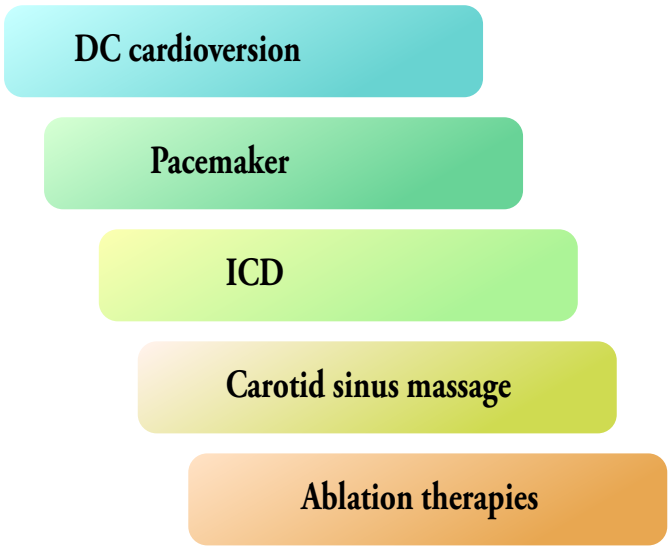



Figure 27: Other therapeutic treatment modalities of arrhythmias

## Conclusion

Current drug therapy for ventricular arrhythmia has been limited by suboptimal efficacy in many patients, resulting in recurrent ventricular tachycardia / ventricular fibrillation events, and by drug toxicity or intolerance leading to discontinuation in a large percentage of patients. Amiodarone and sotalol are the principal agents used in the chronic treatment of ventricular tachycardia. In addition, dronedarone and dofetilide, agents approved for the treatment of atrial fibrillation, and ranolazine, an antianginal agent, have been demonstrated to be protective against ventricular arrhythmia in small clinical studies. Finally, advances in basic electrophysiology have uncovered new molecular targets for the treatment of ventricular arrhythmia, and pharmacologic agents directed at these targets may emerge as promising ventricular tachycardia treatments in the future. [2, Rank 3]

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