

## Preventing Recurrences: Classic and Modern Antiarrhythmic Drugs in Atrial Fibrillation

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### Abstract

Medication for atrial fibrillation (AF) with antiarrhythmic drugs (AAD) has been in use for almost 100 years and today remains an essential part of the treatment in patients with this condition.

The goals of drug treatment include reducing the number, duration and symptoms of atrial fibrillation episodes, reducing mortality and hospitalizations as well as improving the patients' quality of life. AAD use is limited by adverse effects which include proarrhythmia, negative inotropic and non-cardiovascular toxicity. The efficacy of these drugs is limited, which means that there are other invasive options that are clearly more effective for symptomatic control of patients.

**Keywords:** Atrial fibrillation; Anti arrhythmias; ANS; Atrial dilatation

### Introduction

Despite these limitations, AAD medication is, universally, the method most widely used to treat and prevent atrial fibrillation (AF) and research is ongoing to develop new attractive molecules in this pathology.

AF leads to increased wall tension in the atrial chamber, which promotes atrial dilatation. AF has a significant tendency to be self-perpetuating (AF begets AF), therefore, once a rhythm control strategy has been determined, cardioversion (CV) should not be delayed because if the arrhythmia continues over a long period of time and the atrium becomes dilated, CV is often ineffective or, if achieved, recurrences are frequent [1].

The frequency of ventricular response depends on the conduction state of the AV node and this, in turn, is mainly mediated by the autonomic nervous system (ANS). At rest, ventricular response can be maintained within an acceptable range; however increased physical activity or other adrenergic stimulation can lead to high ventricular responses that hemodynamically compromise the patient because the increased frequency is achieved at the expense of shortening the diastolic time, thereby decreasing the ventricular filling time. In addition, ventricles that are chronically subjected to high frequencies eventually present structural alterations that reduce their contractility [2]. This phenomenon, known as tachycardiomyopathy, may become irreversible if the ventricular rate cannot be controlled within a given time. In conclusion, when a rhythm control strategy is unsuccessful or has been rejected, the therapeutic objective will be to control the ventricular response [3].

Due to the fact that complications with arterial thromboembolism have the greatest impact on morbidity and mortality, stroke prevention is a key therapeutic objective in AF. Anticoagulation treatment is very effective at preventing systemic embolism [4] but has potential bleeding complications that should also be taken into consideration whenever evaluating the benefit/risk ratio [5]. Given that the embolic risk in AF is not uniform but varies in relation to different factors, the decision whether or not to anticoagulate patients with AF must be individualized according to existing embolic assessment and bleeding risk scales.

### Maintaining Sinus Rhythm

Several studies comparing rhythm control versus rate control have failed to demonstrate the superiority of one strategy over the other; this is partly due to the toxicity of AAD as well as the risk of embolic events in rhythm control group patients who discontinued anticoagulant therapy [6-10]. With the emergence of these studies, and especially the AFFIRM trial, AAD prescribing dropped significantly, however, with the advent of ablation therapy in recent years, the indication for AAD has again started to increase [11-13].

The recommendations in the latest European Society of Cardiology (ESC) guidelines on AF (Table 1) essentially consider antiarrhythmic therapy in patients with recurrent arrhythmia (paroxysmal and persistent) who present significant symptoms despite adequate rate control during episodes [14]. These indications are based on several meta-analyses and systematic reviews that have confirmed the effectiveness of AAD at the same time as indicating signs for concern relating adverse events and mortality with the use of these drugs [15-18]. For this reason, it is important to emphasize that AAD therapy should mainly be used to control refractory symptoms due to recurrent AF, and the principal of safety must always prevail.

### Short-or Long-Term Treatment?

AAD therapy is usually given as long-term treatment, however, the FLEC-SL (Flecainide Short Long) study published in 2012 [19] randomized 635 patients (mean age 64 years, 64% male, 97% left ventricular ejection fraction preserved, 6% with coronary artery disease, mean left atrial diameter 47 mm) to receive the following: 1) no AAD treatment, 81 patients; 2) long-term therapy, 263 patients; or

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3) AAD only for 4 weeks after cardioversion, 261 patients. The trial demonstrated the hypothesis that short-term therapy was not inferior to long-term therapy during a 6 month follow-up. The effectiveness of short-term therapy was estimated to be 80% compared to flecainide treatment continued for 6 months. A previous study, which compared amiodarone administered until reversion to sinus rhythm with continued amiodarone, demonstrated that amiodarone does not seem suitable for short-term treatment due to being less effective than sustained treatment [20].

Altogether, the available information suggests that short-term antiarrhythmic drugs after cardioversion should not be the initial treatment by default, and especially with amiodarone, but it may still be useful in patients who have infrequent AF recurrences or a high risk profile for adverse effects from AAD.

### Effectiveness of AAD in Maintaining Sinus Rhythm

The effectiveness of AAD in preventing recurrent atrial fibrillation, according to a meta-analysis of 44 randomized controlled trials which compared antiarrhythmic drugs against placebo or no treatment, showed that these drugs significantly reduced the recurrence of AF, and that AAD approximately doubled the probability of maintaining sinus rhythm. Amiodarone was superior to any class I drug or sotalol. This meta-analysis highlighted that the suspension of AAD due to side effects was common (1 per 9-27 patients), although mortality was low in all studies (0 to 4.4%) due to the inclusion of relatively healthy patients. The use of sodium channel blocking drugs was associated with increased mortality (OR 2.39, 95% CI: 1.03 to 5.59, P = 0.04) [21].

### Classic AADs

Although AAD cannot be perfectly adapted to any specific classification scheme given that many of them have effects on multiple ion channels and adrenergic receptors implicated in cardiac muscle cell action potential (Figure 1), the classification created by Vaughan Williams in 1970 is still currently used [22]. This scheme classifies these drugs based on their main mechanism, however many antiarrhythmic agents have multiple mechanisms of action such as, for example, amiodarone which for its effects would be located in all groups. Another historical limitation is that some drugs, such as digoxin or adenosine, had no place in the classification system.

Most currently available AAD exert a predominant effect on the flow of sodium or potassium. Sodium channel blocking drugs are also called “membrane stabilizers” because they decrease the excitability of cardiac tissue, and those that have an effect on potassium flows prolong the duration of action potential and refractory periods. The effects on different ion channels have their electrocardiographic translation for each drug (Table 2).

Under the Vaughan Williams classification there are four main types of antiarrhythmic agents: (Table 3)

**Class I:** drugs that block voltage dependent Na<sup>+</sup> channels. They inhibit sodium flows and, therefore, decrease the rate of cardiac conduction and excitability:

- Group Ia: drugs with intermediate recovery kinetics
- Group Ib: drugs with fast recovery kinetics
- Group Ic: drugs with slow recovery kinetics

**Class II:** Agents that oppose the sympathetic nervous system, most of them are β-blockers.

**Class III:** Agents that affect K<sup>+</sup> efflux, these are drugs that cause prolongation of the action potential, and therefore, the refractory period.

**Class IV:** Agents that affect Ca<sup>2+</sup> channels dependent on the L-type voltage, inhibiting calcium flux decreases the conduction velocity and the refractory period of the sinus and atrioventricular node.

### Class IA AAD

These are drugs that bind to the channel in active state, reducing sodium influx and slowing conduction. The longer the channels are open (active), the more the drugs act (higher activity with high heart rates). They are used in the treatment of supraventricular arrhythmias.

### Quinidine

This is derived from the cinchona plant and was identified as a possible antiarrhythmic drug a century ago. It has a vagolytic effect, blocking sodium channels and also possesses certain potassium channel (Ito channels) blocking effects. It is rarely used for AF due to a meta-analysis that showed increased mortality secondary to QT prolongation and risk of torsades de pointes [21]. However, due to its effect on potassium channels, it has generated interest as a potential therapy for Brugada syndrome and early repolarization syndrome associated with ventricular fibrillation [22].

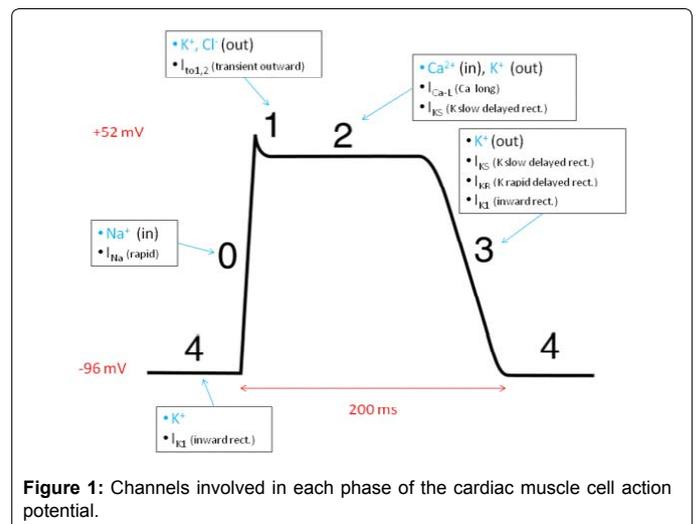


Figure 1: Channels involved in each phase of the cardiac muscle cell action potential.

ESC rhythm control recommendations	Class Level	Evidence level
Rhythm control is recommended in patients with symptomatic (EHRA score >2) AF despite adequate rate control.	I	B
Rhythm control in patients with AF and AF-related heart failure should be considered for improvement of symptoms.	Ila	B
Rhythm control as an initial approach should be considered in young symptomatic patients in whom catheter ablation treatment has not been ruled out.	Ila	C
Rhythm control should be considered in patients with AF secondary to a trigger or substrate that has been corrected (e.g. ischaemia, hyperthyroidism).	Ila	C

ESC: European Society of Cardiology  
EHRA: European heart rhythm association

Table 1: Recommendations for rhythm control from the latest ESC guidelines for the management of AF (2010). (14)

Antiarrhythmic	Year of development or approval	Channel block	Electrocardiographic manifestations
Quinidine	1918	$I_{Na}^+$ , $I_{Kr}^+$ , $I_{to}^+$ , $I_{ACh}^+$ , $\alpha$	↑ Heart rate ↑ QT ↑ QRS
Disopyramide	1962	$I_{Na}^+$ , $I_{Kr}^+$ , acetylcholine	↑ Heart rate ↑ QT ↑ QRS
Amiodarone	1967	$I_{Kr}^+$ , $I_{Na}^+$ , $I_{KUr}^+$ , $I_{to}^+$ , $I_{CaL}^+$ , $I_f$ , $\beta$ , $\alpha$ , acetylcholine	↓ Heart rate ↑ PR ↑ QRS ↑ QT
Flecainide	1975	$I_{Na}^+$	↓ Heart rate ↑ PR ↑ QRS
Propafenone	1976	$I_{Na}^+$ , $\beta$	↓ Heart rate ↑ PR ↑ QRS
Sotalol	1992	$I_{Kr}^+$ , $\beta$	↓ Heart rate ↑ PR ↑ QT
Dofetilide	2000	$I_{Kr}^+$	↑ QT
Dronedarone	2009	$I_{Kr}^+$ , $I_{Na}^+$ , $I_{Ca}^+$ , $\beta$ , $\alpha$ , acetylcholine	↓ Heart rate ↑ PR

**Table 2:** emergence of different drugs over time, affected channels and electrocardiographic manifestations.

Class	Mechanism	Action	Examples
IA	Sodium channel blockers with intermediate binding kinetics. Frequency dependent. Slows action potential in phase 0 and 3.	Inhibition of sodium flow, thereby decreasing conduction velocity and cardiac excitability.	Procainamide, quinidine, disopyramide, ajmaline.
IB	Sodium channel blockers with rapid binding kinetics. Minimal effect on phase 0, increases phase 3 speed.		Lidocaine, mexiletine, phenytoin.
IC	Sodium channel blockers with slow binding kinetics. Frequency dependent. Depresses phase 0 depolarization. Most powerful action in Class I.		Flecainide, propafenone.
II	Blocking of $\beta_1$ -receptors, catecholamine inhibition. Prolongs phase IV action potential.	Sympatholytic. Decreases sinus node automaticity.	Atenolol, metoprolol, propranolol, etc.
III	Preferentially act on potassium channels. Mainly slowing phase 3 action potential.	Prolongation of action potential delaying repolarization and increasing the refractory period.	Amiodarone, dronedarone, dofetilide, sotalol, ibutilide.
IV	Calcium channels blocking.	Interferes with the flow of calcium in the action potential.	Diltiazem, verapamil.

**Table 3:** Vaughn Williams classification of antiarrhythmic drugs

Its non-cardiovascular side effects include diarrhea as well as cinchonism (tinnitus and headache) and thrombocytopenia. In association with verapamil, it can suppress early post-depolarizations thereby reducing the risk of torsades de pointes associated with its use [23].

### Disopyramide

This is distinguished for being a sodium channel blocker with a potent anticholinergic and negative inotropic effect, so much so that, although scientific evidence is scarce, it has been recommended for patients with vagal AF [22]. The negative inotropic effects of this drug also make it a viable option for patients with AF and hypertrophic cardiomyopathy [24]. It should be avoided in narrow-angle glaucoma, prostatic hypertrophy or myasthenia gravis.

### Procainamide

This has a very similar effect to quinidine but its use is limited to ventricular arrhythmias. It has adverse effects, similar to lupus, that disappear when the drug is withdrawn. In patients with renal insufficiency it has been associated with accumulation of N-acetylprocainamide (NAPA), its active metabolite, which leads to the risk of torsades de pointes.

### Class IB AAD

These act on the inactive conformation channels and have increased activity on tissues with longer action potential (ventricles) therefore they are more effective in ventricular than atrial arrhythmias, as a result they are not used in AF.

### Class IC AAD

These act on the open channel as do Class IA, but have slow kinetics; therefore they remain bound for a longer period and produce a stabilizing effect on the membrane. They produce a great decrease in the maximum depolarization velocity, reducing atrioventricular conduction and myocardial contractility.

### Flecainide y propafenone

These were initially evaluated in paroxysmal AF, but are also used to maintain sinus rhythm after cardioversion. They can be safely administered in patients without significant structural heart disease, but should not be used in patients with coronary disease or those with decreased left ventricular function (moderate negative inotropic effect). Caution should be exercised in the presence of intraventricular conduction disorders, and especially left bundle branch block. Besides

its sodium channel blocker effect, flecainide also has mild effects on the potassium channel (IKr) but in general this is not significantly related to QT interval prolongation. As for propafenone, it also has a  $\beta$ -blocking effect and therefore certain negative chronotropic effects.

When initiating treatment with these drugs, or increasing their doses, periodic ECG monitoring is recommended and, in cases where QRS duration is increased by 25%, the dose should be reduced or discontinued due to the risk of proarrhythmia. Special attention should be given to patients with ST-segment elevation in precordial leads suggestive of a Brugada pattern, since the group 1C AADs are contraindicated in this field.

The use of these drugs requires a concomitant atrioventricular node blocker due to the possibility of converting the AF to atrial flutter with very good conduction through the atrioventricular node and aberrant intraventricular conduction, known as IC flutter. Dizziness and visual disturbances represent the most frequently observed non-cardiovascular side effects with flecainide (5% to 10%). The main non-cardiovascular adverse effects of propafenone include a metallic taste, as well as dizziness and visual disturbances.

## Class II AAD

$\beta$ -blocker drugs, which are widely used in clinical cardiology, have a very modest effect in preventing AF recurrences, with the exception of thyrotoxicosis and exercise-induced AF (adrenergic AF).

## Class III AAD

The main characteristic of this group is that they prolong action potential duration and the refractory period (phase 0, II and III). They have a complex mechanism of action which is still not well understood. These mainly act on potassium channels but also act on calcium channels through  $\beta$ -blocker mechanisms.

### Amiodarone

This is the antiarrhythmic drug most prescribed in atrial fibrillation [18]. It is an iodinated compound which, through its active metabolite, blocks various sodium, potassium and calcium channels ( $I_{Kr}$ ,  $I_{Na}$ ,  $I_{Kur}$ ,  $I_{to}$ ,  $I_{CaP}$ ,  $I_{KACH}$  and  $I_p$ ) in addition to possessing a non-competitive agonists of  $\alpha$ - and  $\beta$ -adrenergic receptors. It is a multi-channel blocking drug. It has a very long half-life, up to several weeks, and significant distribution in fatty tissue. It is the most effective antiarrhythmic drug currently available, but is limited by its side effects. The major cardiovascular side effects of amiodarone are bradyarrhythmias and QT interval prolongation.

Amiodarone requires monitoring at liver, lung and thyroid levels due to potential toxicity in these organs. Liver toxicity is manifested by mild elevation of transaminases. Pulmonary toxicity can manifest as an acute hypersensitivity reaction with scattered infiltrates or as a chronic process with interstitial fibrosis or solitary pulmonary nodules. Amiodarone inhibits T4 to T3 conversion, and elevated TSH can be expected during the first few months of therapy, therefore hypothyroidism should not be diagnosed unless free T4 levels are suppressed. Hyperthyroidism occurs most frequently in the early years and recurrent AF may be the first sign. There is a Type 1 that often occurs with the pre-existence of a thyroid nodule or Graves' disease, and a Type 2 which is a destructive thyroiditis that finally leads to hypothyroidism. Due to its long half-life, adverse effects of amiodarone can persist after administration is stopped.

The most important interaction of amiodarone is produced by

enhancing the effect of warfarin through CYP2C9 inhibition. The combination of amiodarone with simvastatin has been associated with increased risk of myositis. This risk seems to be lower when combined with pravastatin which does not use cytochrome P450 for its metabolism [25]. Another interaction of amiodarone is reduced clearance of digoxin due to P-glycoprotein inhibition.

### Dronedarone

This is the first of a group of drugs that have been designed to be similar to amiodarone but with fewer side effects. It is a derivative of benzofuran related to amiodarone but without iodine. It acts by blocking sodium and potassium channels; a non-competitive adrenergic antagonist which possesses certain calcium antagonist properties.

The EURIDIS and ADONIS trials in 2007 showed dronedarone to be superior to placebo in reducing recurrences in patients with paroxysmal atrial fibrillation [26]. The use of this drug is not recommended in patients with decompensated heart failure because of the results of the ANDROMEDA study, a study that was designed to evaluate its effects in advanced heart failure, which showed increased mortality in these patients [27]. Subsequent studies into its effectiveness in healthier AF patients have shown a reduction in cardiovascular hospitalizations and mortality without significant extracardiovascular toxic effects [28,29]. In addition, in the ATHENA study, dronedarone was the only antiarrhythmic drug that demonstrated a reduction in the risk of stroke, hospitalization and death in patients with AF, but without being able to determine whether this reduction was due to the maintenance of sinus rhythm or some other factor [30]. The PALLAS study associated dronedarone in permanent AF with a greater risk of stroke, cardiovascular death and hospitalization therefore, currently, dronedarone should be avoided in patients with permanent AF, and periodic heart rate monitoring is recommended [31].

Dronedarone, like amiodarone, interacts with P-glycoprotein leading to an increased concentration of digoxin, it also interacts with CYP3A4, and in combination with simvastatin it may increase the risk of myositis. Dronedarone does not increase the international normalized ratio in patients taking warfarin.

In 2011, the FDA issued a warning concerning dronedarone based on reported cases of severe hepatotoxicity that occurred within the first 6 months of treatment [32]. As a result, the European Medicines Agency recommends routine liver function monitoring during the first 6 months of therapy (<http://www.ema.europa.eu/ema/>).

### Sotalol

This is a potassium channel blocker (IKr) with non-selective  $\beta$ -blocking effects. It has minimal cardiovascular side effects and a high rate of use (26% of annual prescriptions in the United States). It is eliminated by the kidneys and is prescribed twice daily unless creatinine clearance is between 30-60 ml/min, in which case it should be prescribed just once per day. QT prolongation (if  $\geq 500$  ms the dose must be reduced or the treatment stopped) and bradycardia should be monitored as these were demonstrated to be proarrhythmic risk markers [33]. Females, patients with marked left ventricular hypertrophy, severe bradycardia, ventricular arrhythmias, renal dysfunction, hypokalemia or hypomagnesemia have an increased risk of proarrhythmia [34]. In the SAFE-T study, the efficacy of sotalol to maintain sinus rhythm was not demonstrated to be inferior to amiodarone in the subgroup of patients with ischemic heart disease [35].

## Dofetilide

This is also an IKr channel blocker but without other electrophysiologic effects. It is eliminated renally and doses should be adjusted according to creatinine clearance. It was approved for use by the FDA in 2000 with a mandatory hospitalization period of 3 days but it is not available in Europe. Dofetilide is more effective for maintaining sinus rhythm than for use in pharmacological cardioversion [36]. It has been shown to be reasonably safe in heart failure and post-myocardial infarction [37,38].

## New AADs under development

Current pharmacological weapons for treating AF have important limitations, including incomplete effectiveness and frequent proarrhythmic risk. Therefore, the majority of new antiarrhythmic drugs under development are formulated with the intention of reducing proarrhythmic toxicity, with effects on multiple ion channels and a specific presence in atrial tissue.

## Vernakalant

This blocks several types of ion channels, its greatest effect is over potassium flows in atrial tissue (Ito, Iach and IKur channels) but also with an effect on sodium channels. By blocking these channels vernakalant can prevent abnormal electrical activity that can lead to AF. It must be clarified that, to date, this medication has been proven effective intravenously for acute reversion of AF, [39-41] nevertheless, an oral formulation to prevent recurrences is currently under development. The main side effects of vernakalant include cough, sneezing, and dysgeusia. It should not be used in patients who may be hypersensitive to any of its ingredients, those with severe aortic stenosis, advanced heart failure, severe bradyarrhythmias or within 30 days of an acute coronary syndrome. The concomitant intravenous use of "Class I and III" antiarrhythmic agents should be avoided during the four hours before and after the infusion of vernakalant.

## Budiodarone

This is a structural analogue of amiodarone with similar ion-blocking properties. It is an iodinated compound, but is extensively metabolized in blood and by CYP3A4 in liver tissue. This difference with respect to amiodarone allows faster metabolism and a lower likelihood of adverse effects. This drug has been evaluated in a study of paroxysmal AF patients fitted with pacemakers, and demonstrated decreased frequency and duration of episodes [42].

## Ranolazine

A new drug approved for chronic angina pectoris. A blocker of a number of ion flows (Ina, CaL and IKr). Preliminary clinical data with the use of ranolazine as an anti-ischemic drug have shown a reduction in supraventricular arrhythmias, including AF [43]. There is also evidence from experimental studies that demonstrate a synergistic potential with amiodarone or dronedarone [44,45]. The inhibition of sodium flows with ranolazine or vernakalant could theoretically reduce the risk of torsades de pointes associated with potassium channel blocking AADs, but this still has to be proven in clinical trials [46,47].

## Proarrhythmic effect of AAD

Sodium channel blocking drugs favour slow conduction and, in susceptible patients with pre-existing fibrosis or ischemia, may promote the development of reentrant ventricular arrhythmias. This effect was demonstrated in the classic CAST trial, where it was shown that the reduction of ventricular arrhythmias after myocardial infarction was

associated with increased mortality when using these drugs [48]. As previously noted with flecainide and propafenone, atrial flutter is a common arrhythmia with these drugs, typically, the atrial rate is slower which can promote 1:1 atrioventricular conduction with an aberrant QRS due to intraventricular conduction disorders produced by these agents. In patients with loss-of-function mutations in sodium channels, such as some patients with Brugada syndrome, ventricular arrhythmias may appear secondary to the use of these drugs.

Potassium channel blocking drugs carry a risk of torsades de pointes, in most cases this occurs through the reduction in the potassium flow (IKr) and is more commonly seen in slow heart rates, especially after a pause subsequent to the conversion of AF to sinus rhythm. Other predisposing factors to the development of arrhythmias include hypokalemia, hypomagnesemia, female gender, prolonged baseline QT and the concomitant use of other therapies that prolong the QT interval. The risk of QT prolongation and torsades de pointes is related to the doses of sotalol and dofetilide, but not to quinidine or disopyramide. Amiodarone often prolongs the interval but its association with this arrhythmia is very uncommon.

In a mixed comparison analysis by Freemantle, which compared the effect of each of the most commonly used AADs against placebo on the incidence of arrhythmic events, it was shown that dronedarone, propafenone, sotalol and flecainide were all associated with increased proarrhythmic events, as would be expected, but dronedarone presented the lowest risk Figure 2 [30].

## AAD choice

### Which is the best for my patient?

The choice of AAD is made according to the safety profile for the individual patient and not on the basis of its effectiveness.

The latest guidelines for the American College of Cardiology (ACC), American Heart Association (AHA) and the European Society of Cardiology (ESC) agree on the use of flecainide, propafenone, sotalol, amiodarone or dronedarone in patients without significant underlying structural heart disease, such as heart failure, coronary artery disease or severe left ventricular hypertrophy [14,49].

They also agree on the use of sotalol, amiodarone and dronedarone in patients with coronary artery disease and only amiodarone for patients with symptomatic congestive heart failure. Patients with mild left ventricular hypertrophy have the same drug options as those without structural heart disease, however severe left ventricular hypertrophy (thicker than 14 mm) is considered a risk for toxicity with potassium and/or sodium channel blocking drugs, dronedarone/

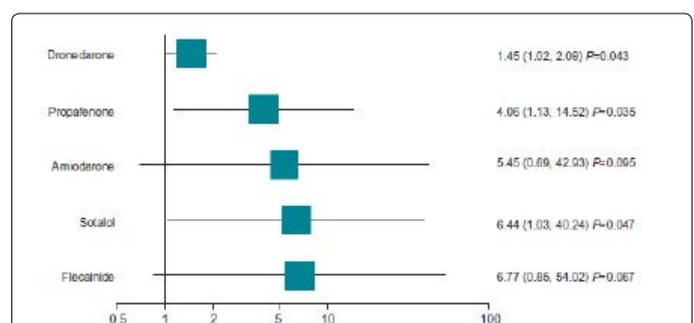


Figure 2: Comparative mixed analysis of proarrhythmic events with various drugs compared to placebo, with the OR, 95% confidence interval and its significance. Dronedarone had the lowest increase in risk.(30)

amiodarone (ESC) or amiodarone (ACC/AHA) have been suggested as possible options.

There are some differences between European and American guidelines with respect to certain indications, for example, the ESC guidelines suggest that disopyramide could be considered in patients with AF associated to vagal triggers, whereas quinidine, procainamide and disopyramide are completely omitted by the ACC/AHA. Dofetilide is not approved for use in Europe, but according to ACC/AHA guidelines it could be indicated in all patients.

In conclusion, it can be said that in clinical practice, propafenone, flecainide, sotalol, or dronedarone can be used as first-line therapies in patients without structural heart disease. In patients with solitary AF without structural heart disease, the initial choice of drug may be based on the presence of clear vagal or adrenergic arrhythmia triggering (use of  $\beta$ -blockers or disopyramide). If no such relationship exists, the drugs previously described should be used. Dofetilide and amiodarone are a second option, firstly due to the requirement of hospitalization for the initial dose, and secondly, for the risk of toxicity.

Sotalol or dronedarone are first-line therapies (relatively preserved left ventricular function) in patients with ischemic heart disease. If coronary artery disease is associated with left ventricular dysfunction, dofetilide or amiodarone should be evaluated.

The drugs of choice in patients with AF and congestive heart failure are dofetilide or amiodarone (Table 4).

### Which is the most effective AAD?

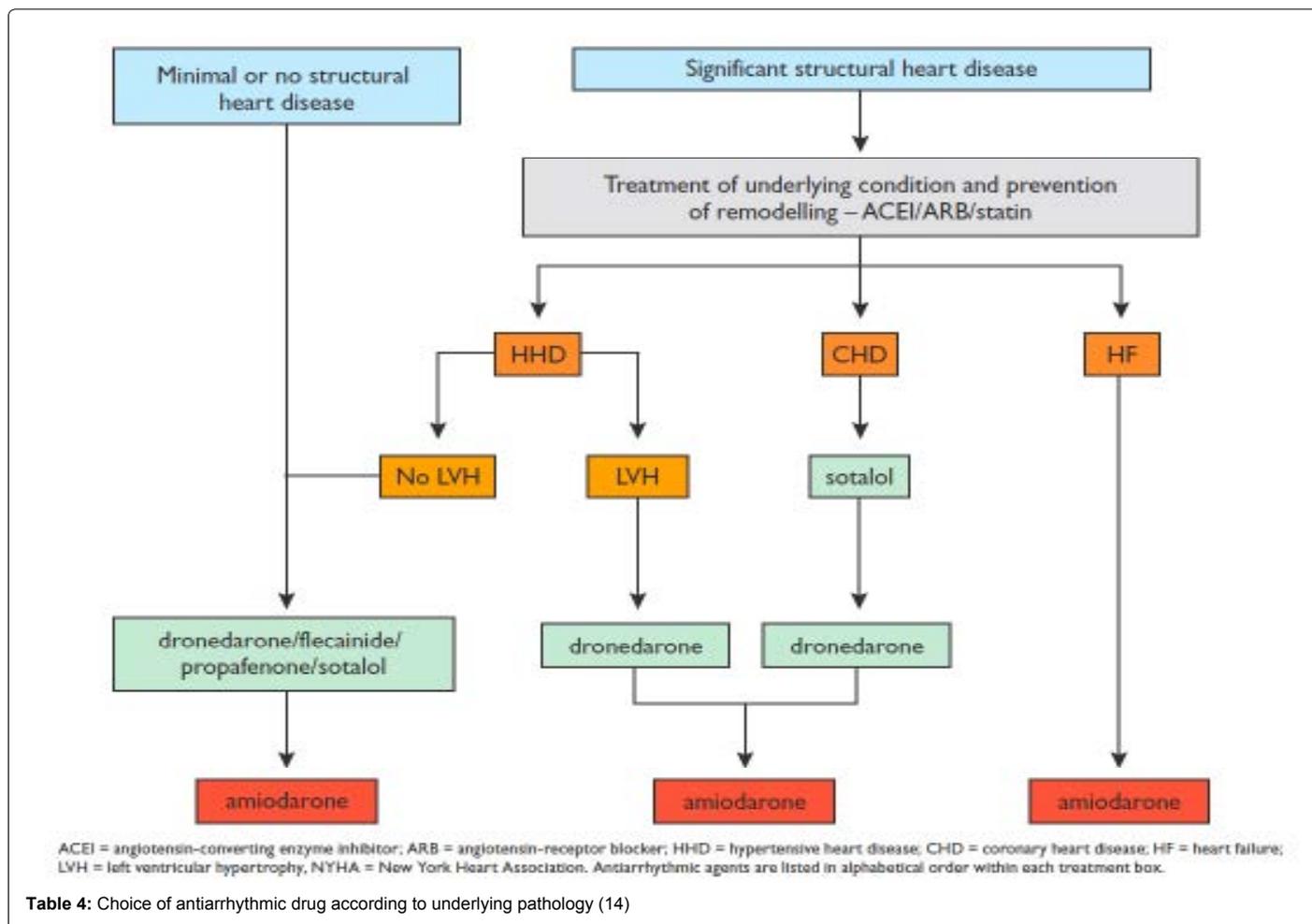
Amiodarone has been directly compared with dronedarone, sotalol and propafenone and has proved to be the most effective in maintaining sinus rhythm, 65% of patients without AF recurrences at 1-year follow-up, the overall recurrence-free rate for the other antiarrhythmic drugs was between 30-40% (Table 5) [15,50-53].

Dronedarone has been directly compared with amiodarone in a short-term study which demonstrated that unsuccessful chemical cardioversion or arrhythmia recurrence after cardioversion was more common with dronedarone than amiodarone, 64% versus 42% [50]. Two large studies which compared dronedarone versus placebo after 12 months' follow-up showed efficacy rates of 35%. However, dronedarone was the best tolerated AAD, with the lowest rate of serious adverse events and a significant reduction in the risk of stroke [28,30].

Dofetilide AAD has also been associated with a sinus rhythm maintenance rate of 50% at 1 year, with greater success in those patients that can tolerate maximum doses [36].

### Conclusion

Based on the review of published studies, the data published up to now do not support a generalized strategy for the restoration of sinus rhythm in the majority of patients with atrial fibrillation. Frequency control has shown equal or better survival, quality of life and other "end points". This is due in part to poor efficacy of current antiarrhythmic



Trial	Patients included and monitoring	Drugs	Percentage of patients free of recurrence
CTAF (Canadian Trial of Atrial Fibrillation)	403, 16 months	Amiodarone Sotalol Propafenone	65% 37% 37%
SAFE-T (Sotalol Amiodarone Atrial Fibrillation Efficacy Trial)	665, 33 months	Amiodarone Sotalol Placebo	65% 25% 10%
PAFAC (Prevention of Atrial Fibrillation After Cardioversion)	848, 9 months	Sotalol Quinidine Placebo	33% 35% 17%
DIONYSOS (Efficacy and Safety of Dronedaronne Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation)	504, 7 months	Amiodarone Dronedaronne	58% 36%

**Table 5:** comparing the effectiveness of various antiarrhythmic drugs in different studies. (15,50-53)

drugs and their potential adverse cardiac and extracardiac events. Ablation with pulmonary vein isolation, carried out in specialized centres, is an effective therapeutic tool for selected patients that, in the future, may promise a re-evaluation of our behaviour, however, solid long-term evidence is still pending.

Our goal with the use of any antiarrhythmic drug is to reduce the frequency of symptomatic episodes of AF, with occasional expected recurrences which do not necessarily constitute a reason to discontinue AAD treatment.

The clinical use of antiarrhythmic drugs must be guided, primarily by the risk of toxicity, and then by their effectiveness.

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