Prophylactic Antiarrhythmic Drug Therapy in Atrial Fibrillation

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Abstract

In patients with recurrent atrial fibrillation (AF), the hallmark of treatment has been the use of antiar-rhythmic drugs (AADs). Goals of therapy include reduction in the frequency and duration of episodes of arrhythmia as well an emerging goal of reducing mortality and hospitalizations associated with AF. Safety and efficacy are important factors when choosing an antiarrhythmic drug for the treatment of AF, hence, if AAD are required for maintenance of sinus rhythm, their safety profile, together with individual patient characteristics, should be of utmost concern. In the next paragraphs we would like to review some aspects (electrophysiologic effects, metabolism, side effects, current evidence and indication) of the most commonly used AAD for the management of patients with AF, following the Vaughan-Williams classification. However, this system is mainly based on ventricular activity, therefore, and due to its relatively atrial selective actions, some agents will not readily fit in the Vaughan Williams AAD classification. For that reason, in the final part of the manuscript, new promising agents will be reviewed separately.

Introduction

Prophylactic Antiarrhythmic Drug therapy in AF

In patients with recurrent atrial fibrillation (AF), the hallmark of treatment has been the use of antiarrhythmic drugs (AADs). These types of drugs are generally prescribed when AF episodes are frequent and/or symptomatic. Goals of therapy include reduction in the frequency and duration of episodes of arrhythmia as well an emerging goal of reducing mortality and hospitalizations associated with AF. Safety and efficacy are important factors when choosing an antiarrhythmic drug for the treatment of AF, hence, if AAD are required for maintenance of sinus rhythm, their safety profile, together with individual patient characteristics, should be of utmost concern.

In the following paragraphs we would like to review some aspects (electrophysiological effects, metabolism, side effects, current evidence and indication) of the most commonly used AAD for the management of patients with AF.

Classification

AAD do not lend themselves to a strict classification scheme. Many of these drugs have effects on multiple ion channels and adrenergic receptors. The majority of available drugs exert predominant effects on cardiac sodium or potassium currents.

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The Vaughan-Williams system (Table 1) groups drugs according to their major mechanisms of action, that is, according to which channels they bind and block on the cardiac cell membrane1. However, this classification has well-recognized limitations such as the oversimplification of concepts about AAD, the common grouping of drugs with dissimilar actions, the inability to group certain drugs accurately, and the failure to take into account many actions of AAD.[2] That is the reason why new schemes have been approached: the "Sicilian Gambit" takes into account the type and degree of blockade of channels, the antagonistic and agonistic effects on receptors, the effects on the sodium–potassium pump, the time constants of binding to cellular sites, effects on second messengers, and the affinity for binding on the basis of whether the cell is in an active or inactive state.[3] This result in a tabular list of virtually everything that makes it more complex, and although certainly helpful to basic researchers, it is less useful from the clinical point of view. Hence, the Vaughan-Williams system, with all its limitations, remains the most useful means of categorizing AAD and it will be the system that will use throughout this review. However, as it is known, this system is mainly based on ventricular activity, therefore, and due to its relatively atrial selective actions, some agents will not readily fit in the Vaughan Williams AAD classification. On the other hand, in the present era, among current strategies for suppression of AF is the development of antiarrhythmic agents that preferentially affect atrial. Accordingly, Antzelevitch recently introduced the concept of atrial-selective sodium channel block as a novel strategy for the management of AF. For that reason, in the final part of the manuscript, new agents

will be review separately (section new AAD).

Commonly Used Drugs

Class I Antiarrhythmic Drugs

Flecainide

Electrophysiological effects: Flecainide produces a substantial slowing in conduction velocity, directly related to the prolonged binding-unbinding time (i.e., the slow binding kinetics) of the drug (30 seconds). Thus, flecainide is virtually continuously bound to the sodium channel, and therefore produces slow conduction even at low heart rates (i.e., at rest) although as a result of binding kinetics, the degree of sodium-channel blockade increases as the heart rate increases (use dependence).[2] It has a pronounced negative inotropic effect.[4]

Metabolism: Flecainide is well absorbed from the gastrointestinal tract, and peak plasma levels are reached 2–4 hours after an oral dose. It is mainly metabolized by the liver (70%), but 30% is excreted unchanged by the kidneys and has a long elimination half-life (12–24 h).[2] It may increase digoxin levels. On the other hand, flecainide levels are increased by amiodarone, haloperidol, quinidine, cimetidine, and fluoxetine.[5]

Side Effects: Metallic taste, dizziness and visual disturbance represent the common non cardiovascular side effects (5% to 10%). Concomitant atrioventricular node blockade is recommended because of the potential of flecainide to convert AF to atrial flutter, which then may be conducted

Table 1		Vaughan-Williams Classification System of Antiarrhythmic Drugs

Class I: Sodium-Channel-Blocking Drugs

 Class IA: Moderately slow conduction and moderately prolong action potential
 duration by increasing action potential duration:
 Quinidine, Procainamide, Disopyramide.

 Class IB: Minimally slow conduction and shorten action potential duration:
 Lidocaine, Mexiletine, Tocainide, Phenytoin.

 Class IC: Markedly slow conduction and minimally prolong action potential duration:
 Flecainide, Encainide, Propafenone.

Class II: Beta-Blocking Drugs

Class III: Prolong Action Potential Duration
 Amiodarone, Sotalol, Ibutilide, Dofetilide.

Class IV: Calcium-Channel-Blocking Drugs

Table 2 | Summary of the Most Relevant Studies Performed with Flecainide

Study/Type	Aim	Type of Employed Drugs	Year Publication	Number Patients	Follow Up	Adverse Effects	Conclusion
Nacca-relli et al 12/ Randomized trial	To compare the efficacy and long-term toler-ability of fle-cainide acetate versus quinidine	Flecainide acetate versus quinidine	1996	239	1 year	Gastro-intesti-nal side effects.	Flecainide and quinidine are equally effective in the acceptable sup-pression of symp-tomatic paroxys-mal AF; flecainide is better tolerated than quinidine and is less likely to be discontinued due to adverse effects.
CAST13/ Random-izeded trial	To test the hypothesis that suppression of ventricular premature com-plexes (VPCs) in survivors of acute MI would reduce arrhyth-mic death risk	Encainide-flecainide-moricizine versus placebo	1991	725	10 months	Proar-rhyth-mic event rate	Neither encainide nor flecainide should be used in the treatment of patients with asymptomatic or minimally symp-tomatic ventricular arrhythmia after MI.
Alboni et al.14/ Cohort studies	To evaluated the feasibility and the safety of self-administered oral loading of flecainide and propafenone in terminating AF of recent onset outside the hos-pital	Flecainide- propafe-none	2004	268	15+/-5 months	Atrial flutter at a rapid ven-tricular rate in 1 patient and noncar-diac side effects in 11 patients	In a selected, risk-stratified popula-tion of patients with recurrent atrial fibrillation, pill-in-the-pocket treatment is fea-sible and safe, with a high rate of compliance by pa-tients, a low rate of adverse events, and a marked reduction in emergency room visits and hospital admissions
Alboni et al.15/ Cohort study	To investi-gate whether tolerance to iv administration of flecainide or propafenone might predict the safety of pill-in-the-pocket treatment-the out-of-hospital self-adminis-tration of these drugs after the onset of palpita-tions-in patients with AF of recent onset	Flecainide- propafe-none	2010	122	11+/-4 months	One syncope, two pre-syncope, one sinus arrest	The patient's toler-ance of intravenous administration of flecainide or propafenone does not seem to predict adverse effects dur-ing out-of-hospital self-administration of these drugs

rapidly, resulting in 1:1 atrioventricular conduction with a wide QRS morphology due to slowed conduction which can result in hemodynamic collapse. Another precaution that must be taken into account is that in patients with loss-of-function sodium channel mutations, as for instance, patients with Brugada syndrome, sodium channel blocking drugs can also present a risk of proarrhythmia. As a matter of fact, in our series, from 611 patients with AF, 11 were unmasked after initiation of a class-I AAD, two of them with tragic consequences (resuscitated sudden cardiac death shortly after initiation of the drug).[6]

Finally, sodium channel blocking drugs slow conduction and, in susceptible patients, with preexisting scar or ischemia, can promote the development of reentry and ventricular tachyarrhythmias.

Upon Initiation of Long Term Flecainide Therapy, Regular ECG Monitoring is Recommended an increase in QRS duration of 25% on therapy compared with baseline is a sign of potential risk of proarrhythmia, so, if that happens, the drug should be stopped or the dose reduced.[7] Similarly, when the flecainide dose is increased, QRS duration should be monitored.

Evidence: More than 20 years ago several studies demonstrated that flecainide delay the first recurrence of AF and also decreased time spent in AF.[8] Additionally, several uncontrolled studies found that flecainide delayed recurrence of AF.[9,11] Most relevant studies are shown in table 2.

Indication: Flecainide is currently recommended to acute restore sinus rhythm in patients without structural heart and new onset AF. For this purpose it is available as an intravenous agent in Europe (but not in the United States). It can be administered orally at high-doses (200–300 mg) or i.v. (usual dose is 2 mg/kg over 10 min) to patients with AF of short duration (specially, 24 h). The same indications for propafenone are common for flecainide: in the long term, as first line therapy, for patients without or with minimal heart disease and also for patients with hypertension but without substantial LVH. In selected, highly symptomatic patients with infrequent (e.g. between once per month and once per year) recurrences, the 'pill-in-the-pocket' approach (with

flecainide or propafenone) can be considered. In order to implement it, patients should be screened for indications and contraindications, and the efficacy andsafety of oral treatment should be tested in hospital.[16]

Propafenone

Electrophysiological Effects: Propafenone produces potent blockade of the sodium channel, similar to other Class IC drugs. Unlike other Class IC agents, propafenone also causes a slight increase in the refractory periods of all cardiac tissue. In addition, propafenone has mild beta-blocking (negative inotropic) and calcium-blocking properties (negative chronotropic effects).

Metabolism: Propafenone is well absorbed from the gastrointestinal tract. The drug is 90% protein bound and it is metabolized by the liver.[2,5] The elimination half-life is 6 or 7 hours after a steady state is reached. The initial marketed preparation was recommended to be taken 3 times daily due to the rapid absorption by the gut when taken orally and also the rapid metabolism by the liver. Since then, a sustained-release preparation of propafenone has been developed that allows the drug to be taken twice daily. With regards to the interactions it may decrease the metabolism of warfarin and increase the digoxin levels.[4]

Side Effects: Propafenone should not be used in patients with left ventricular dysfunction, as these patients are at high risk of suffering from proarrhythmic effects; Patients being treated with propafenone should be monitored for the potential development of ischemia or heart failure.[7] The major non-cardiovascular adverse effects include metallic taste, as well as dizziness and visual disturbances.

Current Evidence: Two interesting studies related to the use of propafenone have been published in the last decade, the RAFT17 and a linked study conducted in Europe, the EHRA study.[18] The first one (The Rythmol Atrial Fibrillation Trial) showed that 3 doses of sustained-release (SR) propafenone (425, 325, or 225 mg) given twice daily significantly lengthened the time to first symptomatic AF recurrence compared with placebo; the median time to recurrence was 41 days in the placebo group, and

more than 300 days, 291 and 112 with propafenone SR 425,325 and 225 mg respectively.

The European Rythmol/Rytmonorm Atrial Fibrillation Trial (ERAFT), a double-blind, multicenter, placebo-controlled (n=293) showed that the SR formulation of propafenone was superior to placebo in preventing symptoms of paroxysmal AF. There were significant increases in the arrhythmia-free periods from day 5 of randomization to the first recurrence of symptomatic atrial arrhythmia in both the propafenone SR 325 mg and 425 mg also twice daily groups as compared with placebo. The median arrhythmia-free time was 9 days in the placebo group, 35 days in the propafenone SR 325 mg and 44 days in the propafenone SR 425 mg. The percentage of patients with >/=1 serious adverse event was between 10.0% and 11.2% in the active group versus 1,1% in the placebo group.

When compared versus amiodarone, propafenone seems to be less effective in a randomized multicenter study in which patients were assigned to amiodarone, or sotalol or propafenone.[19] However, although no significant difference, adverse events requiring the discontinuation of drug therapy occurred in 18% of the patients receiving amiodarone, as compared to the 11% of those treated with sotalol or propafenone (p=0.06).

Indications: In the maintenance of sinus rhythm, propafenone is indicated as first line therapy (together with dronedarone, flecainide and sotalol) for those patients without or with minimal heart disease and also for patients with hypertension but without substantial left ventricular hypertrophy. These recommendations are common in both European[16] and American guidelines.[7]

Disopyramide

Electrophysiological Effects: Disopyramide is distinguished as a sodium channel blocking drug with potent anticholinergic and negative inotropic effects.[4]

Metabolism: Absorption is high (80–90%), and peak blood levels occur 2–3 hours after administration. Approximately, 60% of the drug is excreted by the kidneys, and 40% is metabolized in the liver.[2] Hence, dose should be reduced in patients with renal or hepatic dysfunction.[5] The elimination half-life is 8–9 hours. Drug interactions include the decreasing of plasma disopyramide levels by phenobarbital, phenytoin, and rifampin. Other drugs with negative inotropic effects can exacerbate the myocardial depression seen with disopyramide.

Side Effects: The major adverse effects of disopyramide are related to myocardial depression and anticholinergic side effects; thus, it should not be used in patients with any degree of ventricular dysfunction. Non-cardiovascular toxicity secondary to the strong anti-muscarinic properties include dry mouth, eyes, nose, and throat, urinary difficulty or urinary retention; it can precipitate closed-angle glaucoma and can also produce hypoglycemia in occasional cases, apparently by increasing insulin levels.[20]

Evidence: In a retrospective series of 106 patients with thyrotoxicosis-induced fibrillation (87% of them had suffered from AF for more than 12 months), cardioversion was attempted using disopyramide and then electric shock: 98 of 106 patients (92.5%) underwent successful cardioversion, and 67.3% remained in sinus rhythm after 80.6+/-37 months.[21] The Cochrane Central Register of Controlled Trials (CENTRAL) of The Cochrane Library suggested that disopyramide was one of the drugs that maintained sinus rhythm but was associated with increased AEs and increased mortality.[22]
Finally, although in the setting of patient with obstructive hypertrophic cardiomyopathy (HCM), a Multicenter study of the efficacy and safety of disopyramide in this specific population, showed that two-thirds of obstructed HCM patients treated with disopyramide could be managed only medically with amelioration of symptoms and about 50% reduction in subaortic gradient over >/=3 years without proarrhythmic.[21]

Indications: The role of disopyramide in treating patients with AF is unclear. Of note, disopyramide prescriptions represent 1% to 2% of annual AAD prescriptions in the United States.[23] Due to the strong anti-muscarinic properties, it is usually confined to patients with high vagal tone.[7] Despite little supporting evidence, the European guidelines17 mention that it could be considered in those

Table 3 | **Summary of the Most Relevant Studies Performed with Amiodarone**

Study	Aim	Type of Employed Drugs	Year Publication	Number Patients	Follow up	Adverse Effects	Conclusion
CHF-STAT24/ double-blind, placebo-controlled study	To evaluate the long-term effects of amiodarone on morbidity and mortality in patients with congestive heart failure (CHF) and AF	Amiodarone – placebo.	1998	667	12 months	---------------	Dronedarone was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia
CTAF25/ prospective, multicenter trial.	To test the hypothesis that low doses of amiodarone would be more efficacious in preventing recurrent AF than therapy with sotalol or propafenone	Amiodarone-sotalol-propafenone.	2000	403	16 months	Pulmonary abnormalities, hypo-hyperthyroidism.	Amiodarone is more effective than sotalol or propafenone for the prevention of recurrences of atrial fibrillation.
SAFE-T26/ double-blind, placebo-controlled trial.	To compared the ability of sotalol and amiodarone to restore and maintain sinus rhythm in patients with permanent AF	Amiodarone- sotalol- placebo	2005	665	For 1 to 4.5 years	---------------	Amiodarone and sotalol are equally efficacious in converting AF to sinus rhythm. Amiodarone is superior for maintaining sinus rhythm, but both drugs have similar efficacy in patients with ischemic heart disease. Sustained sinus rhythm is associated with an improved quality of life and improved exercise performance

patients without or with minimal structural heart disease with "vagally mediated AF". As previously mentioned, the negative inotropic effects of this drug make it a therapeutic option for patients with AF and hypertrophic cardiomyopathy.

Class III

Amiodarone

Electrophysiological Effects:Amiodarone displays activity from all four antiarrhythmic classes. Its major electrophysiologic effect is a homogeneous prolongation of the action potential, and therefore of refractory periods, due to blockade of the potassium channels, reason why it is classified as a Class III antiarrhythmic drug. Additionally, it produces a mild-to-moderate blockade of the sodium channel (a Class I effect), a noncompetitive beta blockade (a Class II effect), and some degree of calcium-channel blockade (a Class IV effect).[2] It is the most effective antiarrhythmic drug currently available but its use is limited by a countless of non-cardiovascular side effects.

Metabolism: The clinical pharmacology of amiodarone is complex and not completely understood. After an oral dose, 30–50% is absorbed from the gastrointestinal tract. It is distinguished by a half-life of weeks and significant distribution into adipose tissue. Administration with food is also recommended because it significantly increases the rate and extent of amiodarone absorption. Amiodarone is metabolized in the liver. Very little amiodarone is excreted in the urine or the stool; essentially, it is stored, not excreted. Hence elimination may actually be the gradual and natural sloughing of amiodarone packed epithelial cells. The half-life of the drug has been reported as being between 2 weeks and 3 months.[5]

The most important interaction of amiodarone occurs with the potentiation of the anticoagulant effect of warfarin through inhibition of CYP2C.[9] In addition, amiodarone inhibits P glycoprotein transport and can reduce digoxin clearance.[4]

Table 4		Summary of the Most Relevant Studies Performed with Sotalol					
Study	Aim	Type of Employed Drugs	Year Publication	Number Patients	Follow Up	Adverse Effects	Conclusion
SWORD31/ randomized trial.	To investigated whether d-sotalol could reduce all-cause mortality in patients left ventricular dysfunction after myocardial infarction .	Sotalol-placebo.	1996	3121	the trial was stopped (148 days average)	Arrhythmias.	The prophylactic use of sotalol in this particular population does not reduce mortality, and may be associated with increased mortality in high-risk patients after myocardial infarction.
Sotalol Atrial Fibrillation/Flutter Study Group32/ randomized trial.	To evaluate the efficacy, safety, and dose-response relation of 3 fixed doses of d,l-sotalol (80, 120, and 160 mg twice daily) for the maintenance of sinus rhythm in patients with AF and/or atrial flutter	d,l-sotalol (80, 120, and 160 mg)-placebo.	1999	253	12 months	There were no reports of deaths, polymorphic ventricular tachycardia, torsade de pointes, sustained ventricular tachycardia, or ventricular fibrillation. Bradycardia and fatigue	D,l-sotalol appeared to be both safe and effective in maintaining sinus rhythm in patients with symptomatic AF and/or flutter. Further, the 120-mg twice daily dose appeared to provide the most favorable benefit and/or risk.
SAFE-T26/ double-blind, placebo-controlled trial.	To compared the ability of sotalol and amiodarone to restore and maintain sinus rhythm in patients with permanent AF	Amiodarone- sotalol- placebo	2005	665	For 1 to 4.5 years		Amiodarone and sotalol are equally efficacious in converting AF to sinus rhythm. Amiodarone is superior for maintaining sinus rhythm, but both drugs have similar efficacy in patients with ischemic heart disease. Sustained sinus rhythm is associated with an improved quality of life and improved exercise performance
Plewan A et al 33/ randomized trial.	To compare the efficacy and safety of sotalol and bisoprolol in the maintenance of sinus rhythm after electrical cardioversion of atrial fibrillation.	Sotalol-bisoprolol.	2001	128	12 months	Proarrhythmic effects, in terms of torsades de pointes tachycardias, occurred in the maintenance of sinus rhythm after electrical cardioversion of atrial fibrillation.	This study demonstrates that sotalol (160 mg x day(-1)) and bisoprolol (5 mg x day(-1)) are equally effective in maintaining sinus rhythm. Because of the side effects of sotalol, bisoprolol seems to be advantageous for maintenance of sinus rhythm after cardioversion of atrial fibrillation

Side Effects: One major cardiovascular side effect of amiodarone is sinus bradycardia. QT prolongation is common but very rarely associated with torsades de pointes, possibly due to multiple ion channel inhibition. Hepatic toxicity is manifest as low-level transaminase elevation, which, if not detected and managed with discontinuation of amiodarone, can result in cirrhosis. Pulmonary toxicity can manifest as an acute hypersensitivity type of reaction with patchy infiltrates after weeks of therapy or as a more chronic process with interstitial fibrosis. Amiodarone-associated thyroid dysfunction is an important clinical issue as it can cause major adverse cardiovascular events such as

recurrence of arrhythmias and heart failure. Although a clear-cut differentiation between the two main forms is not always possible amiodarone-associated thyrotoxicosis is divided into type I and II. Type I occurs mainly in patients with an underlying thyroid condition, in which an excess of thyroid hormone is produced. Type II is a form of thyroiditis which is due to the direct toxic effect of amiodarone, which releases an excess of thyroid hormone. Finally, in the setting of intravenous administration, it can produce phlebitis and hypotension.

Evidence: Amiodarone prevents recurrent AF bet-

Table 5		Summary of the Most Relevant Studies Performed with Dofetilide					
Study	**Aim**	**Type of Employed Drugs**	**Year Publication**	**Number Patients**	**Follow Up**	**Adverse Effects**	**Conclusion**
SAFIRED36/ randomized trial.	To determined the efficacy and safety of dofetilide in converting AF or atrial flutter to sinus rhythm and maintaining it for 1 year	Dofetlide-placebo.	2000	325	1 year	Two cases of torsade de pointes occurred (day 2 and 3); One sudden cardiac death, classified as proarrhythmic, occurred on day 8.	Dofetilide, a new class III antiarrhythmic agent, is moderately effective in cardioverting AF or AFl to SR and significantly effective inmaintaining SR for 1 year. In-hospital initiation and dosage adjustment based on QTc and Cl(Cr) are necessary to minimize a small but nonnegligible proarrhythmic risk
DIAMOND37/ randomized trial.	Dofetilide was investigate for effects on all-cause mortality and morbidity in patients with left-ventricular dysfunction after myocardial infarction.	Dofetlide-placebo.	2000	1510	12 months	--------------------	In patients with severe left-ventricular dysfunction and recent myocardial infarction, treatment with dofetilide did not affect all-cause mortality, cardiac mortality, or total arrhythmic deaths. Dofetilide was effective in treating AF or flutter in this population
Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group38/randomized trial.	To evaluate whether dofetilide affects survival or morbidity among patients with reduced left-ventricular function and congestive heart failure	Dofetlide-placebo.	1999	628	16 months	QT prolongation	In patients with congestive heart failure and reduced left ventricular function, dofetilide was effective in converting AF, preventing its recurrence, and reducing the risk of hospitalization for worsening heart failure.

ter than propafenone and sotalol. The number of patients needed to treat is 3 with amiodarone,4 with flecainide,5 with dofetilide and propafenone, and 8 with sotalol.[16] Most relevant studies are also shown in table (table 3).[24-26] Prophylactic amiodarone therapy has shown to reduce significantly the incidence of AF after open heart surgery, resulting in a shorter time of intensive care unit and hospital stay in the majority of studies performed in this field, and could also have a significant role in high-risk patients.[27-30]

Indications: Amiodarone is the most commonly prescribed antiarrhythmic drug for AF, even though it is not approved for AF in the US. The most common indications are the following:

• Amiodarone can be used to get an acute rate control in those individuals with severely depressed LV function.

• In long-term rhythm control, amiodarone is a good therapeutic option in patients with frequent, symptomatic AF recurrences despite therapy with other AAD, at expenses of potentials severe extra cardiac adverse events. In patients with heart failure, amiodarone is probably the drug of choice after cardioversion for AF. In those with hypertension and left ventricular hypertrophy it is recommend as second line therapy after dronedarone.

Sotalol

Electrophysiological Effects: Sotalol is a non-cardioselective beta blocker with Class III antiarrhythmic effect which produces prolongation of the cardiac action potential in both the atria and the ventricles. It produces a dose-related prolongation in the QT interval, which appears to reflect both its antiarrhythmic properties and its propensity to cause torsades de pointes. Inherently, it displays reverse use dependence, so its effect— including QT-interval prolongation— increases with lower heart rates.[2]

Metabolism: Sotalol is well absorbed from the gastrointestinal tract, and peak plasma concentrations occur within 2–3 hours after an oral dose. The drug is not metabolized; it is excreted unchanged by the kidneys, reason why dosage should be re-

duced in patients with renal insufficiency.[2] The elimination half-life is 7–8 hours.

Side Effects: The major side effects of sotalol are related to its non-cardioselective beta-blocking effects (e.g., bradyarrhythmias, negative inotropy, and exacerbation of asthma) and to its propensity to cause torsades de pointes. Exacerbation of congestive heart failure is most commonly seen in patients whose left ventricular ejection fractions are less than 0.35, especially if the patients also have a history of heart failure. The magnitude of QT-interval prolongation must be assessed during sinus rhythm, that is, when the heart rate is slowest and the risk of torsades de pointes is highest. With regards to this, there is a study that evaluated the safety of sotalol in 3257 patients treated for cardiac arrhythmias.[31] The overall incidence of proarrhythmia was reported in 141 patients (4.3%), predominantly torsades de pointes (4.1%) and was more prevalent in patients with congestive heart failure and low ejection fraction.

In the SWORD trial there were 10 episodes (one fatal) of torsade de pointes tachycardia, all associated with sotalol use.[32] Hence, careful monitoring of the QT interval must be performed, and due to the fact that the risk of developing torsades de pointes with sotalol is clearly related to QT-interval prolongation, QTc should be kept below 500.

Evidence: see table 4.

Indication: Sotalol can be used in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 ms. In the EHRA guidelines,[16] sotalol is recommended in the long-term rhythm control as second line (after beta-blockers) treatment for patients with AF and none or minimal structural heart disease where the pattern of arrhythmia onset is suspected to be adrenergically mediated. In patients with underlying coronary artery disease sotalol can be used as first-line therapy.[7,16]

Dofetilide

Electrophysiological Effects: Dofetilide is a "pure" Class III drug that acts blocking the potassium channels resulting in prolongation of the ac-

| Table 6 | | Summary of the Most Relevant Studies Performed with Dronedarone | | | | | |

Study	Aim	Type of employed Drugs	Year Publication	Number Patients	Follow Up	Adverse Effects	Conclusion
EURIDIS44/ randomized trial.	The primary end point was the time to the first recurrence of AF or flutter in patients with at least one episode of atrial fibrillation in the preceding 3 months, and in sinus rhythm for at least 1 hour before randomization	Dronad-erone-placebo	2007	828	12 months	Elevation of serum creatinine	Dronedarone was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia
ATHE-NA45/ Placebo-Controlled, Double-Blind, Parallel Arm Trial	To evaluate the use of dronedarone in patients with AF who had additional risk factors for death	Dronad-erone-placebo	2009	4268	21+/-5 months	The dronedarone group had higher rates of bradycardia, QT-interval prolongation, nausea, diarrhea, rash, and an increased serum creatinine level than the placebo group	Dronedarone reduced the incidence of hospitalization due to cardiovascular events or death in patients with AF.
PALLAS46 / randomized trial.	To test if dronedarone would reduce major vascular events in high-risk permanent AF.	Dronad-erone-placebo	2011	3236	1 year	Diarrhea, asthenic condition, nausea and vomiting, dizziness, dyspnea, and bradycardia. An elevation of alanine aminotransferase	In patients with CHF, amiodarone has a significant potential to spontaneously convert patients in AF to sinus rhythm, with patients who convert having a lower mortality rate than those who do not
ERATO47/ randomized trial.	To test which was the change in mean ventricular rate between baseline and day 14, as assessed by 24-hour Holter	Dronad-erone-placebo	2008	174	6 months	Gastrointestinal disturbances were also common in both groups occurring in 20% of patients receiving dronedarone versus 13.5% of those receiving placebo	In addition to its reported rhythm-targeting and rate-targeting therapeutic actions in paroxysmal and persistent AF, dronedarone improves ventricular rate control in patients with permanent AF. Dronedarone was well tolerated with no evidence of organ toxicities or proarrhythmias in this short-term study
ANDROM-EDA48/ randomized trial.	The primary end point was the composite of death from any cause or hospitalization for heart failure symptomatic heart failure in patients with severe left ventricular systolic dysfunction.	Dronad-erone-placebo	2008	627	2 months (prematurely terminated for safety reasons)	Increases in the serum creatinine concentration	In patients with severe heart failure and left ventricular systolic dysfunction, treatment with dronedarone was associated with increased early mortality related to the worsening of heart failure

tion potential and of refractory periods in both the atria and the ventricles. It displays a dose-dependent prolongation of the QT interval and reverse use dependence.[2]

Metabolism: Dofetilide is fully absorbed after oral administration. While it is eliminated by both the kidneys and the liver, the renal route of elimination is particularly important clinically so it must be adjusted in patients with reduced creatinine clearances.[5] Drug interactions are very important with dofetilide. Hence, its coadministration is contraindicated with drugs that can reduce its elimination and thus increase its plasma concentration (verapamil, cimetidine, trimethoprim, prochlorperazine, and megestrol)4. Moroever, it should also be avoided in combination with drugs that can also prolong the QT interval, including all Class I and Class III AAD, tricyclic antidepressants, erythromycin, phenothiazines, cisapride, bepridil. Hydrochlorothiazide increases dofetilide levels. Before dofetilide initiation, amiodarone must be discontinued at least 3 months before.

Side Effects: Its major side effect is torsades de pointes. The incidence of torsades de pointes in dofetilide clinical trials ranged from 0.3% to 4.7% depending on dose administration and patient characteristics. Regarding the non-cardiovascular toxicity, the potential apparition of headache, gastrointestinal disturbances, sleep disorders, and "flulike" symptoms[36] it should be mentioned.

The drug is available only to hospitals and physicians that have been certified to administer it and is dispensed only by a limited number of pharmacies, moreover, is not approved for use in Europe. Patients must be hospitalized to receive dofetilide in order to monitor the QT interval and the dose must be adjusted for the creatinine clearance.

Evidence: See table 5.[36-38]

Indications: Dofetilide is indicated for conversion to normal sinus rhythm, and especially for the maintenance of sinus rhythm, in patients with highly symptomatic AF or atrial flutter. It´s moderately effective in converting AF, but it´s more useful in maintaining sinus rhythm after successful conversion. Due to the fact that it has minimal hemodynamic effects, it can be used in patients with heart failure. In the current American guidelines,[7] dofetilide is approved for maintenance of sinus rhythm, as second line therapy, together with amiodarone in patients without or minimal heart disease and also as second line in patients without substantial left ventricular hypertrophy.

New Antiarrhythmic Drugs

Among the current strategies for suppression of AF is the development of antiarrhythmic agents that preferentially affect atrial, rather than ventricular electrical parameters. Atrial-specific strategies were conceived with the intention of avoiding the adverse effects of traditional agents in the ventricles.[39] On the other hand, although no selective, in the last years another, new agents as dronedreone and azimilide have also be introduced in the therapeutic arsenal and will be discuss briefly.

Single and Multichannel Blockers

Azimilide

Mechanism: Azimilide is a selective class III antiarrhythmic drug that blocks both the rapid (IKr) and the slow (IKs) components of the delayed rectifier potassium channel. Azimilide prolongs cardiac APD and refractory periods in both the atria and the ventricles.

Metabolism: Azimilide has very predictable pharmacokinetics, is predominantly hepatically metabolized, and has no significant drug interactions with digoxin or warfarin. Its long half-life (up to 4 days) allows once-daily dosing and limits major fluctuations in blood concentrations.

Side Effects: The most frequent reported side effect is headache, with rare serious adverse events of early reversible neutropenia and Torsades de Pointes. In long-term follow up, the patient withdrawal rate has been low.

Evidence: Several randomized placebo-controlled clinical trials have demonstrated the efficacy of azimilide in prolonging the symptom-free

interval in patients with AF or atrial flutter.[40-42]

Indications: At the present time the precise effects of the drug with respect to maintaining sinus rhythm remain unclear, so it´s not recommended in the present guidelines.

Dronaderone

Mechanism: Dronedarone is a novel, non-iodinated benzofuran derivative with class I, II, III, and IV antiarrhythmic properties: it blocks sodium channels at rapid pacing rates, and it lengthens the duration of cardiac action potentials and refractoriness. It has Ca^{2+} antagonist activity, and has non-competitive anti-adrenergic activity. It is similar in structure to amiodarone with the addition of a methylsufonamide group and absence of iodine moieties. The former deletion is postulated to result in little or no thyroid toxicity and the latter addition is said to decrease lipophilicity. Because of that dronedarone was thought to resemble and replace amiodarone due to fewer non cardiovascular side effects.

Metabolism: Because it is less lipophilic than amiodarone, dronedarone tends to accumulate less in tissue and has a smaller volume of distribution. Dronedarone has an elimination half-life of only 13–19 h and requires no dosing adjustment for patients with renal failure. Steady state is reached in 4–8 days. Regarding the interactions it is worth mentioning that dronedarone does not increase the international normalized ratio in association with warfarin use. It interacts with the P glycoprotein transporting system (digoxin should be dose reduced or discontinued) and with CYP3A.[4] In combination with simvastatin it may increase the risk of myositis.

Side Effects: Dronedarone is generally well tolerated although the incidence of gastrointestinal side effects is relatively frequent (10%). The absorption and gastrointestinal tolerance are improved if administered with meals. Recently, the Food and Drug Administration released a warning for dronedarone based on 2 reported cases of severe hepatotoxicity occurring within 6 months of treatment initiation.[43] Hence, signs and symptoms of liver disease should be monitored periodically. Evidence: See table 6.[44-48]

Indications: Based on the available data previously mentioned, dronedarone is recommended by the current European and American guidelines as one of the several first-line agents for the prevention or rate control of recurrent AF in patients with minimal or no heart disease, hypertension with left ventricular hypertrophy, coronary artery disease, and stable New York Heart Association (NYHA) class I/II congestive heart failure. In the guidelines, dronedarone is not recommended for patients with recently unstable heart failure (within 4 weeks), NYHA class IV (American guidelines), NYHA class III and IV (European) or ejection fraction <35% (Canada).[49] It is also not recommended for pharmacological conversion of recent-onset AF and for rate control of permanent AF. Finally, is remarkable the fact that the United States Food and Drug Administration (FDA) approved dronedarone for the prevention of hospitalizations due to recurrent AF, only as a secondary endpoint.

Atrial-Selective Antiarrhythmic Drugs

Vernakalant

Mechanism: Vernakalant is an anti-arrhythmic agent that acts preferentially in the atria by prolonging atrial refractoriness and by rate-dependently slowing impulse conduction. These anti-fibrillatory actions on refractoriness and conduction are thought to suppress reentry, and are potentiated in the atria during AF. Because of its relatively atrial selective actions, vernakalant does not readily fit in the Vaughan Williams anti-arrhythmic drug classification (which mainly is based on ventricular activity). Vernakalant does not appear to impede atrioventricular conduction; therefore, the addition of a rate-controlling agent during AF recurrences may become imperative.

Metabolism: Most studies were performed with intravenous administration, which is the recommended administration route for the present application. Cytochrome P450 2D6 appears to be the major isoenzyme able to transform vernakalant into the major metabolite (RSD1385). Plasma concentrations of vernakalant declined rapidly after administration half-life of 2 to 3 hours. Glucuronidation and renal excretion are the main mechanisms of elimination.

Side Effects: taste alterations, sneezing, and paresthesia.

Evidence: Several trials have been published regarding the pharmacologic cardioversion of AF using the IV formulation. The AVRO (Active-Controlled, Multi- Center Study of Vernakalant Injection vs. Amiodarone in Subjects with Recent Onset Atrial Fibrillation), the Atrial Arrhythmia Conversion Trials (ACT I, II, and III), the CRAFT step-dose50 (parallel-group phase 2 study) trial and the open-label ACT IV study.[51] These studies showed promising results regarding conversion to sinus rhythm without remarkable proarrhythmic effects. However, the ACT V trial raised a safety concern, a cardiogenic shock was experienced by a patient with AF receiving vernakalant. Very recently, in a phase 2/3, randomized, double-blind, placebo-controlled trial Vernakalant did not restore sinus rhythm in patients with AFL and modestly slowed AFL and ventricular response rates.[52]

Indications: Although not mentioned yet in the current guidelines, vernakalant has been recently approved in the European Union, Iceland, and Norway for the rapid conversion of recent-onset AF to sinus rhythm in adults for nonsurgical patients with AF of duration 7 days or less and for post cardiac-surgery patients with AF of duration 3 days or less.

Ranolazine

Mechanism: Ranolazine is an innovative anti-ischemic and antianginal agent that inhibits the late Na current, thereby reducing the Na-dependent Ca-overload, which improves diastolic tone and oxygen handling during myocardial ischemia. In addition, a beneficial atrial selectivity of ranolazine has been suggested that may be helpful for the treatment of AF. Ranolazine exerts antiarrhythmic capacities very likely via inhibition of late I_{Na}, but also peak I_{Na} and rapid delayed rectifier potassium current I_{Kr}.

Metabolism: Ranolazine is metabolized in the liver, particularly by one of the cytochrome CYP3A enzymes, a member of the cytochrome P450 system.

Side Effects: QT prolongation.

Evidence: In the MERLIN TIMI-36 trial, patients treated with ranolazine were less likely to have a new onset of AF. While 75 patients developed new AF in the placebo group, only 55 individuals had new-onset AF during treatment with ranolazine. However, this trial was not designed and statistically powered to investigate new onset of AF.[53]

Miles et investigated the effects of ranolazine compared to amiodarone to prevent AF following bypass surgery: Ranolazine (generally 1,500 mg preoperatively followed by 1,000 mg twice daily for 10 days) was given to 111 patients and 145 patients were treated with amiodarone (generally 400 mg preoperatively followed by 200 mg twice daily for 10 days). Patients treated with ranolazine were significantly less likely to experience AF, with an incidence of 15 % compared to 26 % in patients treated with amiodarone.[54]

Finally, although in a small series of patient (n=33), addition of ranolazine to standard amiodarone therapy has shown to be equally safe and appears to be more effective compared to amiodarone alone for conversion of recent-onset AF.[55]

Indications: At the present time there is no a categorical indication. Actually it can be said that there is a need for clinical studies to investigate the effects of ranolazine on persistent and paroxysmal AF. Two placebo-controlled studies were recently initiated, the Ranolazine in Atrial Fibrillation Following An Electrical Cardioversion (RAFFAELLO) trial (www.ClinicalTrials.gov; NCT01534962) and the HARMONY trial (www. ClinicalTrials.gov: NCT01522651). Once available they will bring light to a coadjutant strategy in the management of patients with AF.

Conclusions

AADs play an important role in the management of AF. A thorough understanding of the patient groups most appropriate for individual therapies is critical for the safe and effective use of these drugs. Moreover, selection of an AAD is based on several factors, as the AF type and duration, symptom type and severity, associated cardiovascular disease, patient age, associated medical conditions and short and long-term treatment goals.[60] For instance, patient presenting with a

single previous episode, rare, hemodynamically well-tolerated and short-lasting AF episodes, in the perioperative setting or during acute myocardial infarction or other acute diseases, could avoid any antiarrhythmic therapy. On the other hand, for patients with infrequent hemodynamically well-tolerated AF episodes (< 1 per month), long enough to require emergency room intervention or hospitalization, the "pill-in-the-pocket" treatment could be an appropriate approach to be taken. As mentioned above, if this approach is selected, some cautions should be undertaken.

In the present review we have emphasized the importance of the selection of the most suitable AAD according to patient's characteristics. Summarizing, in individuals with coronary artery disease, sotalol can be given as initial therapy unless contraindicated, followed by amiodarone as the second choice. Flecainide can be safely administered to patients without significant structural heart disease, but should not be used in patients with coronary artery disease or in those with reduced left ventricular ejection fraction. Dronedarone has emerged as an alternative in patients with AF with minimal or no heart disease, hypertension without left ventricular hypertrophy, or coronary artery disease unless there were left ventricular hypertrophy or heart failure, when it is specifically contraindicated. The European Society of Cardiology guidelines suggest dronedarone or amiodarone for severe left ventricular hypertrophy, whereas the US guidelines suggest only amiodarone. In patients with structural heart disease, amiodarone represents an appropriate choice because of its safety profile4. The European guidelines[7] suggest that disopyramide should be considered for patients with a vagal trigger associated with AF, whereas quinidine, procainamide, and disopyramide are completely omitted from the US guidelines.[17] Finally, Dofetilide is not approved for use in Europe but is indicated in all clinical categories in the US guidelines.

New AADs are under evaluation and could have a place in a near future. However, newer end points including stroke risk, hospitalization, cost and mortality will all likely play important roles in the development of new drug therapies. Very promising are the newer atrial-selective agents which will offer safety as well as effectiveness especially in the context of rational and judicious combination therapy.

Disclosures

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