Chapter

Antiarrhythmic Drugs in Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) represents the most common sustained heart rhythm abnormality. It presents in paroxysmal and persistent forms. The pathogenesis of AF is still debatable with several proposed mechanisms. The main pathway for diagnosis of AF is through electrocardiographic record. Treatment strategies can be divided into two strategies: rate and rhythm control. For rhythm control, antiarrhythmic drugs, direct current cardioversion, and electrophysiological ablation are used, while for rate control, chronotropic drugs are being used, while AV node ablation is required in order to reduce rapid ventricular rate, which is often observed in patients with AF. The rhythm control strategy implies the use of cardioversion to convert AF to normal, sinus rhythm. Cardioversion can be either pharmacological or electrical. Rate control strategy can be implied to patients with permanent AF but should also imply for the patients with paroxysmal AF when relapse occurs. Rapid ventricular rates can cause palpitations or even a syncope and other rate-related symptoms; however, these high ventricular rates lead to degradation of left ventricle performance, mitral regurgitation, and further dilatation of the left atrium. The main antiarrhythmic drugs used in treatment of AF are propafenone, flecainide, beta-blockers, amiodarone, dronedarone, dofetilide, vernakalant, and ranolazine.

Keywords: atrial fibrillation, antiarrhythmic drugs, propafenone, flecainide, amiodarone, dronedarone, dofetilide

1. Introduction

Atrial fibrillation (AF) represents the most common sustained heart rhythm abnormality, one of the most common cardiovascular diseases and a major cause of stroke in developed countries. It presents in paroxysmal and persistent forms. Paroxysmal form of AF is defined with a duration less than 7 days and can terminate spontaneously, while persistent forms are further classified as persistent and permanent forms with a duration of greater than 7 days with only difference in possibility of conversion to normal, sinus rhythm; in persistent form conversion to sinus rhythm is possible, while in permanent form, conversion to normal rhythm is not possible.

Atrial fibrillation can occur in isolated form (without associated comorbidities), yet it is more commonly seen with other cardiovascular diseases, cardiomyopathies, hypertension, diabetes mellitus, and obesity. When seen in association with these

comorbidities, atrial fibrillation deeply affects quality of life and increases mortality and morbidity [1].

AF affects 1–1.5% of the population in the developed world with approximately 3 million people with a diagnosis of AF in the USA [2]. The prevalence and incidence of AF are sharply increased with age with a rise from 0.7% in the age group of 55–59 years to 17.8% in those aged 85 years or above. With such a big prevalence, treatment of AF represents a significant burden to the healthcare systems. The data from the US databases from 2001 showed the estimated total annual cost of AF treatment at 6.65 billion US$ [3].

The pathogenesis of AF is still debatable with several proposed mechanisms. The traditional theory suggests multiple reentrant atrial activation by migrating wavelets and contraction rate of 350–900 beats per minute [4, 5]. Several animal models have shown that AF is triggered by a focal source, which rapidly fires signals and is usually found in superior pulmonary veins. It stimulates multiple wavelet reentry mechanism within the atrial substrate or engages a spiral or rotor for the reentry [6–8]. Research also showed that in patients with AF, there is a sympathetic predominance over parasympathetic; however, in certain patients, it can be characterized with predominance of vagal or an adrenergic form of AF [9]. Besides that, AF can be related to temporary causes, such as drugs, alcohol, thyrotoxicosis, surgery, myocardial infarction, myocarditis, pericarditis, pulmonary embolism, and others. Obesity, sleep apnea and metabolic syndrome have also been linked to AF. Besides temporary causes, AF can be associated with permanent heart disease, such as valvular disease in which context AF is called valvular AF. Coronary heart disease, heart failure, hypertension, left ventricular hypertrophy, all forms of cardiomyopathies, and cardiac tumors have been associated with a high incidence of AF and carry a worse prognosis when compared to isolated form of AF. As mentioned, AF can occur in isolated or familial forms, without apparent identifiable underlying disease [3].

The main pathway for diagnosis of AF is through electrocardiographic record. A first-detected or recorded episode of AF is defined as the first one, despite the fact whether the patient was symptomatic or not and the possibility of the previous undetected episodes. Presentation of the patients with AF can differ, from with vague non-specific symptoms to thromboembolic consequences. Generally speaking, symptoms of AF depend of the rate of ventricular response, irregularity of the rhythm, functional status, duration of AF, and many more factors. As previously noted, the diagnosis of AF requires 12-lead electrocardiographic documentation or ambulatory Holter monitoring (especially in patients with daily paroxysms, but its usefulness is less in patients who have paroxysms at intervals more than 24 h). In patients with paroxysm with intervals that are greater than 24 h, implantable loop record devices, such as Reveal LINQ or CONFIRM, are used, as well as atrial high-rate episode recordings in patients with implantable dual-chamber pacemakers [1, 3].

2. Treatment strategies

Before initiating a treatment in patient with AF, we should first consider the probability of reoccurrence and/or persistence of the arrhythmia as well as patient symptomatology. Treatment strategies can be rate and rhythm control. For rhythm control, antiarrhythmic drugs, direct current cardioversion, and electrophysiological ablation are used, while for rate control, chronotropic drugs are being used, while AV node ablation is required in order to reduce rapid ventricular rate response which is often observed in patients with AF.

2.1 Rhythm control strategy

The rhythm control strategy implies the use of cardioversion to convert AF to normal, sinus rhythm. Cardioversion can be either pharmacological or electrical. Depending on the factors that lead to AF, not all attempts of cardioversion are successful, with about 50% of patients reverting to AF within a year of cardioversion [10]. Pharmacological cardioversion is preferred over electrical, especially in patients who present with AF within 48 h, while electrical is a standard procedure for AF with duration of more than 48 h. Rhythm control strategy by using antiarrhythmic drugs is an essential part in management of AF whose goals are prevention of reoccurrence and modification of recurrences by making them less symptomatic, less frequent, and less sustained [3].

Patients with persistent AF should be considered for either pharmacological or direct current cardioversion (DCCV) despite symptomatology, unless there are contraindications. Antiarrhythmic drugs may be prescribed to patients before and/or after successful DCCV for a period of time in order to prevent reoccurrence of AF. The use of antiarrhythmic drugs before DC conversion can also improve successfulness of DC conversion by prolongation of atrial refractoriness [11]. Besides antiarrhythmic drugs, patients may also require antithrombotic therapy. The recommendations for anticoagulation therapy are the same for both pharmacological and electrical cardioversion.

Antiarrhythmic drugs express their effect by blocking ion channels by which they affect atrial or junctional automaticity or refractoriness. By this mechanism, antiarrhythmic drugs suppress the trigger of AF (frequent atrial premature beats, rapid atrial tachycardia, etc.). Besides that, these drugs decrease excitability and conduction velocity by discouraging reentry mechanism or by changing autonomic stimulation (such as beta-blockers).

Side effect profiles, safety, and underlying heart diseases and their nature influence the choice of antiarrhythmic drugs; however, drugs with the greatest effects are also the ones that have bigger proarrhythmic effects and negative inotropic effects.

In the most cases, optimal beta-blockade represents the first line or is already administered for underlying heart diseases or for ventricular rate control in AF. If beta-blockers fail in rhythm control strategy or are contraindicated, a specific antiarrhythmic drug may be used. The selection of specific antiarrhythmic drug depends mostly on associated cardiovascular disease. Typically, patients can be divided into four categories: those with no or minimal heart disease, hypertensive heart (with or without significant left ventricular hypertrophy), ischemic heart disease, and heart failure. Also, besides this classification, patients can also be divided into two categories according to the presence of heart failure with reduced ejection fraction (ejection fraction <35%) or not (ejection fraction >35%) [1].

In patients with no or minimal heart disease, generally flecainide and propafenone are the first-line drugs. Dofetilide and dronedarone are the second-line drugs; since monitoring is required and expenses are high, amiodarone is reserved as the last-line therapy, while sotalol is being avoided because of the need for hospitalization and acquired long QT syndrome. **Figure 1** shows the optimal choice of antiarrhythmic drugs according to the underlying heart disease.

For patients who have left ventricular hypertrophy and AF, only two drugs are available: dronedarone and amiodarone. Thus, in patients with severe hypertrophy, there is only sufficient clinical experience with amiodarone. Sotalol and dofetilide should be avoided in the presence of significant left ventricular hypertrophy, since there is significant risk of QT prolongation and development of malignant arrhythmias. Antiarrhythmics of class Ic (propafenone and flecainide) are also not used because of proarrhythmic effect.

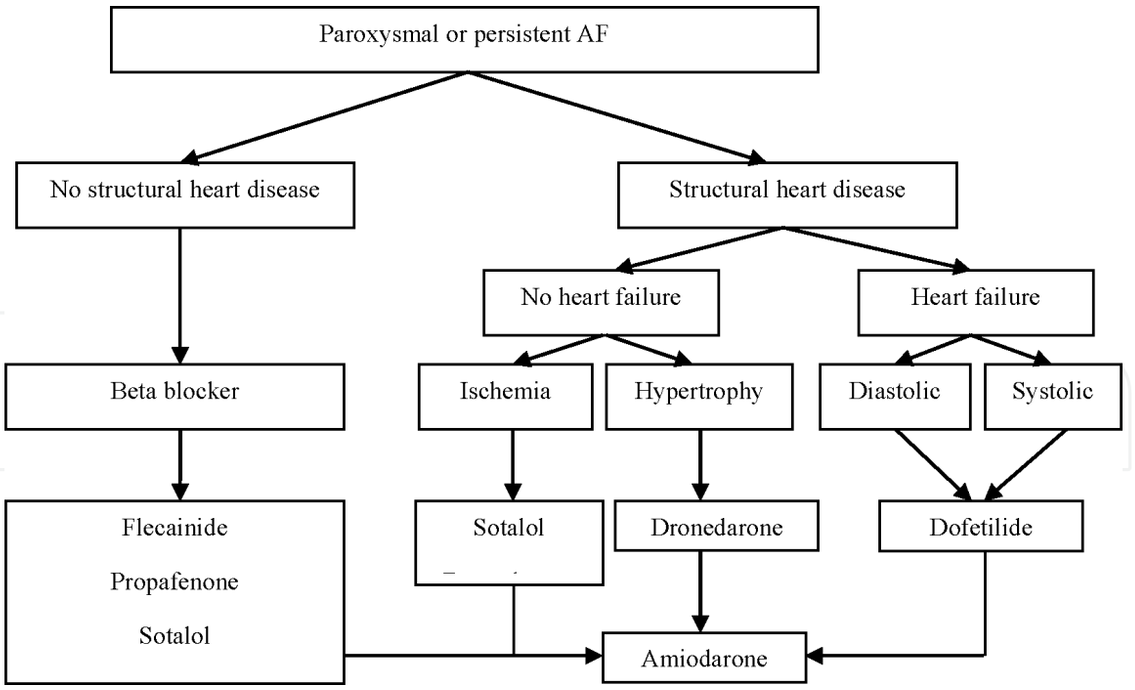

Figure 1.
Optimal choice of antiarrhythmic drug in different clinical settings [modified from Shenasa and Camm [1]].

Patients with coronary artery disease and paroxysmal or persistent AF should be treated with sotalol, amiodarone, or dronedarone, since they are both anti-ischemic and antiarrhythmic; however, sometimes sotalol and dronedarone are avoided because of proarrhythmic risk or progression to permanent AF. Propafenone and flecainide are contraindicated in patients with coronary artery disease since increased mortality was observed in the Cardiac Arrhythmia Suppression Trial (CAST) in patients with post-myocardial infarction with active ischemia [12].

For patients with heart failure and paroxysmal and persistent AF, only amiodarone and dronedarone can be considered for all grades of heart failure. However, dronedarone should be avoided in patients with recently unstable New York Heart Association (NYHA) class IV heart failure, particularly in patients with ejection fraction of left ventricle less than 35%. Even though there is no or little alternative to amiodarone for patients with heart failure in Europe, there are some concerns regarding the use of amiodarone in NYHA class III heart failure.

For acute pharmacological cardioversion, oral or intravenous antiarrhythmics with class Ic (flecainide and propafenone) or III (amiodarone, ibutilide, and dofetilide) can be used or new, atrial selective agent—vernakalant [3]. Depending on the agent as well as factors that lead to the development of AF, the rate of successful conversion to normal, sinus rhythm differs [13]. Out-of-hospital conversion of AF can also be achieved in patients with persistent AF with pill-in-the-pocket strategy which consists of self-administration of single oral dose of class Ic antiarrhythmics on the onset of symptoms of AF.

Assessment of rhythm control strategy should not be led by the presence or absence of symptoms since many clinical trials concluded that there is often little or no association between symptoms and reoccurrence of AF; therefore, prolonged monitoring is advised. In situation where patient is adequately anticoagulated, frequent visits are not necessary; however, if the initiation of anticoagulation therapy is based on the frequency of arrhythmia episodes, detailed and prolonged monitoring is required (24 h ECG Holter monitoring, 48 h ECG Holter monitoring, 7-day ECG Holter monitoring or implantable loop recorded implantation).

2.2 Rate control strategy

In patients with permanent AF, control of the ventricular response rate is important, since a lot research suggested that high heart rates were associated with poor outcomes in the terms of mortality. Besides patients with permanent AF, the rate control strategy should be also implied for the patients with paroxysmal AF when relapse occurs, especially if the patients are symptomatic or hemodynamically compromised by it. Rapid ventricular rates can cause palpitations or even a syncope and other rate-related symptoms; however, these high ventricular rates lead to degradation of left ventricle performance, mitral regurgitation, and further dilatation of the left atrium. If the heart rate exceeds 125 beats per minute, even a normal ventricle may dilate, but in patients with impaired left ventricle function, even less heart rates can cause further dilatation. On the other hand, the loss of atrial contraction (observed in patients with AF), which approximately accounts for 20–30% of the total stroke volume of left ventricle, leads to further reduction in cardiac output. Besides these two mechanisms, irregularity in ventricle rhythm additionally impairs left ventricle function. That is why the goal of rate control strategy is heart rate below 115 beats per minute in light and/or moderate physical activity and below 80 beats per minute in rest. However, sometimes ventricle rates at rest do not adequately represent effective control during exercise [1, 14].

Principles of rate control strategy may be easy to implement in patients with permanent AF and then in those with paroxysmal or persistent form since the control of the heart rate in arrhythmia and in sinus rhythm can and are often different, especially in patients with dysfunction of sinus node. In these circumstances, symptomatic bradycardia with long sinus pauses can occur. In these patients, heart rate support is needed, and implantation of dual-chamber pacemaker is often needed. Therefore, the main reason for rate control strategy in patients with intermittent AF is failure to find adequate blend of the effect on heart rate during AF and when sinus rhythm occurs. It should be noted that effects of different antiarrhythmic drugs have different effects on AV node, whereas beta-blockers have less marked effect on AV node than calcium channel blockers and cause sinus bradycardia more often.

Three different classes of drugs are being used for rate control: digitalis, calcium channel blockers, and beta-blockers. Beta-blockers and calcium channel blockers are preferred over digitalis and should be used in most of the patients with chronic AF without heart failure, while in patients with chronic AF and heart failure, digoxin or amiodarone should be used in order to control ventricular rate. By using digitalis, adequate control of exercise heart rate is rarely achieved, so in patients who are mildly to moderately physically active, there will be no benefit. Digitalis is also less efficacious than amiodarone and calcium channel blockers and in some studies even beta-blockers. Most patients should be treated with beta-blocker (usually beta-2 specific beta-blocker like bisoprolol, metoprolol, carvedilol, or nebivolol) or calcium channel blocker with rate-limiting effect, such as verapamil or diltiazem. In patients whom adequate control of heart rate is not achieved, a combination of drugs is needed; however, it is not advised in patients with reduced left ventricle function. Amiodarone is reserved as a last-line therapy, especially for patients with heart failure and with reduced ejection fraction. It is a powerful and very effective heart rate-limiting drug, but many adverse effects are the main drawback of amiodarone therapy [15–18] .

Besides traditional therapy for rate control, in patients with AF and in whom rate is not adequately achieved, the use of sotalol and amiodarone can slow the AV conduction, but they are not commonly used for long-term rate control because of the proarrhythmic risk. In situations where rapid control of heart rate is needed, oral administration is not feasible, but intravenous administration of diltiazem

can be considered, while in patients without heart failure or accessory pathways, intravenous beta-blockers (esmolol, metoprolol, and propranolol), diltiazem, and verapamil may be used. If the patient has accessory pathway, only intravenous amiodarone is indicated [3].

The doses of drugs used for rate control strategy are given in **Table 1** [1].

If the rate control cannot be established, interventional approach can also be performed by ablation of AV node/His bundle alongside with implantation of pacemaker.

For the assessment of rate control strategy, palpation of the radial pulse with auscultation of heart murmurs, and electrocardiography can be easily obtained and provide sufficient information for most of the patients. If needed, 6 min walk test or 24 h ambulatory Holter ECG monitoring can be implemented giving more reliable information regarding resting and exercise heart rate.

2.3 Direct current cardioversion

Prior to DC conversion it is important to evaluate each patient for appropriateness, maintaining normal, sinus rhythm thereafter, as well as probability of successful cardioversion [3]. Several factors can influence success of the cardioversion and/or reoccurrence of AF, such as age, underlying valve disease, duration of AF, size of the left atrium, low functional class, and possibility of concomitant administration of antiarrhythmic drugs. DC cardioversion has been extensively used with vitamin K-dependent anticoagulants (VKAs), while more recently direct oral anticoagulants (DOACs) have been also used for thromboembolic prevention in patients who are undergoing DC conversion.

DC cardioversion is being performed short-acting general anesthetics or under heavy sedation, while assessment of potassium levels and therapeutic levels of digoxin is indicated in all patients, since hypokalemia and supratherapeutic levels of digoxin can precipitate ventricular arrhythmias in patients with DC cardioversion. Synchronization is used to avoid discharging on T waves since it can result in ventricular arrhythmias.

Drug	Average dose	Clinical setting	Adverse effects
Digoxin	Loading dose: 250 mcg every 2 h; up to 1500 mcg Maintenance dose: 125–250 mcg daily	As monotherapy in elderly patients; not physically active patients	Bradycardia; AV blocks; proarrhythmic
Bisoprolol	5–10 mg daily	Patients with coronary artery disease; heart failure	Hypotension; bradycardia, especially in paroxysmal AF; AV blocks; impairment of pulmonary function in chronic obstructive pulmonary disease or asthma
Metoprolol	50–200 mg daily		
Carvedilol	25–100 mg daily		
Nebivolol	5–10 mg daily		
Sotalol	80–320 mg daily	Recurrent AF	Not recommended in permanent AF; bradycardia; QT prolongation; proarrhythmic
Verapamil	80–360 mg daily	Patients with chronic obstructive pulmonary disease and asthma	Hypotension; AV blocks; heart failure
Diltiazem	120–360 mg daily		
Amiodarone	200 mg daily	Recurrent AF; heart failure	Bradycardia; AV blocks; QT prolongation; proarrhythmic

Table 1.
Average doses of antiarrhythmic drugs used for rate control in AF [1].

If monophasic DC cardioversion is being used, an initial 300 J biphasic shock or 150 J monophasic shock should be given, followed by the second 200 J monophasic or 300 J biphasic shock if the first one fails. If the second shock fails, the third and final one can be delivered with the same magnitude as the second one. Biphasic shocks at high output are more successful than monophasic shocks at the same output [3].

2.4 Ablation strategies

Currently, the main way of nonpharmacological rhythm control is catheter ablation of AF, without the risk of long-term antiarrhythmic therapy maintaining normal, sinus rhythm. It has been shown that catheter ablation significantly improves LV function, symptoms, exercise capacity, and quality of life. In addition, some meta-analyses have shown that catheter ablation was superior to antiarrhythmic drugs for the control of AF. The benefit of catheter ablation was even greater in paroxysmal AF when compared to medical therapy [18]. Catheter ablation was also better than antiarrhythmics in terms of higher rates of freedom from both AF and antiarrhythmic medications [19]. However, no mortality benefit was observed in patients who have undergone catheter ablation of AF, so the procedure is currently reserved for patients with symptomatic AF [20].

Besides catheter ablation, one more way of treatment of AF includes surgical ablation of AF. The procedure involves creating series of incisions in both the left and the right atria, by which propagation of sinus impulse is directed through both atria and at the same time disabling multiple macro-reentrant circuits. Currently, the standard surgical technique has been replaced with linear epicardial ablation using unipolar or bipolar radiofrequency ablation, cryoablation, laser, high-frequency ultrasound, and microwave energy. Also, surgical instrumentation now enables minimally invasive approaches through mini-thoracotomies with video assistance. Stand-alone surgical and epicardial AF ablation may be considered for patients who are symptomatic and were refractory to one or more attempts of catheter ablation or for patients who are not candidates for catheter ablation. Hence, there are no studies that compared effects of surgical and catheter ablation of AF, degree of patient discomfort, longer hospitalizations, and the risk of bleeding following left atrial appendage excision, patients prefer catheter ablation to surgical [20].

2.5 Anticoagulant therapy

Anticoagulation therapy is one of the cornerstones in management of patients with AF, since the most common consequence of AF is stroke.

The recommendations for anticoagulation therapy are the same for both pharmacological and electrical cardioversion. CHA_2DS_2-VASc risk score is being used in order to assess whether the patient is in need for anticoagulation therapy, while HAS-BLED score assesses the risk of bleeding in patients on anticoagulation therapy. Anticoagulation therapy can be either with the use of direct oral anticoagulants (DOACs), such as apixaban, rivaroxaban, dabigatran, or edoxaban, or the use of vitamin K-dependent anticoagulants (VKAs) such as warfarin and acenocumarol. In patient with VKAs, assessment of INR is very important and should always be within 2.0–3.0 unless there are other cofactors (mechanical valves, etc.).

3. Pharmacology of antiarrhythmic drugs

The choice of antiarrhythmic drug and its superiority of one over another are not well investigated due to many reasons, such as enrolment of patients with different

underlying heart diseases or suboptimal design. Doses, indications, and the main adverse effects of the most commonly used antiarrhythmics are given in **Table 2** [1].

3.1 Flecainide and propafenone

As antiarrhythmic drugs of class Ic, propafenone and flecainide are frequently used for rhythm control in patients with AF and no or minimal underlying heart disease (such as heart failure, left ventricular hypertrophy, coronary artery disease, or previous myocardial infarction).

Flecainide expresses its effect with potent blockade of sodium and potassium channels, however, not prolonging the QT interval.

Propafenone has similar effects as quinidine, although it possesses some beta-blocking activity without prolonging the action potential.

In clinical trials that investigated recurrence rates, both propafenone and flecainide reduced the recurrence rate by 70%. Co-administration of AV-slowing agents such as beta-blockers is advised because of the possibility of organization of AF into atrial flutter. When directly compared, there was no superiority of propafenone over flecainide [21].

Drug	Dose	Clinical setting	Adverse effects
Flecainide	100–200 mg two times per day	Minimal or no structural heart disease	Bradycardia; AV blocks; organization into atrial flutter; deterioration of renal function
Flecainide XL	200 mg one time per day		
Propafenone	150–300 mg three times per day		Bradycardia; AV blocks; organization into atrial flutter; new onset of myocardial ischemia; metallic taste
Propafenone SR	225–425 mg two times per day		
Sotalol	80–160 mg two times per day	Stable coronary artery disease without previous myocardial infarction; hypertension without significant left ventricle hypertrophy	Bradycardia; AV blocks; proarrhythmic; potassium level disorders
Dofetilide	125–500 mcg two times per day	Previous myocardial infarction; heart failure	Torsade de pontes; bradycardia; AV blocks; proarrhythmic
Amiodarone	100–200 mg one time per day	Heart failure; hypertrophic cardiomyopathy; significant left ventricular hypertrophy	Bradycardia; AV blocks; thyrotoxic; pulmonary fibrosis; hepatic toxicity; eye toxicity, skin rash; abdominal pain; peripheral edema; dyspnea
Dronedarone	400 mg two times per day	Heart failure NYHA I–II; coronary artery disease; left ventricular hypertrophy	Bradycardia; AV blocks; diarrhea; rash

Table 2.
Doses, indications, and adverse effects of the most commonly used antiarrhythmic drugs [1].

3.2 Beta-blockers

The most effective antiarrhythmic drugs in prevention of AF are considered as beta-blockers. Even though they are mainly used in rate control strategy, in AF caused by thyrotoxicosis, after cardiac surgery or any adrenergically mediated AF, they represent the first-choice therapy. Between the groups of beta-blockers, there is limited evidence of superiority of one over another. Some, such as carvedilol, may be more potent because of synergistic effect on ion channels as well as adrenergic blockade; however, in direct comparison to bisoprolol, no benefit was observed [22, 23].

3.3 Sotalol

Sotalol, an antiarrhythmic drug of class III and beta-blocker, offers additional benefit of slowing heart rate during reoccurrences in AF episodes. It is recommended for use in patients with AF and stable coronary artery disease without previous myocardial infarction and/or dysfunction of the left ventricle and patients with AF and hypertension without significant left ventricle hypertrophy.

When compared with amiodarone, it showed inferior results with 30% of patients remaining in sinus rhythm after 2 years of therapy, while in the group of amiodarone, 60% remained in sinus rhythm. In comparison with antiarrhythmics class Ic, it showed similar effects [24–26].

Bradycardia and hypotension represent the most common side effects, while prolongation of QT with proarrhythmic effect was less common. Due to its relatively simple pharmacokinetics, it has very few drug interactions; however, it should be noted that sotalol decreases the threshold for cardiac defibrillation.

3.4 Dofetilide

Dofetilide is also one of the antiarrhythmic drugs of class III, but unlike sotalol or antiarrhythmics class Ic, it is recommended for use in patients with previous myocardial infarction and in patients with heart failure. It does not produce blockade of other potassium or sodium channels, but the rate of recovery from the blockade is slow; therefore, the extent of blockade shows little dependence on stimulation frequency.

Dofetilide has a dose-dependent effect; increased dose resulted in increased proportion of patients converted to sinus rhythm. However it comes with the cost. Its major concern is development of torsade de pontes which is also dose-related and often occurs in the first days after dofetilide initiation; therefore, in-hospital initiation is mandatory. Treatment with dofetilide should be initiated based on the rate-corrected QT interval (QTc) and serum electrolytes. A baseline QTc greater than 450 ms, bradycardia with heart rate less than 50 beats per minute, and hypokalemia are relative contraindications.

Since 80% of oral dose is being eliminated unchanged by the kidneys and its dose-related side effects, dofetilide dosage must be based on the estimated creatinine clearance [27].

3.5 Amiodarone

Amiodarone is one of the most commonly used antiarrhythmic worldwide, as a result of its broad spectrum of antiarrhythmic action.

Amiodarone markedly prolongs the duration of action potential, thus prolonging the QT interval. Despite its belonging to class III of antiarrhythmics, it also

blocks inactivated sodium channels and has weak adrenergic and calcium channel blocking effect by which it slows down heart rate and AV node conduction.

It has great potential to maintain sinus rhythm in patients with underlying cardiovascular conditions. Its effect on rhythm control has been largely investigated; however, one main drawback of amiodarone use is its side effects. Looking on proarrhythmic effects, it has low potential to induce torsade de pontes; however, non-cardiac side effects are numerous. It did not show effect on all-cause mortality; however, it can be used in management of AF in clinical settings of heart failure, hypertrophic cardiomyopathy, and significant left ventricular hypertrophy caused by hypertension [28].

Amiodarone side effects are a result of dose and accumulation in many tissues (lungs, liver, skin, and even heart). It also blocks the peripheral conversion of thyroxine to triiodothyronine and may result in hyperthyroidism and hypothyroidism, which in many cases are the most frequent side effects.

3.6 Dronedarone

Besides sotalol, dofetilide, and amiodarone, dronedarone is also a member of class III of antiarrhythmic and has been widely used in prevention of recurrence of paroxysmal or persistent AF and is also effective in slowing ventricular rated during AF.

It is structural analog of amiodarone in which iodine atoms have been removed, therefore eliminating action on thyroxine metabolism.

Large clinical trials have demonstrated that dronedarone reduced relative risk of hospitalizations due to cardiovascular causes and death, differed the time to the first hospitalization for cardiovascular disease or death from any cause, and significantly reduced deaths from cardiovascular diseases [29]. Based on the antiarrhythmic trial with dronedarone in moderate to severe heart failure evaluating morbidity decrease (ANDROMEDA) study with patients with severe congestive heart failure, which was stopped ahead of time because excess death was revealed in dronedarone group, dronedarone should not be used in patients with severe heart failure [30]. Therefore, dronedarone is currently recommended for use in patients with paroxysmal AF with reducing the need of hospitalization for cardiovascular events or after conversion of persistent AF; however, it should be avoided in patients with permanent AF or advanced heart failure (**Table 3**).

3.7 Other antiarrhythmics

Ranolazine, an antianginal agent, belongs to more recently developed antiarrhythmics or recently investigated as antiarrhythmic drug. It blocks several ion channels and foremost on atrial level. Clinical investigations have demonstrated that it has potential to facilitate electrical cardioversion in refractory patients, efficacy as the pill-in-the-pocket approach, and enhancing pharmacological cardioversion with its synergistic effect with amiodarone [31, 32]. When combined with dronedarone, it also showed promising results [33]. However, further studies are needed to explore its full antiarrhythmic potential.

Vernakalant is relatively a new antiarrhythmic drug, and its main effect is achieved by blocking the sodium channels. Besides sodium channels it also blocks other channels and mild QT interval prolongation. Besides oral, vernakalant can also be administered intravenously, making it a preferable choice for rapid conversion of AF. It has been investigated for converting recent-onset AF. In some clinical trials, it showed superior efficacy when compared to amiodarone for acute conversion of AF [34]. It is recommended in patients with AF and no or minimal ischemic or structural heart disease and may be considered in patients with AF and mild to

Vaughan-Williams class		Mechanism of action	Drug	Dose	Clinical setting	Adverse effects
I class	*Ia class*	Moderate blockade of sodium channels	*Quinidine*	200–600 mg three times per day	Brugada syndrome; atrial fibrillation and flutter as last-line drug	Diarrhea; prolongation of QTc; enhances digitalis toxicity; proarrhythmic
			Disopyramide	400–800 mg two to three times per day	Ventricular arrhythmias	Proarrhythmic; dry mouth; blurred vision; hypotension; increased incidence of heart failure
	Ib class	Weak blockade of sodium channels	*Lidocaine*	1–1.5 mg/kg i.v.	Ventricular arrhythmias in acute myocardial infarction	Hypotension; edema; methemoglobinemia
			Mexiletine	200–300 mg three times per day	Ventricular arrhythmias	Proarrhythmic; bradycardia; AV blocks
	Ic class	Strong blockade of sodium channels	*Flecainide*	100–200 mg two times per day	Minimal or no structural heart disease	Bradycardia; AV blocks; organization into atrial flutter; deterioration of renal function
			Propafenone	150–300 mg three times per day		Bradycardia; AV blocks; organization into atrial flutter; new onset of myocardial ischemia; metallic taste
II class		Beta 1 selective	*Bisoprolol*	5–10 mg daily	Patients with coronary artery disease; heart failure	Hypotension; bradycardia, especially in paroxysmal AF; AV blocks; impairment of pulmonary function in chronic obstructive pulmonary disease or asthma
		Beta 1 selective	*Metoprolol*	50–200 mg daily		
		Nonselective	*Carvedilol*	25–100 mg daily		
		Strong beta 1 selectivity and vasodilatation	*Nebivolol*	5–10 mg daily		
III class		Blockade of potassium channels and increasing effective refractory period	*Sotalol*	80–320 mg daily	Stable coronary artery disease without previous myocardial infarction; hypertension without significant left ventricle hypertrophy	Bradycardia; AV blocks; proarrhythmic; potassium level disorders

Vaughan-Williams class	Mechanism of action	Drug	Dose	Clinical setting	Adverse effects
		Dofetilide	125–500 mcg two times per day	Previous myocardial infarction; heart failure	Torsade de pontes; bradycardia; AV blocks; proarrhythmic;
		Amiodarone	100–200 mg one time per day	Heart failure; hypertrophic cardiomyopathy; significant left ventricular hypertrophy	Bradycardia; AV blocks; thyrotoxic; pulmonary fibrosis; hepatic toxicity; eye toxicity, skin rash, abdominal pain; peripheral edema; dyspnea
		Dronedarone	400 mg two times per day	Heart failure NYHA I–II; coronary artery disease; left ventricular hypertrophy	Bradycardia; AV blocks; diarrhea; rash
IV class	Slow non-dihydropyridine calcium channel blockers	*Verapamil*	80–360 mg daily	Patients with chronic obstructive pulmonary disease and asthma	Hypotension; AV blocks; heart failure
		Diltiazem	120–360 mg daily		

Table 3.
Antiarrhythmic drugs, Vaughan-Williams class, mechanism of action, doses, clinical settings, and adverse effects [1].

moderate structural heart disease as well as post-cardiac surgery AF. It is also more effective than flecainide and propafenone, again in recent-onset AF, and is well tolerated while to most common side effects including paresthesia, dysgeusia, dizziness, sneezing, and nausea [35, 36].

4. Conclusions

AF represents as one of the most common cardiovascular diseases and a major cause of stroke in developed countries. Treatment strategies can be divided into two strategies: rate and rhythm control. For rhythm control, antiarrhythmic drugs, direct current cardioversion, and electrophysiological ablation are used, while for rate control, chronotropic drugs are being used, while AV node ablation is required in order to reduce rapid ventricular rate which is often observed in patients with AF. **Table 3** summarizes all antiarrhythmics with Vaughan-Williams class, mechanism of action, doses, clinical settings, and adverse effects.

Patients with paroxysmal or persistent form of AF should be considered for either pharmacological or DC despite symptomatology, unless there are contraindications. Rapid ventricular rates can cause palpitations or even a syncope and other rate-related symptoms; however, these high ventricular rates lead to degradation of left ventricle performance, mitral regurgitation, and further dilatation of the left atrium; therefore, if the conversion is not achievable, patients should be treated with rate control strategy.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

AF	atrial fibrillation
DC	direct current cardioversion
NYHA	New York Heart Association classification
DOAC	direct oral anticoagulants
VKA	vitamin K-dependent anticoagulants
QTc	corrected QT interval

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