

Pharmacological Options to Maintain Sinus Rhythm in Atrial Fibrillation: Old and New Drugs, Future Directions

Introduction

Atrial fibrillation (AF) is the most prevalent clinically important arrhythmia, and its incidence increases with age. On an electrocardiogram (ECG), AF is characterized by a chaotic undulating baseline without evidence of regular, organized atrial activity. Atrial fibrillation usually is triggered by ectopic beats that come from pulmonary veins (PVs). The left upper pulmonary vein is the most common source, followed by the right upper pulmonary vein, the left inferior vein, and the right inferior pulmonary vein. These beats originate from muscular sleeves extending from the left atrium to the PVs. Less commonly, atrial tissue itself and the muscular sleeves of other cardiac veins, including the coronary sinus vein, the vein of Marshall, and the superior vena cava, may be the source of tachyarrhythmias and AF. Although ectopic beats may be generated at regular intervals, they transmit to the atrial tissue in an intermittent and irregular fashion causing AF. Another theory to explain the pathophysiology of AF is reentry, with multiple wavelets occurring in both atria. Autonomic imbalance also plays a role, at least in a portion of patients with AF. The terms vagally mediated and adrenergically mediated AF refer to atrial fibrillation induced by increased vagal (eg, after large meals) and adrenergic tone (eg, hyperthyroidism, pheochromocytoma), respectively. Atrial fibrillation is associated with anatomical and electrical remodeling of the heart. Anatomical changes due to AF include left atrial and left atrial appendage enlargement, reduced atrial contractility, and cardiomyocyte degeneration, which are associated with increased propensity to clot formation within the left atrium. Atrial fibrillation is also associated with shortening of the atrial refractory period and loss of normal adaptation of atrial refractoriness to heart rate. The result is a better substrate for AF recurrence, and this is why “AF begets AF.”¹⁻⁴

A number of conditions such as hypertensive heart disease, coronary artery disease, valvular heart disease (eg, mitral stenosis), heart failure, hypertrophic cardiomyopathy, congenital heart diseases, obesity, hyperthyroidism, alcohol intoxication, and surgery are associated with increased incidence of AF. Atrial fibrillation is associated with significant mortality and morbidity, mainly secondary to clot formation in the heart with subsequent stroke and also inducing or worsening of heart failure. While there are several radiofrequency ablation techniques for treatment of AF, pharmacological approaches fall mainly into two groups: rate control versus rhythm control. Recently more evidence has emerged that some drugs [eg, angiotensin converting enzyme (ACE) inhibitors] may reduce the incidence of AF by reversal of anatomical and electrical remodeling of the heart.

Indications for Rhythm Control

Two important clinical trials, AFFIRM and RACE, and other smaller studies showed no statistically significant difference in mortality among patients treated with rhythm control versus rate control strategies. In the AFFIRM trial, patients in the rhythm control arm had more adverse effects from the drugs and more hospitalization with a trend toward higher mortality. The results of these two trials did not show any significant difference between the two strategies and, therefore, the rate control strategy became the preferred method in most patients due to lack of side effects of antiarrhythmic drugs. If the rate control strategy is chosen, it is important to control the heart rate adequately to minimize tachycardia-mediated cardiomyopathy. Adequate rate control may be confirmed with 24-hour ambulatory ECG monitoring if necessary. The rhythm control strategy is indicated when adequate rate control cannot be achieved secondary to the adverse effects of the rate control medications, or when symptoms (palpitations,

dyspnea, lightheadedness, angina, and syncope) are not well controlled. In addition, cardioversion to sinus rhythm is used, especially in young patients, at the onset of AF with low risk of recurrence. The goal with antiarrhythmic medications is to achieve sinus rhythm; however, paroxysmal AF happens frequently and the majority of the episodes may be asymptomatic. Therefore, anticoagulation therapy should be continued in appropriate patients during the rhythm control strategy. In fact, the most important factor in reducing the incidence of stroke and mortality is appropriate and adequate anticoagulation, and not rate versus rhythm control.⁵⁻⁸

Antiarrhythmic Drug Options

Class Ia, Ic, and III antiarrhythmic medications have been evaluated for treatment of AF. The efficacy of the drug in reducing the duration and number of symptomatic episodes of AF and the side-effect profile are the most important factors in choosing the antiarrhythmic drug.

CLASS IA ANTIARRHYTHMIC DRUGS

This class includes procainamide, disopyramide, and quinidine. They are Na channel blockers with some vagolytic activity and prolongation of action potential duration (APD). Several studies showed increases in mortality with the use of this class of drugs to treat AF, mainly because of sudden arrhythmic death secondary to the pro-arrhythmic effects of these drugs. In the Stroke Prevention in Atrial Fibrillation (SPAF) trial the main antiarrhythmic therapy was with quinidine; in patients receiving such antiarrhythmic drug therapy, cardiac mortality was increased 2.5-fold ($P = .006$) and arrhythmic death was increased 2.6-fold ($P = .02$). Among patients with a history of congestive heart failure, those given antiarrhythmic medications had a relative risk of cardiac death of 4.7 ($P < .001$, 95% CI, 1.9-11.6) compared with that of patients not so treated; the relative risk of arrhythmic death in the treated group was 3.7 ($P = .01$, 95% CI, 1.3-10.4). A similar result was obtained by meta-analysis of several clinical trials. Procainamide has a common side effect of lupus-like symptoms (ie, drug-induced lupus), and quinidine has several side effects such as gastrointestinal intolerance and a syndrome of headache, dizziness, and tinnitus (cinchonism). Disopyramide has stronger vagolytic activity than the other two drugs in this group. It is associated with anticholinergic side effects such as urinary retention, dry mouth, blurred vision, constipation, and worsening of preexisting glaucoma. In addition, disopyramide has a negative inotropic

effect which makes its use contraindicated in patients with heart failure. Disopyramide and procainamide have not been commonly used for treatment of AF. In those patients with no structural heart disease and at low risk for developing ventricular arrhythmias, especially torsade de pointes, quinidine has had a role in maintaining sinus rhythm. One should keep in mind that treatment of AF is individualized, based on the patient's presentation, symptoms, and risk factors. For instance in a young patient with no structural heart disease and with vagally mediated AF, disopyramide may be considered for maintaining sinus rhythm if the rhythm control strategy is chosen. Also, in the presence of ventricular pre-excitation and AF, the drug of choice is procainamide. Disopyramide, amiodarone, and ibutilide are other alternatives, while AV nodal blocking drugs should be avoided before increasing the refractoriness of the bypass tract with the above drugs.⁹⁻¹²

CLASS IC ANTIARRHYTHMIC DRUGS

Flecainide and propafenone are two important antiarrhythmic drugs in this class. They are Na channel blockers similar to class Ia but they generally do not prolong the action potential and they do not have antimuscarinic effects. Propafenone has some structural similarities to propranolol and possesses weak β -blocking activity. Their Na channel blockade effect has use-dependency, which means they are more effective at higher heart rates. The efficacy and safety of these two drugs are comparable. In a clinical trial, although these two drugs showed equal efficacy in suppressing AF and atrial flutter episodes, there was a trend toward a higher rate of side effects in the patients treated with propafenone. These side effects were mainly gastrointestinal intolerance but significant enough to discontinue the treatment. Larger clinical trials with longer periods of follow up are needed to evaluate the differences in efficacy and safety between these two drugs. The indication for these drugs became limited to patients with no structural heart disease after the results of The Cardiac Arrhythmia Suppression Trial were published. This clinical trial showed a significantly higher mortality rate in patients treated with flecainide or encainide following myocardial infarction (MI). Flecainide and encainide were used to suppress premature ventricular contractions (PVCs), the rationale behind this study being the observation that frequent PVCs are associated with sudden cardiac death (SCD) following MI; therefore, suppression of PVCs could potentially reduce the risk of SCD. However, it became clear that

mechanisms of ventricular tachycardia (VT), ventricular fibrillation (VF) and SCD are multifactorial and more complex, and although these antiarrhythmic drugs suppress PVCs, probably their proarrhythmic effects increase the risk of VF and VT in hearts with post-MI remodeling. While this study was not done in patients with AF, the concept of avoiding these drugs in patients with structural remodeling of the heart can be applied to patients with AF.¹³⁻¹⁶

CLASS III ANTIARRHYTHMIC DRUGS

This class of antiarrhythmic drugs prolongs the action potential by prolonging repolarization. Amiodarone, sotalol, and dofetilide are used for maintaining sinus rhythm in AF. Ibutilide is used only for acute cardioversion and is available only in intravenous form. Several newer antiarrhythmic drugs in this class such as dronedarone, azimilide and tedisamil are under investigation.

Amiodarone

Amiodarone prolongs the action potential by inhibition of K outward current; IKr and IKs. In addition to K channel blocking, amiodarone has some degree of β -blocking and Na and Ca channel blockade effects. This broad effect on ion channels accounts for its relative safety and effectiveness in controlling both atrial and ventricular arrhythmias. Several studies have shown superior efficacy of amiodarone compared to other antiarrhythmic drugs such as propafenone, a class IC drug, and sotalol, another class III drug, in treatment of AF. For instance, in a double-blind, placebo-controlled clinical trial performed on 668 patients showed that amiodarone was superior to sotalol in treatment of AF, with the median time to a recurrence of AF being 487 days in the amiodarone group versus 74 days in the sotalol group, and six days in the placebo group. However, in a subset of patients with ischemic heart disease in this study the difference in time to a recurrence between the amiodarone and sotalol groups was not statistically significant. In patients with ischemic heart disease, the median time to a recurrence of AF was 569 days with amiodarone therapy and 428 days with sotalol therapy ($P=.53$). A meta-analysis of 13 randomized controlled trials of prophylactic amiodarone in patients with recent MI or congestive heart failure (CHF) showed that the total mortality was reduced by 13%. Arrhythmic/sudden death was reduced by 29%. There was no effect on non-arrhythmic deaths and there was no significant difference in treatment effect between the post-MI and CHF studies. The risk of arrhythmic/sudden death in

control-group patients was higher in the CHF than in the post-MI studies (10.7 vs 4.1%). The proarrhythmic side effect of amiodarone is lower than that of other antiarrhythmic drugs, but it should be remembered that amiodarone causes bradycardia and may cause heart block in susceptible individuals. It also has significant noncardiac side effects, including pulmonary fibrosis, hepatitis, skin lesions, corneal microdeposits, and optic neuritis. Amiodarone not only blocks the peripheral conversion of T4 to T3 but also is a source of a large amount of iodine; therefore, its consumption may lead to either hypothyroidism or hyperthyroidism. Baseline laboratory value and interval tests should be obtained to monitor these side effects.¹⁷⁻²⁰

Amiodarone has also been studied for prevention of postoperative AF. A randomized double-blind study showed >50% reduction in the rate of AF after cardiac surgery in patients who took amiodarone compared to placebo. In that study, therapy consisted of 600 mg of amiodarone per day for seven days, then 200 mg per day until the day of discharge from the hospital. The mean (\pm SD) preoperative total dose of amiodarone was 4.8 ± 0.96 g over a period of 13 ± 7 days. Short-term use of amiodarone does not have the significant side effects that are seen with long-term usage.²¹

Sotalol

Sotalol prolongs the action potential and has nonselective β -blocking effects; therefore, it gives sinus rhythm control with some degree of rate control. It has a dose-dependent risk of arrhythmia, especially torsade de pointes, and may exacerbate preexisting left ventricle (LV) dysfunction. It is excreted by the kidneys and it should be avoided or its dose should be reduced in renal impairment. While it is more effective than placebo in maintaining the sinus rhythm, it is not as effective as amiodarone. Sotalol appears to be as effective as class IA and class IC drugs such as quinidine and propafenone. However, the results of a randomized clinical trial that studied the safety and efficacy of amiodarone, propafenone, and sotalol in 214 patients suggested that amiodarone and propafenone were superior to sotalol in maintaining long-term normal sinus rhythm in patients with AF, and that amiodarone tended to be superior to propafenone, though its long-term efficacy was limited by adverse side effects. Current recommendations from the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) suggest using either sotalol, propafenone or flecainide in those patients who do not have significant structural abnormality of the heart. Among these three

drugs, flecainide and propafenone are contraindicated in patients with coronary artery disease (CAD) while sotalol is an option in these patients, although its efficacy is reduced in the presence of CAD. A staged care strategy, which is treating the patient with one antiarrhythmic drug (eg, propafenone) and then adding the second one (eg, sotalol), may improve overall efficacy and safety.^{19,22-29}

Dofetilide

Dofetilide prolongs the action potential by blocking the rapid component of the delayed rectifier of the outward potassium current, IKr. It has a proarrhythmic side effect with a narrow therapeutic window and a toxicity that is associated with QT prolongation and torsade de pointes. Most of the drug is excreted by the kidneys and the dosage should be modified in cases of renal failure. This newer antiarrhythmic drug has been proved to be more effective than placebo in maintaining the sinus rhythm in both patients with normal LV function and in those with LV dysfunction and heart failure. A meta-analysis of clinical trials with patients who were treated with dofetilide showed that the unadjusted hazard ratio for risk of death (dofetilide/placebo) was 1.4 (95% CI, 0.4-5.1) and after adjusting for the effects of arrhythmia diagnosis, age, sex, and structural heart disease, the hazard ratio was 1.1 (95% CI, 0.3-4.3). Therefore, these data provided reassurance regarding the safety of dofetilide in patients with supraventricular arrhythmias. The ACC/AHA/ESC recommendations suggest using dofetilide as a second-line drug in patients with normal structure of the heart after propafenone, flecainide, and sotalol. However, it is suggested as a first-line drug in patients with heart failure or CAD. Clinical studies have not shown any significant noncardiac side effects for dofetilide.^{28,30-36}

Dronedaronone

Amiodarone has been a relatively successful drug in maintaining sinus rhythm with a low likelihood of causing ventricular arrhythmia. However, it has several noncardiac side effects. In one meta-analysis of four clinical trials in which the mean amiodarone dose per day ranged from 152 to 330 mg and for a minimal duration of 12 months, the drug administration was associated with thyroid, neurologic, skin, ocular, and bradycardic adverse effects leading to discontinuation of the drug in 22.9% of the patients. Therefore, new attempts have focused on developing related compounds with the same favorable cardiac profile but with reduced noncardiac adverse effects.³⁷

Dronedaronone is a new antiarrhythmic drug with structural similarities to amiodarone without iodine in its structure. The drug is still under investigation and in 2005 a request for regulatory approval was filed with both the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products. Dronedaronone is classified as a class III antiarrhythmic agent with a blockade effect on potassium channels and causing prolongation of action potential duration (APD). Dronedaronone also has inhibitory effects on Na and Ca channels and adrenergic receptors. The Dronedaronone AF Study After Electrical Cardioversion (DAFNE) clinical trial, a double-blind randomized study with a six month follow-up, showed that the time to AF relapse increased on dronedaronone 800 mg, with a median of 60 days versus 5.3 days in the placebo group. No significant effect was seen at higher doses. There were no proarrhythmic reactions and drug-induced QT prolongation was only noticed in the 1600 mg group. Premature drug discontinuations affected 22.6% of subjects given 1600 mg dronedaronone versus 3.9% on 800 mg and were mainly due to gastrointestinal side effects. No evidence of thyroid, ocular or pulmonary toxicity was found. This study suggested dronedaronone, at an 800 mg daily dose, for the prevention of AF relapses after cardioversion. Recently, the results of two important identical double-blind randomized clinical trials were published: The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedaronone for the Maintenance of Sinus Rhythm (EURIDIS) and the American–Australian–African Trial with Dronedaronone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS). In the European trial, the median times to the recurrence of arrhythmia were 41 days in the placebo group and 96 days in the dronedaronone group ($P=.01$). The corresponding durations in the non-European trial were 59 and 158 days ($P=.002$). At the recurrence of arrhythmia in the European trial, the mean (\pm SD) ventricular rate was 117.5 ± 29.1 bpm in the placebo group and 102.3 ± 24.7 bpm in the dronedaronone group ($P<.001$); the corresponding rates in the non-European trial were 116.6 ± 31.9 and 104.6 ± 27.1 bpm ($P<.001$). Rates of pulmonary toxic effects and of thyroid and liver dysfunction were not significantly increased in the dronedaronone group. Also, the rates of death from any cause and sudden death in the dronedaronone group did not differ significantly from those in the placebo group. This suggests that dronedaronone may not have common adverse effects like amiodarone. However, a previous study, the Antiarrhythmic Trial with Dronedaronone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA), was

discontinued early because an interim safety analysis suggested a potential increase in the risk of death with dronedarone therapy. Therefore dronedarone may not be appropriate in high-risk patients, especially those with heart failure. Another issue to be resolved is the efficacy of dronedarone compared with other antiarrhythmic drugs such as amiodarone. Efficacy & Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation (DIONYSOS) is the name of an ongoing clinical trial that tries to answer this important question.³⁸⁻⁴⁰

Azimilide

Azimilide is a new investigational class III antiarrhythmic drug that blocks both the rapidly (I(Kr)) and slowly (I(Ks)) activating components of the delayed rectifier potassium current. Therefore, it prolongs the action potential over a wide range of heart rates with no reverse-use dependency. The results of clinical trials on the efficacy of azimilide to suppress AF recurrence have been controversial. Some studies suggested that azimilide in the dose range of 100 to 125 mg per day is more effective than placebo to control AF, while other studies failed to show such effectiveness. In the ALIVE study, which was a multinational randomized double blind clinical trial, showed that azimilide was mildly effective in reducing the recurrence of AF in a high-risk population who survived MI with moderate-to-severe LV systolic dysfunction. However, azimilide did not demonstrate clinically important or statistically significant efficacy in reducing the risk for AF recurrence in patients with structural heart disease in another study. A-COMET-II, a randomized, six month double-blind, placebo-controlled, parallel group-design study to compare the efficacy of azimilide 125 mg per day with placebo or sotalol 160 mg b.i.d. in patients with persistent AF, demonstrated that the antiarrhythmic efficacy of azimilide is slightly superior to placebo but significantly inferior to sotalol in patients with persistent AF. The modest antiarrhythmic efficacy and high rate of Torsade de Pointes and marked QTc prolongation limit azimilide utilization for the treatment of AF. Both the safety and efficacy of this drug should be further evaluated with large randomized clinical trials before any conclusion regarding to its application in the medical treatment of AF.⁴¹⁻⁴⁷

Tedisamil

Tedisamil is a new investigational class III antiarrhythmic drug. A multicenter, double-blind, randomized, placebo-controlled, sequential ascending dose-group

trial tested the efficacy of intravenous tedisamil compared to placebo in conversion of AF or atrial flutter (AFL) to sinus rhythm. Of 175 patients representing the intention-to-treat sample, conversion to normal sinus rhythm was observed in 41% (25/61) of the tedisamil 0.4 mg/kg group, 51% (27 of 53) of the tedisamil 0.6 mg/kg group, and 7% (4/59) of the placebo group, with an average time to conversion being 35 minutes in patients receiving tedisamil. There were two instances of self-terminating VT, both in patients receiving 0.6 mg/kg tedisamil. Although this study points out the effectiveness of tedisamil in terminating AF or AFL, more and larger randomized clinical trials are required especially to evaluate the safety and efficacy of the drug in maintaining the sinus rhythm after cardioversion.⁴⁸

Future Direction; Atrial Selective Antiarrhythmic Drugs, ACE Inhibitors, Angiotensin II Receptor Blockers, and Statins

Modulation of the atrially expressed ion channel subunit Kv1.5 [conducting the ultra-rapid delayed rectifier, I(Kr)] is a potential therapeutic option for AF with atrial selectivity now under investigation. Similarly, modulation of the atrial expression of connexin 40, a protein which is localized in gap junctions and downregulated in AF, is a potential therapeutic approach. Acetylcholine-activated current (I(KACH)) is increased in human AF and is another novel candidate target for drug therapy. RSD1235 blocks atrial selective IKur and Ito channels and also has frequency-dependent sodium channel blockade property. AVE0118 also blocks IKur and Ito. In addition it blocks IKACH. AZD7009 blocks IKr, IKur, and Ito in addition to the sodium current and NIP-142 inhibits IKur IKACH channels. These drugs have to be further tested regarding their efficacy of treating AF and their safety before becoming an option.⁴⁹⁻⁵³

In recent years it has been shown that the renin-angiotensin system has a significant role in the anatomical and electrical remodeling of the heart which leads to arrhythmias. Infusion of angiotensin II induces significant myocardial fibrosis and hypertrophy in animal models and this may lead to arrhythmia by a variety of mechanisms, including conduction block and reentry. Therefore ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) have been tested for prevention of AF and maintaining the sinus rhythm. Two large randomized clinical trials, Val-Heft and CHARM, showed the efficacy of candesartan and valsartan in maintaining sinus rhythm in patients

with heart failure. Two other randomized clinical trials, LIFE and VALUE, suggested that losartan and valsartan are effective in preventing AF in hypertensive patients. ACEI and ARBs may have value in the prevention of postoperative AF; however, this needs further evaluation with larger randomized studies. A retrospective cross-sectional and longitudinal analysis of participants in the Stroke Prevention using an Oral Thrombin Inhibitor in AF (SPORTIF) III and V trials, in relation to the use (or nonuse) of ACEI/ARBs, showed that patients aged older than 75 years taking ACEIs or ARBs had lower mortality (hazard ratio 0.71, 95% CI, 0.52–0.95). Current evidence suggests using ACEIs and ARBs for prevention of AF in hypertensive patients and those with heart failure. Using these drugs for prevention of AF and maintaining sinus rhythm in other populations such as the elderly and postoperative patients needs further investigation.⁵⁴⁻⁶²

Recent data suggest that inflammation and oxidative stress are involved in the development, recurrence and persistence of AF. Thus, the known anti-inflammatory effects of HMG-CoA reductase inhibitors (statins) led to investigations of these drugs in reducing the incidence of AF. Several studies suggested that statins are effective in reducing the recurrence of AF after electrical cardioversion. A recent study also suggested that patients presenting with acute coronary syndrome (ACS) were much less likely to have new-onset AF if they were on a statin at the time of presentation. Treatment with atorvastatin 40 mg/d, initiated seven days before elective cardiopulmonary bypass surgery was shown to be effective in reducing the incidence of postoperative AF, and it shortened hospital stay.⁶³⁻⁶⁸

Hybrid Therapy

Many patients develop AFL after initiation of antiarrhythmic drugs, and radiofrequency (RF) ablation is a very effective treatment for AFL. Schumacher et al studied 187 patients from an AF registry with paroxysmal AF who were orally treated with flecainide or propafenone. Twenty-four patients (12.8%) developed AFL during the course of treatment. In 20 of these patients (10.7%), EP study revealed typical AFL. These patients underwent RF ablation of AFL. Recurrence of AF was assessed by ambulatory Holter monitoring and serial questionnaires. During a mean follow-up of 11±4 months, the incidence of AF episodes was significantly lower in patients receiving the combined therapy (2.7±3.6 per year) compared both to control subjects receiving the drug treatment only (7.8±9.2 per year, $P < .05$) and to patients before the therapy (10.2±5.4 per year, $P < .001$). The

efficacy of this approach was confirmed in other studies. Also Kocheril et al studied the effects of adding a standardized right atrial catheter ablation procedure to a regimen of previously ineffective antiarrhythmic drugs on AF episode frequency and symptoms among a population of highly symptomatic, drug-refractory patients in a multicenter clinical trial. In this study, all subjects underwent a right atrial catheter ablation procedure with a standardized lesion set while continuing their current regimen of antiarrhythmic drugs. There were statistically significant improvements in 6 months of follow-up in all outcome measures, including AF episode frequency, the occurrence of clinical arrhythmia symptoms as well as condition-specific and global health-related quality of life. This study along with other available evidence suggests using this approach as an option in patients with refractory AF.^{65,69-73}

Summary

Atrial Fibrillation is a common clinical problem. Although clinical evidence suggests using rate control strategy in majority of the patients, the rhythm control strategy is indicated when adequate rate control can not be achieved secondary to the adverse effects of the rate control medications or when symptoms (palpitations, dyspnea, lightheadedness, angina, and syncope) are not well controlled. Among antiarrhythmic drugs class Ia, Ib, and class III are used to maintain the sinus rhythm more than other classes. A simplified approach to choose the antiarrhythmic drug based on the current evidence is: (1) The drug of choice in patients with no or minimal heart disease is Flecainide, propafenone, or sotalol, (2) In patients with heart failure (EF < 35%) or significant Left Ventricular Hypertrophy (LVH) the drug of choice is amiodarone, and (3) In patients with coronary artery disease sotalol or amiodarone can be used. Future drugs will be designed in two main directions; (1) Drugs that are atrial selective and therefore have minimum ventricular side effects, and (2) Those drugs that modify the anatomical and electrical remodeling of the heart therefore they treat the underlying substrate for AF. Statins play an antiarrhythmic role by inhibition of oxidative stress while ACE inhibitors and angiotensin II receptor blockers have both anti-oxidative and anti-fibrotic properties. Approaches that consider a combination of antiarrhythmic drug with catheter ablation have been described and new methods may emerge as new ablation techniques and new drugs are discovered.

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CME Questions 3a-d

Please select the best answer for the following:

- 3a. The “rate control” strategy is preferable in many patients with atrial fibrillation and the “rhythm control” strategy is used mainly for those patients who develop side effects to the rate control drugs or remain symptomatic despite rate control medications.
- True
 - False
- 3b. Which one of the following statements is NOT correct?
- Class Ic and III are the main classes of antiarrhythmic drugs that are used to maintain sinus rhythm in atrial fibrillation.
 - Amiodarone does not prolong the action potential.
 - Class Ic drugs (eg, flecainide and propafenone) are not recommended in patients with structural heart disease.
 - Sotalol, a class III antiarrhythmic drug, is recommended in patients with coronary artery disease.
 - Amiodarone can be used to maintain sinus rhythm in patients with atrial fibrillation and structural heart disease.
- 3c. Which one of the following is the focus of the current research to develop new antiarrhythmic drugs for treatment of atrial fibrillation?
- New antiarrhythmic drugs that are structurally similar to amiodarone but have less non-cardiac side effects (eg, dronedarone)
 - Atrial selective antiarrhythmic drugs with less ventricular proarrhythmia
 - Drugs that modify substrates for arrhythmia (ie, drugs with anti-fibrotic and anti-inflammatory effects)
 - All of the above
- 3d. A combination of atrial flutter ablation and previously ineffective antiarrhythmic drug for atrial fibrillation (hybrid therapy) has been shown to be an effective strategy in treatment of atrial fibrillation in selected patients.
- True
 - False