Drug Therapy for Atrial Fibrillation

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KEYWORDS

• Atrial fibrillation • Pharmacologic therapy
• Rhythm control • Prevention

Atrial fibrillation (AF) is the most frequently diagnosed arrhythmia, affecting an estimated 2.3 million people in the United States. Prevalence increases with age, occurring in 3.8% of people age 60 and older and in up to 9% of people over age 80.[1]

One of the fundamental considerations in the management of AF is whether or not to attempt to restore sinus rhythm or to allow AF to continue while controlling the ventricular rates. The decision depends on the severity of symptoms, associated heart disease, age, and other comorbidities that may limit therapeutic options.

AF can be classified as paroxysmal, persistent, or permanent. Paroxysmal AF terminates spontaneously, with episodes typically lasting less than 24 hours but possibly lasting up to 7 days. Persistent AF requires cardioversion (pharmacologic or electrical) to terminate, and episodes last greater than 7 days. Permanent AF describes continuous AF that has failed cardioversion or where cardioversion never has been attempted. Recurrent AF describes two or more episodes of paroxysmal or persistent AF.

Determining how symptomatic patients are from AF can be difficult. Symptoms of palpitations, dyspnea, lightheadedness, or syncope generally are related to rapid, irregular ventricular rates. By slowing the heart rate with atrioventricular (AV) nodal blocking agents, these symptoms may abate. Some patients may notice a subtle decline in exercise tolerance or complain of generalized fatigue despite adequate rate control resulting from loss of atrial mechanical function. Patients who have hypertension, left ventricular hypertrophy, impaired diastolic relaxation, and restrictive cardiomyopathy are particularly sensitive to the loss of AV synchrony and the resultant decrease in diastolic filling. Patients who clearly are symptomatic from AF may benefit from an attempt to control rhythm. In asymptomatic patients who have no appreciable decline in functional status in AF, rate control may be sufficient.

RHYTHM VERSUS RATE CONTROL

Multiple prospective randomized studies have examined the issue of rhythm versus rate control. The two largest trials, Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE), failed to show any benefit in the rhythm-control arm.[2,3] The AFFIRM trial enrolled more than 4000 patients who had paroxysmal and persistent AF. Patients were randomized to receive rate control or antiarrhythmic drug therapy. All patients initially were anticoagulated, but patients in the rhythm-control group who had remained in sinus rhythm for at least 3 months could stop warfarin. There was no significant difference in the primary end point of overall mortality, with a trend toward increased risk in the rhythm-control group (5-year mortality,

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24% versus 21%). A trend toward higher risk for ischemic stroke was seen in the rhythm-control group, however, mainly in patients who were not receiving adequate anticoagulation. This emphasizes the need for indefinite anticoagulation for rate- and rhythm-control methods in high-risk patients, because asymptomatic recurrences of AF predispose to thromboembolic events.

The RACE trial randomized 522 patients who had persistent AF, despite previous electrical cardioversion, into rate- or rhythm-control groups. All patients were anticoagulated. The study protocol allowed patients in the rhythm-control group who had maintained sinus rhythm for 1 month the option of discontinuing warfarin therapy. The primary end point was a composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, or severe adverse reactions to drugs. After a mean of 2.3 years of follow-up, the trial found rate control was not inferior to rhythm control for the prevention of death or morbidity. Only 39% of the rhythm-control group was in sinus rhythm compared with 10% of the rate-control group. Within the rhythm-control group, hypertension and female gender were associated with a higher risk for an event. Higher rates of thromboembolic events occurred in the rhythm-control group, with most of the events associated with subtherapeutic anticoagulation. Cessation of anticoagulation also was associated with a higher risk for thromboembolic events.

To address the issue of whether or not patients had any difference in exercise tolerance with rate versus rhythm control, a substudy of the AFFIRM trial performed serial 6-minute walk tests on 245 study patients.[4] Walk distances improved in both groups over time, with slightly longer distances observed in the rhythm-control group. It was unclear whether or not the difference in walk distances was clinically significant.

Focusing on the heart failure population, a recent multicenter, randomized study from the Atrial Fibrillation and Congestive Heart Failure investigators compared rhythm versus rate control in 1376 patients with a left ventricular ejection fraction of 35% or less. There was no difference between the two groups in cardiovascular mortality, all-cause mortality, stroke, or worsening heart failure.[5]

The results from the AFFIRM and RACE trials are most applicable to elderly patients (mean ages of study patients were 70 and 68, respectively) who have few or no symptoms from AF, for whom anticoagulation and a strategy of rate control may be most appropriate. For younger, symptomatic patients who do not have underlying heart disease, restoration of sinus rhythm must still be considered a valid approach.

RATE CONTROL AGENTS

The goal of rate control is to control the resting heart rate and the heart rate during exercise while avoiding excessive bradycardia. Persistent tachycardia may lead to development of cardiomyopathy, which usually is reversible with adequate rate control. Although criteria for adequate rate control vary among trials, typical goals for ventricular rates range from 60 to 80 beats per minute at rest and between 90 and 115 beats per minute during exercise.[6] Given that rates may be well controlled at rest but may increase significantly during exercise, it is useful to record heart rates during exercise stress testing or by 24-hour ambulatory EKG monitoring.

Ventricular rate during AF is a function of the refractoriness of the AV node, sympathetic and parasympathetic tone, and intrinsic conduction. Agents that prolong the refractory period of the AV node effectively control ventricular rate. β-Blockers, calcium channel blockers, and digoxin all slow conduction through the AV node and may be used alone or in combination for rate control.

β-Blockers are the most effective monotherapy for rate control, especially in high adrenergic states. In the AFFIRM trial, 70% of patients on β-blockers achieved adequate rate control (as defined previously) compared with 54% of patients on calcium channel blockers.[2] In the acute setting, intravenous β-blockade with esmolol, metoprolol, propanolol, or atenolol has a rapid onset. Esmolol may be given as a continuous intravenous infusion. Caution is advised when starting β-blockers in patients who have heart failure or hypotension. In hemodynamically stable patients, oral β-blockade is safe and effective for controlling ventricular rates. Sotalol, a β-blocker with Vaughan-Williams class III antiarrhythmic properties that suppresses AF, is associated with slower ventricular rates with AF recurrences.

Calcium channel blockers (nondihydropyridines) may be preferred in patients who have preserved left ventricular systolic function and severe chronic obstructive pulmonary disease. Verapamil and diltiazem are equally effective in controlling ventricular rates. Given intravenously, calcium channel blockers have a rapid onset of action (2–7 minutes). To maintain effectiveness, a continuous drip usually is given because of the drugs' short half-lives.

Digoxin, once considered first-line treatment for rate control in the acute management of AF, is less effective than β-blockers or calcium channel blockers. Intravenous digoxin requires 60 minutes to take effect, whereas its peak effect may not be seen for 6 hours. Digoxin is not shown more

effective than placebo in converting AF to sinus rhythm. Digoxin may be used in patients who cannot tolerate β-blockers or calcium channel blockers because of heart failure or hypotension. Digoxin is less effective in settings of high sympathetic tone and does not slow heart rates during exercise. In sedentary patients who do not exercise, digoxin alone may be sufficient to control rates at rest.[6] Often, patients require combination therapy to achieve sufficient rate control.

RHYTHM CONTROL: PHARMACOLOGIC CARDIOVERSION

Once the decision is made to proceed with restoration of sinus rhythm, it can be pursued pharmacologically or electrically. The duration of AF is an important factor. Patients who have recent-onset AF (<48 hours) have a high rate of spontaneous conversion, up to 60% at 24 hours.[7] Pharmacologic or electrical cardioversion in this setting allows faster restoration of sinus rhythm, with resolution of symptoms and shorter lengths of stay. Success rates for direct current electrical cardioversion range from 75% to 93%. Administration of antiarrhythmic drugs before electrical cardioversion increases long-term success rates. Achievement of sinus rhythm with pharmacologic cardioversion alone varies by agent, averaging approximately 50% after 1 to 5 hours.[8] Biphasic electrical cardioversion may be more effective than pharmacologic cardioversion but requires pain control (general anesthesia or conscious sedation) and a 6- to 8-hour fasting period.

Once an episode of AF is present for more than 7 days, electrical cardioversion is preferred. Spontaneous conversion rates are much lower after 1 week, and pharmacologic therapy also is less effective. With either method, adequate anticoagulation must be achieved before cardioversion and for a period of 4 weeks after, as the risks for thromboembolic events are similar.

MAINTENANCE OF SINUS RHYTHM

For patients who have recurrent paroxysmal or persistent AF, the choice of agent for long-term antiarrhythmic therapy must be individualized. The benefit of maintaining sinus rhythm must be balanced against the side-effect profile of the antiarrhythmic drug. Even after successful cardioversion, recurrence of AF is high in untreated patients, with relapse rates of 71% to 84% at 1 year.[9] Using a rhythm control strategy, recurrence is reduced by 30% to 50%.[9]

Amiodarone is the most effective drug for preventing recurrence of AF.[9–11] In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial, 665 patients who had persistent AF were randomized to receive amiodarone, sotalol, or placebo and followed for 1 to 4.5 years. Recurrence rates at 1 year were 48% with amiodarone, 68% with sotalol, and 87% in the placebo group. A higher incidence of minor bleeding episodes was seen in the amiodarone group, likely because of interaction with warfarin levels.[12] The Canadian Trial of Atrial Fibrillation found similar results among 403 patients assigned to amiodarone, sotalol, or propafenone. After a mean follow-up period of 16 months, the recurrence rate for the amiodarone group was 35%, compared with 63% in the sotalol or propafenone group. A total of 18% of patients in the amiodarone group withdrew because of adverse events, however, compared with 11% in the sotalol or propafenone group.[10] In a post hoc analysis of the Veterans Affairs Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy, amiodarone facilitated conversion to and maintenance of sinus rhythm in patients who had left ventricular systolic dysfunction. Furthermore, the subset of patients who were maintained in sinus rhythm had lower overall mortality. Amiodarone was not linked to worsening of heart failure.[13] Despite its effectiveness over other agents, the lengthy list of potential adverse effects associated with amiodarone use makes it a second-line agent in patients who do not have contraindications to other antiarrhythmic drugs. Major side effects of amiodarone include potentially fatal pulmonary toxicity, thyroid dysfunction, hepatic toxicity, optic neuropathy, peripheral neuropathy, gastrointestinal upset, skin discoloration, and rarely torsades de pointes.

In patients who have no evidence of structural heart disease, class IC agents are first-line therapy for maintaining sinus rhythm, based on the guidelines recently issued by the American College of Cardiology, American Heart Association, and European Society of Cardiology.[6] Propafenone and flecainide generally are well tolerated, show similar effectiveness, and have a low risk for toxicity.[14] The Rythmol Atrial Fibrillation Trial, a randomized control trial of 523 patients, tested sustained-release propafenone in three doses (225 mg, 325 mg, and 425 mg). At the end of the 39-week follow-up period, recurrence rate of AF was 69% in the placebo group compared with 52%, 42%, and 30% in the propafenone groups (225 mg, 325 mg, and 425 mg, respectively). Similar results were found in the European Rythmol/Rytmonorm Atrial Fibrillation Trial of similar design.[15] There were significantly higher withdrawals because of adverse events in the 425-mg group than any other group.[16] Propafenone may cause

gastrointestinal symptoms, such as nausea, and should be avoided in patients who have severe obstructive lung disease. Flecainide may cause mild neurologic side effects. Side effects of both agents may include hypotension and bradycardia after conversion to sinus rhythm. Class IC agents also may convert AF into a slow atrial flutter. The slow flutter rate may conduct 1:1, causing rapid ventricular conduction with a wide complex QRS, which may be mistaken for ventricular tachycardia. To prevent rapid ventricular rates, an agent to slow AV nodal conduction, such as a β-blocker or calcium channel blocker, may be coadministered with propafenone or flecainide. Because of the negative inotropic effect and proarrhythmic potential of class IC drugs, they should be avoided in patients who have heart failure or ischemic heart disease.

Sotalol, although not a useful agent for cardioverting AF to sinus rhythm, can be used to maintain sinus rhythm. Sotalol is a nonselective β-blocker, in addition to its class III potassium channel-blocking effects. Sotalol has the added benefit of slowing AV nodal conduction should AF recur, which may decrease symptoms during AF episodes. In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial and Canadian Trial of Atrial Fibrillation studies, recurrence rates of AF with sotalol were significantly lower compared with placebo, although higher than with amiodarone.[10,12] Sotalol prolongs the QT interval and has a risk for torsades de pointes. Sotalol should not be used in patients who have significant left ventricular hypertrophy or heart failure.

Dofetilide is a class III antiarrhythmic drug that selectively inhibits the delayed rectifier potassium current and increases the atrial and ventricular effective refractory period, prolonging repolarization. Plasma concentrations peak 2 to 3 hours after oral dosing. The corrected QT interval (QTc) lengthens in a linear, dose-dependent fashion. Unlike class IC agents, dofetilide has no negative inotropic effects. The safety of dofetilide in heart failure has been studied by the Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) study group in two large randomized control trials, DIAMOND-CHF and DIAMOND-AF.[17,18] DIAMOND-CHF enrolled 1518 patients who had severe symptomatic left ventricular dysfunction randomized to dofetilide or placebo. The primary end point was all-cause mortality. After a median of 18 months' follow-up, there was no difference in survival in the two groups (41% versus 42%). DIAMOND-AF was a substudy of 506 heart failure patients who had baseline AF or flutter. Over the course of the study, 44% in the dofetilide group converted to sinus rhythm by 1 year compared with 14% in the placebo group. At 1 year, patients receiving dofetilide had a 79% probability of maintaining sinus rhythm versus 42% in the placebo arm.

Because of its QTc prolonging effect, dofetilide use carries a risk for torsades de pointes. In the DIAMOND-CHF study, the incidence of torsades de pointes was 3.3%, with 76% of cases occurring within 3 days of initiation of dofetilide. During the study, dose reduction based on creatinine clearance decreased the incidence of torsades de pointes.[17] The risk for torsades de pointes can be minimized by adjusting the dose for renal function, along with instituting a 72-hour in-hospital monitoring period on initiation of dofetilide.

The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide tested the safety and efficacy of dofetilide in a group of 325 patients who had persistent AF. The trial reported a 58% efficacy for maintaining sinus rhythm at 1 year (versus 25% with placebo) along with a much lower incidence of torsades de pointes (0.8%) compared with DIAMOND-AF. Dofetilide dosing in this study was reduced for impaired renal function and for prolongation of the QTc over 15% of baseline.[19] Similar results were reported in the European and Australian Multicenter Evaluative Research on Atrial Fibrillation and Dofetilide study.[20] Because of the complexity of dosing regimens, the US Food and Drug Administration has restricted prescription of dofetilide to registered hospitals, physicians, pharmacists, and nurses who have completed specific training in the use of the drug.

Selection of a specific antiarrhythmic agent usually is determined by the presence or absence of underlying cardiac disease (**Fig. 1**). Class IC antiarrhythmic drugs are contraindicated in patients who have marked left ventricular hypertrophy, coronary artery disease, or congestive heart failure because of the risk for ventricular arrhythmias. In patients who do not have structural heart disease, flecainide, propafenone, or sotalol is preferred because of their effectiveness and low risk for toxicity. Among class III drugs, dofetilide and sotalol are associated with QT prolongation and torsades de pointes and should be avoided in the presence of marked left ventricular hypertrophy. In patients who have congestive heart failure, only amiodarone and dofetilide are safe for use.

OUTPATIENT VERSUS INPATIENT INITIATION OF THERAPY

For paroxysmal AF, inpatient versus outpatient initiation of antiarrhythmic drug therapy is an important consideration. For symptomatic

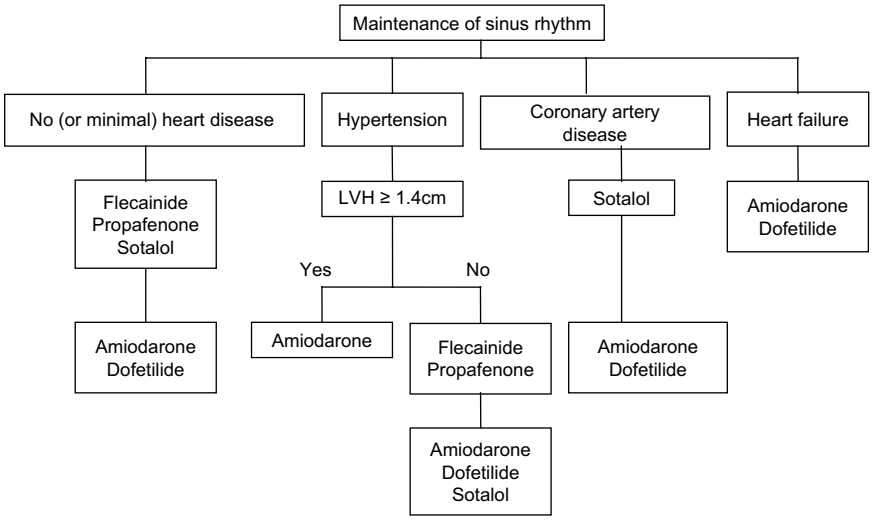

Fig. 1. Algorithm for antiarrhythmic drug selection for maintenance of sinus rhythm.

patients, the ''pill-in-the-pocket'' approach uses self-administration of a single dose of a drug shortly after the start of palpitations. The goal of this method is to terminate an episode and prevent recurrence while decreasing the need for emergency room visits, hospitalizations, and direct current cardioversions. This approach has been studied in patients who do not have structural heart disease, primarily with flecainide and propafenone.[21] After oral administration, an effect usually is seen in 3 to 4 hours.[22]

Certain class III agents may be started as outpatient treatment in certain patient populations under careful observation. Sotalol may be initiated as outpatient treatment in patients who have little or no heart disease, if the baseline QT interval is less than 450 milliseconds, the electrolytes are normal, and there are no predisposing factors to development of torsades de pointes.[6] Amiodarone has low proarrhythmic potential and may be prescribed without an inpatient evaluation in patients who do not have severe conduction disease. Dofetilide, by Food and Drug Administration mandate, requires inpatient monitoring for initiation.

Patients maintained on antiarrhythmic drugs need close follow-up.[23] Those on class III agents should have renal function, potassium, and magnesium levels checked periodically. An EKG should be performed every 6 months to measure the QT interval. Echocardiograms and stress testing should be checked at appropriate intervals for ischemic disease in patients on class IC antiarrhythmics. Amiodarone use mandates semiannual monitoring of thyroid, liver, and pulmonary function and yearly ocular examinations.

FUTURE PHARMACOLOGIC THERAPY

The marginal efficacy and safety of commercially available drugs has stimulated the development of new compounds in two major directions: modification of existing drugs and designing drugs with new targets. **Table 1** is a list of investigational compounds and their putative mechanism of action.[24,25] Although much interest has been generated by the modification of current class III agents, the discovery and characterization of novel ion channels believed to participate in onset and perpetuation of AF has provided a new way forward in drug development. Much of the research has focused on blocking potassium channels but several new ideas are being explored. The next paragraphs review the current evidence that supports the potential usefulness of these novel compounds.

AMIODARONE ANALOGUES

Dronedarone

Dronedarone is an amiodarone-like compound that lacks the iodine moiety that may be responsible for the pulmonary, thyroid, hepatic, and ocular toxicity of amiodarone. Like amiodarone, dronedarone has complex antiarrhythmic properties that span all classes of the Vaughan-Williams classification. Dronedarone inhibits potassium currents INa, IKr, and IKAch and L-type calcium current; has α- and β-adrenergic blocking properties; and prolongs the action potential duration in atria and ventricles with no significant reverse-use dependence. Dronedarone and amiodarone have similar

Table 1
Investigational antiarrhythmic drugs in development[a]

Modification of Existing Compound	Novel Mechanism of Action
Amiodarone analogues	Serotonin type 4 antagonists
Dronedarone (I_{Kr} I_{Ks} β1 I_{Ca} I_{to} I_{Na})	Piboserod
Celivarone (I_{Kr} I_{Ks} β1 I_{Ca} I_{to} I_{Na})	RS100302
ATI-2042 (I_{Kr} I_{Ks} β1 I_{Ca} I_{to} I_{Na})	SB203186
ATI-2001 (I_{Kr} I_{Ks} β1 I_{Ca} I_{to} I_{Na})	Atrial selective repolarization delaying agents
GYKI-16638 (I_{Kr} I_{KI} I_{Na})	AZD 7009 (I_{Kr} I_{Na} I_{Kur})
KB 130015 (I_{KAch} I_{Ca} I_{KATP} I_{Na})	AVE 0118 (I_{Kr} I_{to})
Conventional class III agents	AVE 1231 (I_{Kr} I_{to})
Azimilide (I_{Kr} I_{Ks})	Vernakalant (I_{Kr} I_{to} I_{Na} I_{Ach})
Tedisamil (I_{Kr} I_{to} I_{KTAP} I_{Kur} I_{Na})	Almokalant (I_{Kr} I_{to} I_{Na} I_{Ach})
Bertosamil (I_{Kr} I_{to} I_{KTAP} I_{Kur} I_{Na})	Terikalant (I_{Kr} I_{to} I_{Na} I_{Ach})
SB-237376 (I_{Kr})	Nifekalant (I_{Kr} I_{to} I_{Na} I_{Ach})
NIP-142 (I_{Kur} I_{KAch})	S-9947 (I_{Kur})
L-768673 (I_{Ks})	S-20951 (I_{Kur})
HMR-1556 (I_{Ks})	Miscellaneous compounds
HMR-1402 (I_{Ks} I_{ATP})	ZP-123 (GAP 486)
Miscellaneous compounds	AAP 10 (connexin modulator)
Ersentilide (I_{Kr} β)	GsMtx (stretch receptor)
Trecetilide (I_{Kr} β)	
CP060S (I_{Na} I_{Ca})	
KB-R7943 (I_{Na} I_{Ca})	
Cariporide (I_{Na} I_{H})	
JTV-519 (I_{Na} I_{Kr} I_{CA})	

Abbreviations: β, β-adrenergic antagonist; ICa, inward calcium current; IKach, Ach-sensitive inward potassium current; IKATP, ATP-sensitive inward potassium current; IKI, inward potassium rectifier; IKr, rapid component of the delayed rectifier potassium inward current; IKs, slow component of the delayed rectifier potassium inward current; IKur, ultra rapid component of the delayed rectifier potassium inward current; INa, inward sodium current; Ito, transient outward potassium current.

[a] The drugs are classified by mechanism of action.

Data from Goldstein RN, Stambler BS. New antiarrhythmic drugs for prevention of atrial fibrillation. Prog Cardiovasc Dis 2005;48:193–208; and Pecini R, Elming H, Pedersen OD, et al. New antiarrhythmic agents for atrial fibrillation and atrial flutter. Expert Opin Emerg Drugs 2005;10:311–22.

electrophysiologic properties in animal models, but their pharmacokinetic profiles differ significantly. Dronedarone has a 24-hour half-life and far less tissue accumulation.[26,27]

The Dronedarone Atrial Fibrillation Study After Electrical Cardioversion trial was designed to determine the most appropriate dose of dronedarone for prevention of AF after cardioversion. After 6-months' follow-up, 800 mg daily was deemed the optimal dose.[28] Thyroid, pulmonary, ocular, hepatic toxicity, or proarrhythmic effects were not seen at any of the study doses.

In the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm and its sister trial, the American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm, dronedarone administered at a dose of 400 mg twice daily was effective in preventing symptomatic and asymptomatic recurrences of AF or atrial flutter, the primary end point of the trials. A secondary end point of both trials, mean ventricular rate during AF atrial flutter at first recorded recurrence, also was reduced significantly. The incidence of adverse events in both trials was similar in the dronedarone and placebo groups.[29]

In the phase III study, Efficacy and Safety of Dronedarone for the Control of Ventricular Rate, dronedarone was tested in patients who had symptomatic permanent AF for its effect on heart rate. Dronedarone significantly reduced average

resting and maximal exercise heart rates compared with placebo.[30]

The Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) was a double-blind, placebo-controlled study evaluating the tolerability of dronedarone in high-risk patients who had congestive heart failure and ventricular dysfunction. The primary end point of the trial was death or hospitalization for heart failure. The study was ended prematurely after an interim safety analysis showed an excess risk for death in patients on active treatment.[31]

Because ANDROMEDA raised concerns over the safety of dronedarone in the heart failure population, further studies are needed. The ongoing trial, A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation, was designed to examine further the safety and efficacy of dronedarone compared with placebo in a larger study group of 4628 patients.[32] Twenty-nine percent of the study population had a history of heart failure, although only 12% had evidence of systolic dysfunction. Preliminary results after 21 months of follow-up demonstrated a significant decrease in the combined end point of cardiovascular hospitalization or death in the dronedarone arm. This difference was mainly caused by a decrease in cardiovascular hospitalization and deaths from arrhythmia.[33]

Celivarone

Celivarone (SSR149744C) is a new noniodinated benzofuran derivative structurally related to amiodarone and dronedarone. Like its parent compounds, celivarone inhibits several potassium currents: IKr, IKs, IKAch, IKv1.5, and the L-type calcium current. Studies in canine models show relative atrial selectivity.[34] Two clinical trials currently are evaluating the role of celivarone in conversion and maintenance of AF.

The Maintenance of Sinus Rhythm in Patients with Recent Atrial Fibrillation/Flutter trial, a placebo-controlled, double-blind study of 673 patients, compared celivarone in a range of dosages (50, 100, 200, or 300 mg daily) with placebo for maintenance of sinus rhythm after electrical, pharmacologic, or spontaneous conversion of AF or atrial flutter.[35] The primary end point was recurrence of arrhythmia by ECG or transtelephonic ECG monitoring. Incidence of recurrence at 90 days was 52% in the celivarone, 50-mg arm, compared with 67% in the placebo arm. No thyroid dysfunction or proarrhythmia was seen.

The Double Blind Placebo Controlled Dose Ranging Study of the Efficacy and Safety of ssr149744c 300 or 600 mg for the Conversion of Atrial Fibrillation/Flutter trial has recently been completed and assesses the efficacy of celivarone in converting AF or flutter to sinus rhythm at the time of planned electrical cardioversion.[36]

ATI-2001 and Related Compounds

ATI-2001 is a synthetic amiodarone analogue shown to retain the electrophysiologic properties of amiodarone in regards to ventricular tachyarrhythmia initiation, perpetuation, and termination in guinea pigs isolated hearts.[37] In the same animal model, ATI-2001 was significantly more potent than amiodarone in its atrial and AV nodal electrophysiologic properties.[38] A recent study, however, showed that the half-life of ATI-2001 in human plasma is only 12 minutes, making the drug more suitable for acute termination of arrhythmias than for long-term management.[39] Of the ATI-2001 congeners, ATI-2042 may have more favorable pharmacokinetic properties and currently is in phase 2 development.[40]

TRADITIONAL CLASS III AGENTS

Azimilide

Azimilide is a selective once-daily class III antiarrhythmic agent that prolongs action, potential duration, and refractory periods in both atria and lacks reverse-use dependence.[41] The optimal dose, as determined in the Azimilide Supraventricular Arrhythmia Program, was 125 mg daily.[42] Unfortunately, after 180 days' follow-up, only 50% of patients enrolled maintained sinus rhythm.

The Azimilide Postinfarct Survival Evaluation, a large randomized trial of high-risk patients, as defined by low ejection fraction and recent myocardial infarction, showed no difference in all-cause mortality. The azimilide group, however, had fewer occurrences of AF and higher maintenance of sinus rhythm at 1 year.[43]

Three other studies have evaluated the role of azimilide in the treatment of symptomatic supraventricular arrhythmias.[44] The North American Azimilide Cardioversion Maintenance Trial-I investigated the role of azimilide compared with placebo for maintenance of sinus rhythm after electrical cardioversion of patients who had symptomatic AF. There was no significant difference between placebo and azimilide.[45]

The North American Azimilide Cardioversion Maintenance Trial-II, conducted in Europe, compared azimilide (125 mg daily) with sotalol (160 mg twice daily) or placebo in patients undergoing electrical cardioversion. Although azimilide was superior to placebo, it was inferior to sotalol with regard to efficacy and safety.[46] The Azimilide

Supraventricular Tachyarrhythmia Reduction trial also tested 125 mg of azimilide daily compared with placebo in patients who had symptomatic paroxysmal AF and structural heart disease. The primary end point was the time to the first symptomatic recurrence. No statistically significant difference was seen in the study groups.[47]

Although in these trials azimilide generally was well tolerated, early onset, reversible neutropenia has been reported in 0.2% and torsades de pointes in 0.9% of patients.[48] Based on its modest efficacy and these safety issues, it is unlikely that azimilide will be available for the treatment of AF.

Tedisamil

Tedisamil is a class III antiarrhythmic agent that blocks multiple potassium channels and slows sinus rate. Tedisamil prolongs action potential duration more strongly in the atria than in the ventricles.[49] Tedisamil also possesses significant antianginal and anti-ischemic properties.

In a study of 175 patients, tedisamil was shown to be superior to placebo in acutely terminating AF or atrial flutter.[50] The study, however, showed significant lengthening of the QTc. Two of the patients receiving the higher dose of the drug developed ventricular tachycardia during administration. Larger-scale studies are in progress to assess the safety and efficacy of tedisamil, although the initial report of torsades de pointes may make it a less desirable compound for widespread clinical use. Bertosamil, a structural analog of tedisamil, has similar pharmacologic properties. It has been studied in vitro but no clinical trials to date have been performed to validate its safety and efficacy.

ATRIAL REPOLARIZATION DELAYING AGENTS

Vernakalant

Vernakalant (RSD1235) is a sodium and potassium channel blocker with atrial selectivity and a short half-life (2–3 hours).[51,52] These attributes suggest vernakalant may be an appealing agent for pharmacologic cardioversion. Vernakalant has been demonstrated to be safe in a variety of doses in healthy volunteers.[53] Initial studies showed vernakalant superior to placebo in the acute termination of recent-onset AF, with a 61% conversion rate.[54]

Intravenous vernakalant has been studied in four trials for pharmacologic cardioversion. Atrial Arrhythmia Conversion Trial I and III (ACT I, N = 396; ACT III, N = 285) were phase 3, randomized, placebo-controlled trials of patients with AF or flutter of either short duration (3 hours–7 days) or long duration (8–45 days).[55,56] Vernakalant, 3 mg/kg, or placebo was administered over 10 minutes. If the patient failed to convert to sinus rhythm after 15 minutes, a second infusion of vernakalant, 2 mg/kg, was given. The primary end point was conversion to sinus rhythm within 90 minutes of drug dosage. In both trials, 51% of patients who received vernakalant converted to sinus rhythm, compared with 4% in the placebo group. Median time to conversion was 11 minutes in ACT I and 8 minutes in ACT III. Patients with short duration AF had the highest success rates, with 78% and 71%, respectively. Conversion rates fell to 8% to 9% in the long-duration AF group. The results of ACT IV, an open-label study of 167 patients, were presented at the Boston Atrial Fibrillation Symposium in January 2008, and also demonstrated a 51% conversion rate, with a median time to conversion of 14 minutes.

ACT II assessed the efficacy of intravenous vernakalant for cardioversion in 150 patients who developed AF within 7 days after coronary artery bypass grafting or valve replacement surgery.[57] All patients had AF of short duration (3–72 hours). Forty-seven percent of the vernakalant group converted to sinus rhythm, compared with 14% in the placebo group. Median time to conversion was 12 minutes.

The most commonly reported side effects of verkalant were dysguesia, sneezing, and nausea, occurring in 5% of patients. In ACT I, the QTc was greater than 500 milliseconds in 24% of the vernakalant group compared with 15% in the placebo group. No episodes of torsades de pointes were seen up to 24 hours postinfusion. Analysis of data from two phase II trials showed 5% of patients who received vernakalant developed ventricular arrhythmias in the first 2 hours, and 9% in the 2 to 24 hours after dosing.[58]

A phase 3 superiority study comparing intravenous vernakalant with intravenous amiodarone for pharmacologic cardioversion of recent-onset AF is currently underway.[59]

AVE0118

AVE0118 selectively blocks IKur, Ito, and IKACh in atrial tissue in several preclinical models.[60,61] In animal models, AVE0118 successfully converted 63% of persistent AF and increased the fibrillation wavelength significantly. Unlike dofetilide and ibutilide, AVE0118 did not have any appreciable effect on QT duration. Although preliminary studies of AVE0118 in animal models show promise, safety and efficacy in humans are not yet established.

AZD7009

AZD7009 is a mixed ion channel blocker (IKr, INa, and IKur) that prolongs atrial repolarization.[62] Animal models showed that AZD7009 effectively

terminated all sustained episodes of induced AF and atrial flutter and prevented 95% of recurrences. Although QTc interval prolongation was noted, torsades de pointes were not induced.[63] A phase II clinical trial designed to assess the efficacy and safety of intravenous AZD7009 in conversion of AF currently is in progress.[64]

SEROTONIN ANTAGONISTS

The serotonin type 4 receptors are found in the atria but not in the ventricles. Stimulation of serotonin type 4 receptors of atrial human cells in vitro produces positive chronotropic effects and induces arrhythmias.[65,66] Efficacy of RS-100302, a selective serotonin type 4 antagonist, was tested in a pig model of AF and atrial flutter.[67] In experimental conditions, the agent terminated atrial flutter in 75% of the animals and AF in 88% of the animals and prevented reinduction of sustained tachycardia in all animals. At this time, there are not any positive clinical trial data with serotonin type 4 antagonists.

ADJUVANT THERAPY FOR PREVENTION OF ATRIAL FIBRILLATION

Angiotensin-Converting Enzyme Inhibitors

Remodeling of atrial tissue may contribute to the initiation and perpetuation of AF, especially in the heart failure population (**Table 2**). Recent studies show that blockade of the renin-angiotensin-aldosterone system prevents left atrial dilatation and atrial fibrosis, slows atrial conduction velocity, and reduces inflammation.[68,69] Several human and animal models show that the inhibition of the renin-angiotensin-aldosterone system may help prevent AF.[70] A substudy of the Trandolapril Cardiac Evaluation trial analyzed patients who had sinus rhythm at the time of randomization. After 2 to 4 years of follow-up, significantly more patients in the placebo group developed AF compared with the trandolapril group.[71] Similarly, a retrospective analysis conducted by a single center participating in the Studies of Left Ventricular Dysfunction revealed that treatment with enalapril markedly reduced the risk for developing AF in patients who had heart failure.[72] In a longitudinal cohort study that included hypertensive patients treated with angiotensin-converting enzyme inhibitors or calcium channel blockers, angiotensin-converting enzyme inhibitors were associated with a lower incidence of developing AF.[73] This favorable effect of angiotensin-converting enzyme inhibitors is supported further by meta-analyses of published data.[74,75]

In the Heart Outcomes Prevention Evaluation Study, however, which randomized 8335 patients without heart failure or left ventricular dysfunction to receive either ramipril or placebo, there was no difference in the incidence of new AF after median follow-up of 4.5 years. The overall incidence of new AF in the study was low (2.1%).[76]

The addition of enalapril to amiodarone increases the chances of maintaining sinus rhythm after cardioversion compared with amiodarone alone.[77] A study currently in progress is testing the hypothesis that angiotensin-converting enzyme inhibition with ramipril or aldosterone receptor antagonism with spironolactone decreases the incidence of AF in patients undergoing cardiothoracic surgery.[78]

Angiotensin Receptor Blockers

Clinical and experimental data support the notion that angiotensin-receptor blockers have similar effects as angiotensin-converting enzyme

Table 2
Drugs used as adjuvant therapy of atrial fibrillation and their proposed mechanism of action

Drugs	Proposed Mechanism of Action
ACE-I	Blockade of the RAAS
ARB	Inhibition of atrial remodeling Anti-inflammatory effect
Aldosterone	Inhibition of atrial fibrosis Anti-inflammatory effect
Omega-3 fatty acids	Unclear, may be direct antiarrhythmic effect
Steroids	Anti-inflammatory effect
Statins	Anti-inflammatory effect

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; RAAS, renin-angiotensin-aldosterone system.

inhibitors in affecting atrial structural remodeling and reducing atrial arrhythmias.[79,80] A retrospective analysis of two large randomized clinical trials, Valsartan Heart Failure Trial and Losartan Intervention for Endpoint Reduction in Hypertension, demonstrates that valsartan and losartan significantly reduced new-onset AF compared with the control groups, respectively, placebo and atenolol.[81,82] These findings were confirmed further in a prospective trial of hypertensive patients who had paroxysmal AF randomized to losartan or amlodipine, both in combination with amiodarone.[83] Also, treatment with irbesartan and amiodarone was found more effective than amiodarone alone in preventing recurrence of AF after electrical cardioversion.[84]

Conversely, the Candesartan in the Prevention of Relapsing Atrial Fibrillation trial did not show significant difference in maintenance of sinus rhythm after electrical cardioversion in patients treated with candesartan or placebo.[85]

Larger prospective trials are needed to test the efficacy of angiotensin-receptor blockers in adjunctive treatment of AF. The results of ongoing prospective trials, such as Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation trial using omesartan[86] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation Trial using valsartan,[87] are eagerly awaited.

Further research is also investigating the role of angiotension II in contributing to a prothombotic state in atrial tissue. Increased atrial levels of angiotensin II have been shown to increase expression of vascular cell adhesion molecules, causing increased adhesion of inflammatory cells. This proinflammatory state has been hypothesized to contribute to atrial thrombus formation. The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events is assessing whether angiotension II receptor antagonists may reduce the incidence of stroke in patients with AF.[88]

Aldosterone Antagonists

Although to date no clinical trial has evaluated the effect of aldosterone blockade in AF, in vitro experimental data suggest a beneficial effect. Spironolactone and its major metabolite, canrenoic acid, successfully inactivated the potassium channels HERG, hKv1.5, Kv4.3, and Kv7.1+mink, which generate the human IKur, Ito, and IKs currents when transfected in murine cell lines.[89] Prospective clinical trials testing the efficacy of aldosterone antagonists in AF are currently enrolling patients.[90]

MISCELLANEOUS AGENTS

Anti-Inflammatory Agents: Steroids and Statins

A largely unexplored field is the relationship between inflammation and AF. This seems of particular importance in postoperative states and in cases of myopericarditis. Some experimental models point to a role for steroids as anti-inflammatory agents. The use of prednisone at high doses in a canine model suppresses the expression of markers of inflammation and the onset and perpetuation of atrial flutter and AF.[91]

A recently published trial of patients undergoing coronary bypass graft surgery with or without aortic valve replacement found that perioperative use of corticosteroids decreased the incidence of postoperative AF.[92] The trial corroborated earlier findings from smaller studies,[93,94] but because of their adverse effects, more evidence is needed before the routine use of corticosteroids can be recommended.

Statins exhibit anti-inflammatory properties. Given the theory that AF is linked to inflammation, studies have begun to examine whether or not statins decrease the occurrence of AF.[95,96] In a small study of persistent AF, the use of statins was associated with a significant decrease in the risk for arrhythmia recurrence after successful cardioversion.[97] In an observational study in a large outpatient cardiology practice, statin therapy seemed protective against the development of AF.[98] Statin use has been associated with less AF after lung, esophageal, and coronary bypass surgery.[99,100]

To test whether pretreatment with statins may reduce postoperative AF, the Atorvastatin for Reduction of Myocardial Dysrhythmia After Cardiac Surgery study randomized 200 patients undergoing elective cardiac surgery with cardiopulmonary bypass to pretreatment with atorvastatin, 40 mg, or placebo daily, starting 7 days before surgery. Postoperative AF occurred in 35% of patients receiving atorvastatin compared with 57% in the placebo group.[101] A recent study of 124 patients undergoing elective off-pump coronary bypass surgery showed similar results with patients given atorvastatin, 20 mg daily, starting 3 days before surgery. The incidence of AF was 13% in the atorvastatin group versus 27% in the placebo group.[102] Larger-scale trials are needed to confirm these findings.

The Atorvastatin Therapy for the Prevention of Atrial Fibrillation trial is a prospective randomized, placebo-controlled study that is testing whether or not atorvastatin (80 mg daily) can reduce the recurrence rate of AF after elective electrical cardioversion compared with standard therapy.[103]

Table 3
Currently available drugs for treatment of atrial fibrillation according to the Vaughan-Williams classification, their mechanism of action, and their main adverse effects

Drug	Mechanism of Action	Main Adverse Effect
Class I		
Ia – Quinidine	Sodium channel blockade, delays phase 0 of action potential	Torsades de pointes, diarrhea, dyspepsia, hypotension
Ic – Flecanide	Sodium channel blockade, strongly delays phase 0 of action potential	Ventricular tachycardia, congestive heart failure, increased atrioventricular conduction
Ic – Propafenone	Sodium channel blockage, strongly delays phase 0 of action potential	Ventricular tachycardia, congestive heart failure, increased atrioventricular conduction
Class III		
Amiodarone	Multichannel blockade	Thyroid toxicity, pulmonary toxicity, hepatic toxicity, dyspepsia, QT prolongation, torsades de pointes (rare), hypotension, bradycardia
Sotalol	Potassium channel blockade (mainly I_{Kr}), β-receptor blockage	Torsades de pointes, congestive heart failure, bronchospasm
Dofetilide	Potassium channel blockade (mainly I_{Kr})	QT prolongation, torsades de pointes
Ibutilide	Potassium channel blockade (mainly I_{Kr}), activation of a slow, delayed I_{Na} current that occurs early during repolarization	QT prolongation, torsades de pointes

Omega-3 Fatty Acids

Incorporation of dietary omega-3 fatty acids into rabbit atrial tissue reduces stretch-induced susceptibility to AF.[104] In a study of patients who had paroxysmal atrial tachycardia and an implanted permanent pacemaker, daily intake of omega-3 fatty acids (1 g) reduced the number of episodes and total burden of atrial arrhythmia significantly.[105] Additionally, a recent trial randomized patients undergoing elective coronary bypass surgery to omega-3 fatty acids (2 g daily) or placebo.[106] Patients receiving omega-3 fatty acid had a significantly lower incidence of postoperative AF and a shorter hospital stay than those receiving placebo.

The Rotterdam study prospectively examined the relationship between dietary fish intake, long-chain omega-3 fatty acid supplementation, and the incidence of AF. After a mean follow-up of 6.4 years, neither omega-3 fatty acid nor dietary fish intake was linked to a lower incidence of AF.[107]

Given conflicting results in the current literature, large randomized control trials are needed to delineate better what effect, if any, omega-3 fatty acids have on AF. These trials are in progress.

SUMMARY

Many pharmacologic options are available for the treatment of AF. The results of large clinical trials, such as AFFIRM and RACE, suggest that controlling ventricular rates during AF is a valid approach. For symptomatic patients, sinus rhythm can be restored and maintained using pharmacologic or ablative therapy. The role of antiarrhythmic therapy after AF ablation remains unclear, because further research is needed in this area. **Table 3** lists the antiarrhythmic drugs currently available for use in patients who have AF. In addition to these drugs, several agents that target remodeling and inflammation can be used for prevention of AF or as adjunctive therapy. New and promising pharmacologic agents are under investigation. All of these approaches will increase the ability to control the increasing prevalence of AF, especially in the growing aging population.

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