

Pharmacologic Management of Atrial Fibrillation: Established and Emerging Options

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ABSTRACT

BACKGROUND: In patients with atrial fibrillation (AF), antiarrhythmic drug therapy currently plays a greater role in maintaining sinus rhythm after cardioversion than it does in converting AF to sinus rhythm. Amiodarone is the most effective antiarrhythmic agent for maintaining sinus rhythm after cardioversion in patients with AF. However, its pharmacokinetics is complex; the drug interacts with many commonly used medications; and long-term use can cause thyroid dysfunction, hepatotoxicity, and other severe extracardiac adverse effects. The use of antiarrhythmic strategies in patients with AF has decreased because of evidence of greater safety and lower costs for hospitalization obtained from the use of rate-control strategies instead. Nevertheless, some patients require a rhythm-control strategy. Warfarin is used to prevent embolic stroke in many patients with AF, but its use is also complex and requires monitoring. Therefore, efforts have been made to develop antiarrhythmic agents with improved tolerability and anticoagulants that are easy to use.

OBJECTIVES: To describe the 3 primary goals of pharmacotherapy in patients with AF, compare and contrast the efficacy and safety of established and investigational pharmacotherapies for AF, and recommend a drug regimen for an individual with AF based on patient-specific factors.

SUMMARY: Currently available antiarrhythmic agents differ in their efficacy for maintaining sinus rhythm after cardioversion in AF patients with tolerability problems, comorbidities (particularly heart failure and renal impairment), and potential drug interactions. Hence, when selecting drug therapy to maintain sinus rhythm after cardioversion, it is important to take into consideration patient characteristics, including age, disease states, renal function, and concurrent drug therapies. Outpatient self-administration of single loading doses of flecainide or propafenone with what is referred to as the pill-in-the-pocket approach may be considered for carefully selected patients with recurrent episodes of symptomatic AF. The recently approved antiarrhythmic agent dronedarone has electrophysiologic properties similar to those of amiodarone, but its lack of iodine may improve upon the pharmacokinetic and tolerability issues associated with amiodarone. Vernakalant is another investigational antiarrhythmic agent that may prove useful for cardioversion and maintenance of sinus rhythm after cardioversion in patients with AF. New oral anticoagulants that do not require close laboratory monitoring and are simpler to use than warfarin have been used investigationally for prevention of venous thromboembolism and are in clinical trials for prevention of embolic stroke in patients with AF.

CONCLUSIONS: Pharmacotherapy for patients with AF should be individualized based on patient-specific factors. New therapeutic options may become available to facilitate treatment of these patients.

J Manag Care Pharm. 2009;15(6-b)(Suppl):S10-S18

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DISCLOSURES

This learning activity was sponsored by an educational grant from sanofi-aventis U.S. Kalus reports no conflicts of interest related to the subject of this article. He received an honorarium for his participation in the online symposium and for the preparation of this article.

Susan R. Dombrowski, MS, RPh, provided assistance with the medical writing, and Catherine N. Klein, RPh, and Carla J. Brink, MS, RPh, provided editorial assistance.

Off-Label Disclosure Statement

In this article, the following off-label use of antiarrhythmic agents is discussed: disopyramide and amiodarone for the treatment of atrial fibrillation. Dronedarone was recently approved by the FDA for use in patients with atrial fibrillation who do not have severe heart failure.

Atrial fibrillation (AF) is associated with substantial morbidity and mortality and negatively impacts quality of life. Pharmacologic agents are used in the management of atrial fibrillation for prevention of embolic stroke, control of ventricular rate, and restoration and maintenance of normal sinus rhythm.¹ Optimization of therapy for the patient with AF requires the pharmacist to consider patient comorbidities, medication efficacy, and medication toxicities when designing a treatment regimen and monitoring plan. While currently available agents used in the management of AF have substantial limitations in terms of both safety and efficacy, new therapeutic options may soon become available.

Antithrombotic Therapy

The decision to use antithrombotic therapy and the type of antithrombotic therapy selected to prevent thromboembolic events in patients with AF are based on the risks and benefits of such therapy and the risk of stroke. The CHADS₂ risk scoring system is used to determine the risk for stroke in patients with AF.² Warfarin is used in patients at high or intermediate risk for stroke, but its use is complicated by a narrow therapeutic index, risk for bleeding, and the continuous need for laboratory monitoring.³ Aspirin is recommended for patients at low or intermediate risk for stroke. Overall, aspirin is less effective than warfarin for the prevention of stroke in patients with AF.³

Rate Versus Rhythm Control

There are 2 phases to ventricular rate control in patients with AF. Acute ventricular rate control is provided to reduce heart rate and control symptoms at the time of initial patient presentation. Chronic ventricular rate control is provided as a long-term maintenance strategy. Acute ventricular rate control usually involves the intravenous use of a nondihydropyridine calcium channel blocker (e.g., diltiazem or verapamil), β -blocker, or digoxin. When a long-term rate control strategy will be used to manage

a patient with AF, the patient is allowed to remain in AF, and the heart rate is maintained at a target of less than 80 beats per minute (at rest) or 100 beats per minute (with exercise) using an oral nondihydropyridine calcium channel blocker, β -blocker, or digoxin.¹ Underlying disease states and blood pressure should be considered when selecting drug therapy for acute and chronic rate control. For example, digoxin could be used as a rate-controlling agent in patients with underlying systolic heart failure. Digoxin could also be a useful option when blood pressure is low.¹

Rhythm control involves restoring and maintaining sinus rhythm through the use of antiarrhythmic drugs, electrical cardioversion, or both. There has been considerable debate about the comparative efficacy and cost of rate-control and rhythm-control strategies. Study results suggest that mortality, quality of life, and health care costs are similar regardless of which strategy is used.^{1,4-6} In 1 of the largest randomized studies that enrolled 4,060 patients with AF and at least 1 risk factor for stroke (Atrial Fibrillation Follow-Up Investigation of Rhythm Management [AFFIRM] trial), there was no significant difference in mortality between the rate-control (25.9%) and rhythm-control (26.7%) groups ($P=0.08$).⁴ The incidence of ischemic stroke, a secondary endpoint, also was similar in the 2 groups (5.5% with rate control vs. 7.1% with rhythm control, $P=0.79$). The incidence of torsades de pointes, which is a ventricular tachyarrhythmia with QT interval prolongation, was significantly lower with rate control (0.2%) than with rhythm control (0.8%, $P=0.007$). Pulmonary and gastrointestinal events, bradycardia, and prolongation of the QT interval on the electrocardiogram (ECG) also were significantly less common in the rate-control group than in the rhythm-control group ($P<0.001$). The incidence of hospitalization during follow-up was significantly lower with rate control compared with rhythm control (73.0% and 80.1%, respectively, $P<0.001$).

Findings of the AFFIRM study and other rate versus rhythm studies suggesting greater safety and lower costs for hospitalization from the use of rate-control strategies compared with rhythm-control strategies has led to a reduction in the use of rhythm-control strategies in patients with AF.^{7,8} However, studies comparing rate- and rhythm-control strategies might be limited by the fact that these studies enrolled a mostly elderly and sedentary patient population. Also, an initial criticism of AFFIRM was that the study included few patients with heart failure, a group commonly afflicted with AF. However, the Atrial Fibrillation and Congestive Heart Failure study also demonstrated similar outcomes between a rate- and rhythm-control strategy, echoing the results of AFFIRM.⁹

Patients presenting with hemodynamic instability require rhythm control and should immediately undergo electrical cardioversion.¹ If a patient is hemodynamically stable, the clinician can take some time deciding on a therapeutic strategy (i.e., rate control vs. rhythm control, and pharmacotherapy vs. electrical cardioversion to achieve rhythm control if that strategy is selected).¹

The use of rhythm-control strategies is limited by the toxicity of many antiarrhythmic drugs and higher rate of hospitalization.^{1,4} Nevertheless, rhythm-control interventions may be required for patients whose heart rate remains elevated (>80 beats per minute) despite the use of rate-control strategies; patients who remain symptomatic despite effective ventricular rate control (<80 beats per minute); and patients who are physically active and have poor exercise tolerance with the use of rate-control strategies.¹

Drug therapy plays a minimal role in acute conversion of AF to sinus rhythm because electrical cardioversion is more effective than pharmacologic cardioversion with success rates of 90% and approximately 40%, respectively.¹⁰ Nevertheless, drug therapy may play a role before and after electrical cardioversion to improve the likelihood of successful conversion to and maintenance of sinus rhythm.¹ The rate of recurrence of AF (i.e., relapse) after conversion to sinus rhythm is high, with only about 15% of patients remaining in sinus rhythm 1 year after electrical cardioversion.^{1,11-13}

Class I and class III antiarrhythmic agents are the primary pharmacologic agents used for achieving rhythm control in patients with AF. Patterns of use of these agents have changed in recent years. The use of class Ia agents, particularly quinidine, decreased between 1991 and 2000.¹³ The oral formulation of the class Ia antiarrhythmic agent procainamide was recently withdrawn from the market because of lack of use. There has also been a small decline in the use of class Ic antiarrhythmic agents (e.g., flecainide and propafenone). By contrast, in the 1990s there was a considerable increase in the use of the class III agents amiodarone and sotalol, which are the most commonly used antiarrhythmic drugs for AF.¹³ Changes in use patterns for the various antiarrhythmic drugs have likely resulted from concerns about drug toxicities and efficacy considerations that will be discussed below.

■ Class Ia and Ic Agents

The class Ia antiarrhythmic agents disopyramide and quinidine and class Ic antiarrhythmic agents flecainide and propafenone are used less often than class III drugs in patients with AF primarily because of their potential adverse effects. Disopyramide is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of AF (quinidine, flecainide, and propafenone are FDA-approved for AF).¹⁴ All of these agents are associated with a risk of proarrhythmia. The tolerability of disopyramide and quinidine is particularly poor. Anticholinergic adverse effects (e.g., urinary retention, dry mouth) are associated with disopyramide, and rash, photosensitivity, and gastrointestinal adverse effects (e.g., diarrhea, abdominal pain, and cramps) can occur with quinidine.^{1,15} Flecainide and propafenone are better tolerated than disopyramide and quinidine, but these class Ic antiarrhythmic agents are not safe to use in patients with structural heart disease (e.g., coronary heart disease, left ventricular hypertrophy, heart failure, valvular dysfunction) because they can increase mortality.¹⁶⁻¹⁸

TABLE 1 Advantages and Disadvantages of Currently Available Antiarrhythmic Agents for Maintaining Sinus Rhythm in Patients With Atrial Fibrillation

Antiarrhythmic Drug Class or Agent	Efficacy Assessment and Advantages	Disadvantages
Class Ia		
Disopyramide ^a	Low efficacy	Proarrhythmia (torsades de pointes) Anticholinergic adverse effects
Quinidine	Low efficacy	Proarrhythmia (torsades de pointes) Gastrointestinal adverse effects
Class Ic		
Flecainide	Modest efficacy	Proarrhythmias Not safe in structural heart disease Drug interactions
Propafenone	Modest efficacy	Proarrhythmia Nonselective β blockade (bradycardia, exacerbation of chronic obstructive pulmonary disease) Not safe in structural heart disease Drug interactions
Class III		
Amiodarone	High efficacy Low risk of proarrhythmia Safe in heart failure	Extracardiac effects Drug interactions
Sotalol	Modest efficacy Not expected to interact with drugs metabolized by CYP enzymes	Nonselective β blockade (bradycardia, exacerbation of chronic obstructive pulmonary disease) Proarrhythmia (torsades de pointes) Eliminated renally Inpatient initiation
Dofetilide	Modest efficacy Safe in heart failure Generally well tolerated (except for torsades de pointes)	Proarrhythmia (torsades de pointes) Eliminated renally Drug interactions Inpatient initiation

^aNot approved by the U.S. Food and Drug Administration for atrial fibrillation. Sources = references.^{1,13&15-32}

Class III Agents

Amiodarone

Amiodarone is the most commonly used antiarrhythmic drug in patients with AF, largely because it is the most effective agent for maintaining sinus rhythm (an indication not approved by the FDA) and has a low risk of proarrhythmic effects (Table 1).^{1,19,20} Amiodarone does not increase mortality in patients with heart failure; therefore, it is safe to use in this patient population.²¹⁻²⁴

Nevertheless, amiodarone is among the most toxic antiarrhythmic agents; it is associated with a high incidence of potentially severe extracardiac effects.¹ These effects include neuropathy, thyroid dysfunction (a common effect manifesting as either hypothyroidism or hyperthyroidism), pulmonary fibrosis (a rare but potentially serious complication), hepatotoxicity, rash or photosensitivity, blue-grey skin discoloration, and ophthalmic effects (corneal deposits and optic neuritis).¹ These extracardiac effects may not be observed during initial therapy; however, the risk increases after more than 6 months of treatment.¹

The pharmacokinetics of amiodarone are complex. The drug has a long half-life, which complicates loading dosing, adverse effect management, and transition from amiodarone to another antiarrhythmic drug.²⁵ Amiodarone also has a large volume of distribution into a wide variety of tissues, including extracardiac tissues, which accounts for the relatively high incidence of extracardiac adverse effects associated with this drug.

The potential for drug interactions is an important consideration in the use of amiodarone. Many of these interactions are mediated by cytochrome P-450 (CYP) drug-metabolizing enzymes, specifically potent inhibition of the CYP1A2, 2C9, 2D6, and 3A4 enzymes, which are responsible for significant clinical interaction with drugs such as simvastatin and warfarin.²⁶ Another method by which amiodarone can cause interactions is via transporter-based mechanisms; for example, digoxin inhibits the P-glycoprotein membrane transporter, resulting in increased serum drug concentrations and a potential risk of increased toxicity.^{25,26}

Sotalol

Sotalol is a commonly used class III antiarrhythmic agent that is approved by the FDA for the maintenance of normal sinus rhythm in patients with symptomatic AF/atrial flutter who are currently in sinus rhythm.²⁷ Its efficacy in maintaining sinus rhythm is only modest.¹

Because sotalol is eliminated renally, dosage reduction is required for patients with renal impairment. Proarrhythmia is the major side effect from sotalol. The incidence of torsades de pointes associated with the use of sotalol in patients with AF or other supraventricular arrhythmias ranges from 0.3% to 3.2%, depending on dosage.²⁸ The likelihood of proarrhythmia also depends on patient characteristics (e.g., sex, heart failure, renal function). To minimize the risk of proarrhythmia, sotalol therapy should be initiated on an inpatient basis.¹ The adverse

effect profile of sotalol primarily reflects its β -blocking properties (e.g., asthma, bradycardia, exacerbation of chronic obstructive pulmonary disease).¹ Sotalol is neither metabolized by, nor is it an inducer or inhibitor of, the CYP enzyme system.

Dofetilide

Dofetilide, a class III antiarrhythmic agent, has been available for approximately 10 years. It is indicated for the maintenance of normal sinus rhythm in patients with AF/atrial flutter of greater than one week duration who have been converted to normal sinus rhythm. It is modestly effective for conversion and maintenance of sinus rhythm in patients with AF.^{29,30} Like amiodarone, this drug does not increase mortality and is considered safe to use in patients with heart failure.³¹

Dofetilide is generally well tolerated; however, torsades de pointes is the adverse effect of primary concern.³² The incidence of torsades de pointes in dofetilide clinical trials ranged from 0.3% to 4.7%, depending on dosage and patient characteristics (e.g., sex, renal function).¹ As with sotalol, the kidneys play an important role in elimination of dofetilide; therefore, dosage reduction is required for patients with renal impairment. Additionally, initiation of therapy should be performed on an inpatient basis to minimize the risk of proarrhythmia.³⁰

Dofetilide is associated with numerous drug interactions. Its use concomitantly with verapamil, hydrochlorothiazide, ketoconazole, cimetidine, or trimethoprim is contraindicated because of the potential for increased dofetilide plasma concentrations and increased risk of torsades de pointes.³³ The concurrent use of dofetilide and drugs that prolong the QT interval (e.g., phenothiazines) is not recommended due to the risk for additive QT prolongation.

Comparative Efficacy and Safety

In a meta-analysis, all of the class Ia, Ic, and III agents listed in Table 1 reduced the risk of recurrence of AF in patients in whom sinus rhythm had been restored.³⁴ Amiodarone was most effective, and the class Ia agents were least effective.

Many comparative studies use both efficacy for maintaining sinus rhythm and adverse effects as endpoints in patients with AF. In 1 such study of 254 patients, propafenone was more effective than sotalol with fewer adverse effects.³⁵ In another study of 665 patients, amiodarone and sotalol were similarly effective for conversion of atrial fibrillation and amiodarone was more effective than sotalol for maintaining sinus rhythm.³⁶ There was no significant difference between the 2 drugs in major adverse effects. In another study, amiodarone was more effective than propafenone in maintaining sinus rhythm after conversion in 146 patients with recurrent symptomatic AF, but propafenone caused fewer adverse effects.³⁷ The safety advantage of propafenone outweighed the greater efficacy of amiodarone. While few studies directly compare different antiarrhythmic agents, it is clear that consideration of both efficacy and safety is critical when selecting therapy.

Pill-in-the-Pocket Approach

Certain patients with recurrent episodes of symptomatic AF may be candidates for outpatient self-administration of single loading doses of flecainide or propafenone using what is referred to as the "pill-in-the-pocket" approach to terminating AF.¹ The efficacy and safety of this approach were demonstrated in 210 patients with mild or no heart disease who came to the emergency room with recent-onset AF that was hemodynamically well tolerated.³⁸ If flecainide or propafenone was successful in converting the patient from AF in the emergency room, they were eligible for inclusion in the study. Included patients were advised to take a dose of flecainide or propafenone 5 minutes after the onset of palpitations on an outpatient basis. The mean duration of follow-up was 15 months. Treatment was successful in 534 (94%) of 569 episodes. Compared with the year before study enrollment, there were significantly fewer visits to the emergency room each month (4.9 vs. 45.6, $P < 0.001$) and hospitalizations each month (1.6 vs. 15.0, $P < 0.001$) during the follow-up period. These large reductions in emergency room visits and hospitalization occurred even though there was no significant difference in the mean number of symptomatic episodes per month before and after study enrollment (59.8 and 54.5, respectively). The most recent AF treatment guidelines recommend that this pill-in-the-pocket approach be used if the patient has had a safe response to single-dose therapy as an inpatient. However, this strategy should be avoided in patients without sinus or AV node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome (a hereditary arrhythmia), or structural heart disease.¹

Inpatient Initiation

Because antiarrhythmic drugs can be proarrhythmic, 1 strategy to minimize risk with these agents is to initiate the drug in a hospital or other facility where continuous ECG monitoring, creatinine clearance (CrCl) calculation, and cardiac resuscitation are available.^{28,30} Inpatient initiation is required for both dofetilide and sotalol but is often used for other agents as well.^{27,33} For inpatient initiation, patients should be admitted for at least 3 days. Calculation of the CrCl should be performed, and dosage reductions should be made in patients with renal dysfunction. Potassium and magnesium serum concentrations should be monitored, and electrolyte replacement should be provided as needed. The corrected QT (QTc) interval should be measured at baseline to ensure that it is within normal limits (450 msec or less for sotalol and 440 msec or less for dofetilide) before initiating either of these antiarrhythmics.^{27,33} The QTc interval should be checked several hours after each dose because dosage adjustment or discontinuation of drug therapy may be required if the QTc interval is excessively prolonged. If AF persists for more than 3 days, electrical cardioversion should be attempted to restore sinus rhythm.^{27,33}

Emerging Agents

Problems with proarrhythmia, particularly torsades de pointes, and hospitalization because of AF recurrence or extracardiac toxicities have hindered the use of rhythm-control strategies in patients with AF.⁸ Efforts to develop new antiarrhythmic agents with improved safety and tolerability could cause clinicians to re-examine the debate about rate control versus rhythm control.

Dronedaron

Dronedaron is a recently FDA-approved antiarrhythmic agent with electrophysiologic effects that are similar to those of amiodaron, although dronedaron may be less likely to prolong the QT interval.^{39,40} The chemical structure of dronedaron differs from that of amiodaron in its lack of iodine, which could minimize the impact of dronedaron on thyroid function. The lack of iodine also could make dronedaron less lipophilic and limit its distribution and potential for extracardiac toxicities.⁴⁰

Dronedaron has a considerably shorter half-life than amiodaron (1-2 days vs. 30-55 days), which could make dosing more reliable and facilitate the use of loading doses.⁴⁰ Like amiodaron, dronedaron is a CYP3A4 substrate and inhibits CYP2D6; therefore, interactions with drugs metabolized by these isoenzymes could occur.^{41,42}

Dronedaron has been extensively studied in several phase III randomized, double-blind, placebo-controlled studies. All of these studies involved a dosage of 400 mg orally twice daily, but the patient inclusion and exclusion criteria varied.

The first reported clinical trial results were from 2 identical trials known as EURIDIS (EUROPEAN trial In atrial fibrillation patients receiving Dronedaron for the maintenance of Sinus rhythm) and ADONIS (American-Australian-African trial with Dronedaron In atrial fibrillation patients for the maintenance of Sinus rhythm) that involved a total of 1,237 patients with paroxysmal or persistent (i.e., lasting less than 12 months) AF or atrial flutter.⁴³ Patients with New York Heart Association (NYHA) class III or IV HF were excluded from both studies. One study (EURIDIS) was conducted in Europe, and the other study (ADONIS) was conducted in the United States and other non-European countries. Patients were randomly assigned in a 2:1 ratio to receive dronedaron 400 mg or matching placebo orally twice daily. The mean age was 63 years. Most patients (90%) had AF; 41% had structural heart disease; and NYHA class I or II HF was present in approximately 17% of patients (left ventricular ejection fraction approximately 60%). Thus, the study population was relatively young and free from heart failure, although a substantial number of patients had structural heart disease (type not specified). Patients were followed for 12 months.⁴³ The time to recurrence of AF (primary endpoint) was longer with dronedaron (116 days) than with placebo (53 days, *P* value not reported). The rate of recurrence of AF after 12 months was 64.1% with dronedaron and 75.2% with placebo (*P*<0.001). The rate of hospitalization or death also was significantly lower

in the dronedaron group (22.8%) than in the placebo group (30.9%, *P*=0.01). The only adverse event that was associated with dronedaron was elevation of serum creatinine, which occurred in 2.4% of patients treated with dronedaron and 0.2% of patients treated with placebo (*P*=0.004).

The Antiarrhythmic Trial with Dronedaron in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) study had a planned enrollment of 1,000 patients hospitalized with symptomatic heart failure, moderate or severe left ventricular systolic dysfunction (NYHA class III or IV), and a left ventricular ejection fraction of 35% or less.⁴⁴ The primary endpoint was a composite of death from any cause or hospitalization for heart failure. The study was terminated prematurely after 627 patients had enrolled (median of 2 months) because of a significantly higher rate of all-cause mortality in dronedaron-treated patients (8.1%) compared with placebo-treated patients (3.8%, *P*=0.03). Most of the deaths in the dronedaron group were cardiovascular deaths associated with worsening heart failure. There was no significant difference between dronedaron and placebo in the primary endpoint (53 events [17.1%] with dronedaron and 40 events [12.6%] with placebo, *P*=0.12).

The ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedaron 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter) study involved 4,628 patients with paroxysmal or persistent AF who were (a) aged 70 years or older with hypertension managed with at least 2 antihypertensive medications from different classes; diabetes mellitus; previous stroke, transient ischemic attack, or systemic embolism; large left atrial diameter; or left ventricular ejection fraction of 40% or less; or (b) aged 75 years or older without any of these risk factors.⁴⁵ Exclusion criteria included permanent AF, hemodynamic instability (decompensated heart failure within the previous 4 weeks), NYHA class IV heart failure (HF), bradycardia, and heart block. The mean age was 72 years. Structural heart disease was present in 60% of patients; 21% of patients had a history of heart failure (17% with NYHA class II HF and 4% with NYHA class III HF); and 12% of patients had a left ventricular ejection fraction less than 45%.⁴⁵ Thus, the patients in this study were older and more likely to have structural heart disease compared with those in the EURIDIS and ADONIS studies, although heart failure was not common or severe in these 3 studies.

In ATHENA, the primary outcome was first hospitalization for a cardiovascular event or death.⁴⁵ The mean duration of follow-up was 21 months (range 1-2.5 years). Compared with placebo, dronedaron was associated with a significantly lower incidence of the primary outcome (31.9% vs. 39.4% with placebo, *P*<0.001). Most of this difference was attributed to a significantly lower incidence of cardiovascular hospitalization in the dronedaron group compared with placebo (29.3% vs. 36.9%, respectively, *P*<0.001), and this reduced incidence was driven mainly by a reduction in

hospitalizations for AF (14.6% with dronedarone vs. 21.9% with placebo, $P < 0.001$) and for acute coronary syndrome (2.7% with dronedarone vs. 3.8% with placebo, $P = 0.03$).

Adverse events reported by significantly more dronedarone-treated patients than placebo-treated patients in the ATHENA study included gastrointestinal events (26.2% vs. 22.0%, $P < 0.001$), elevation of serum creatinine (4.7% vs. 1.3%, $P < 0.001$), bradycardia (3.5% vs. 1.2%, $P < 0.001$), rash (3.4% vs. 2.0%, $P = 0.006$), and QT-interval prolongation (1.7% vs. 0.6%, $P < 0.001$).⁴⁵ One case of torsades de pointes was reported in the dronedarone group. There was no significant difference between the dronedarone group and the placebo group in the incidence of pulmonary fibrosis, liver function test elevation, or thyroid dysfunction. Some of the patients were followed for a period as short as 1 year, and whether this duration was sufficient to detect the true incidence of the most serious adverse events might be questioned.

The efficacy for maintaining sinus rhythm and the safety of dronedarone and amiodarone were compared in the DIONYSOS (Efficacy & Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation) study, which has yet to be published.⁴⁶ Results presented in this article are only available from the manufacturer's press release. In this double-blind, parallel-group study, 504 patients with persistent AF were randomized to receive dronedarone 400mg orally twice daily or amiodarone 600mg per day orally for 28 days followed by 200mg per day orally. The primary endpoint was AF recurrence or premature study discontinuation for intolerance or lack of efficacy. After a mean follow-up of 7 months, the primary endpoint had been reached by significantly more patients in the dronedarone group (73.9%) than patients in the amiodarone group (55.3%, $P < 0.001$). The rate of recurrence of AF was 36.5% with dronedarone and 24.3% with amiodarone (P value not reported). There was no significant difference between treatment groups in the incidence of the predefined main safety endpoint, which included thyroid, hepatic, pulmonary, neurologic, skin, ocular, and gastrointestinal adverse events. Of note, neither pulmonary fibrosis nor liver toxicity was noted to occur in either group in this study, although the follow-up may not have been long enough to observe these adverse effects.⁴⁷ The protocol also called for analysis of safety data excluding the gastrointestinal adverse events (e.g., diarrhea, vomiting, nausea), and the number of non-gastrointestinal adverse events was significantly lower in dronedarone-treated patients (61) than in amiodarone-treated patients (99, $P = 0.002$).

The results of dronedarone studies conducted to date suggest that the drug should not be used in patients with moderate or severe heart failure. While the precise language for the explicit label indications for dronedarone were unclear at the time that this article was prepared, dronedarone will have a black-box warning against the use of this drug in patients with severe heart failure. Dronedarone is effective for maintaining sinus rhythm in patients with AF, albeit possibly less so than amiodarone.

However, dronedarone may have some safety advantage over amiodarone, since the occurrence of pulmonary fibrosis, liver dysfunction, and thyroid dysfunction with dronedarone has been shown to be similar to placebo.⁴³

In mid-2009, the role of dronedarone in the care of patients with AF is evolving. Publication of the results of the DIONYSOS study and future clinical trials will provide additional insight into the efficacy and safety of the drug compared with currently available antiarrhythmic agents. Studies with a longer duration than those conducted to date may be needed to provide an accurate assessment of drug tolerability. In March 2009, the FDA Cardiovascular and Renal Drugs Advisory Committee recommended approval of dronedarone in patients with persistent or paroxysmal AF who have an ejection fraction greater than 35%.^{47,48} and the FDA approved dronedarone for use in the United States on July 2, 2009. According to information released by the FDA, the specific label will indicate that dronedarone is "approved to help maintain normal heart rhythms in patients with a history of atrial fibrillation or atrial flutter (heart rhythm disorders). The drug is approved to be used in patients whose hearts have returned to normal rhythm or who will undergo drug or electric-shock treatment to restore a normal heart beat. Dronedarone may cause critical adverse reactions, including death, in patients with recent severe heart failure."⁴⁹ The drug's label will contain a boxed warning, the FDA's strongest warning, cautioning that the drug should not be used in severe heart failure patients.⁴⁹

Vernakalant

Vernakalant is a mixed sodium and potassium channel blocker currently under review by FDA for acute conversion of AF. It is available in both intravenous and oral forms. Phase III studies comparing the intravenous formulation with placebo for acute cardioversion in patients with recent-onset AF have found that the drug significantly improves the likelihood of restoring sinus rhythm (45% vs. 15%, $P < 0.001$).⁵⁰ Most patients included in these studies had AF of recent onset (< 7 days). Conversion rates in these studies ranged from 45% to 61% with the most commonly used regimen (2 mg per kg vernakalant followed by 3 mg per kg 30 minutes later if AF continues).⁴⁶ Conversion rate was greater than with placebo, yet much lower (6% to 9%) in studies that included patients with onset of AF within 8 to 45 days.^{50,51}

An oral formulation has been evaluated for the maintenance of sinus rhythm in patients with AF in phase II, placebo-controlled, dose-ranging studies, with promising results achieved with the use of 300mg or 600mg twice daily.⁵⁰ Commonly reported adverse effects during vernakalant treatment include dysgeusia, sneezing, and paresthesia. Proarrhythmia with the use of vernakalant have not been reported to date and will be important in weighing the risks versus the benefits of this agent. The FDA Cardiovascular and Renal Drugs Advisory Committee has recommended approval of intravenous vernakalant.⁵²

Future Directions in Antiarrhythmic Development

Study of both azimilide and tedisamil for treatment of AF has also been undertaken. However, it is unlikely that either of these agents will be approved in the future for use in patients with AF. While azimilide was found to be safe in patients with structural heart disease in the Azimilide Post Infarct Survival Evaluation (ALIVE),⁵³ the drug does not appear to be efficacious for maintenance of sinus rhythm in patients with either paroxysmal or persistent AF.⁵⁴⁻⁵⁶ Tedisamil was submitted to the FDA for approval as a treatment for acute pharmacologic conversion of AF. While this drug demonstrated efficacy similar to other antiarrhythmic medications for acute conversion, safety concerns led the FDA Advisory Panel to recommend against approval of tedisamil.¹³

Other medications under development for treatment of AF are mostly in the earlier stages of development. The pharmacologic targets of most experimental agents for AF are potassium channels other than the rapid delayed inward rectifying potassium channel (I_{Kr}). Most commonly, drugs targeting the ultra-rapid delayed inward rectifying potassium channel (I_{Kur}) are being developed.⁵⁷ Targeting this channel may allow for antiarrhythmic efficacy with fewer proarrhythmic side effects, since these channels are mainly found in atrial tissues.⁵⁶

Nonantiarrhythmic Agents

Activation of the renin-angiotensin-aldosterone system has been proposed as a contributing factor in AF.¹ Re-analysis of data from randomized controlled studies of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) found a significant reduction in the risk of new-onset AF from the use of these drugs compared with placebo or active control (e.g., a β -blocker).⁵⁸⁻⁶² Pooling data from other controlled studies of patients with AF revealed lower rates of AF recurrence after cardioversion associated with the use of ACE inhibitors or ARBs usually in combination with amiodarone compared with placebo or with amiodarone alone (odds ratio = 0.39, $P = 0.005$).^{58,62,63,64,66} Additional research is needed to clarify the role of ACE inhibitors and ARBs in preventing AF and maintaining sinus rhythm after cardioversion in patients with AF. Neither of these uses of ACE inhibitors or ARBs is approved by the FDA.

Oral Anticoagulants

Rivaroxaban, a factor Xa inhibitor, and dabigatran, a direct thrombin inhibitor, are investigational oral anticoagulant agents that have been used successfully to prevent venous thromboembolism (VTE) in patients undergoing orthopedic surgery.⁶⁷ Clinical trials of these agents for the prevention of embolic stroke in patients with AF are also in progress. Rivaroxaban and dabigatran offer several potential advantages over warfarin. Neither of these agents requires the close laboratory monitoring that is required during warfarin therapy. Rivaroxaban and dabigatran also have more predictable pharmacodynamics than warfarin, which should facilitate dosing. In March 2009, the

FDA Cardiovascular and Renal Drugs Advisory Committee recommended approval of rivaroxaban for the prophylaxis of VTE in patients undergoing hip- and knee-replacement surgery.⁶⁸ FDA approval of dabigatran is not anticipated before 2010. While data with these agents are not yet available, studies are ongoing. Therefore, these agents could emerge as an alternative to long-term anticoagulation with warfarin in patients with AF. Pharmacoeconomic considerations will need to be assessed in addition to efficacy and safety issues when these new anticoagulants are evaluated for the management of AF.

Conclusions

Although rate-control strategies are currently favored in patients with AF, rhythm-control strategies are required for some patients. The choice among antiarrhythmic drug therapies is based on patient-specific characteristics. Emerging antiarrhythmic agents with potentially improved safety and anticoagulants that require less frequent monitoring than warfarin may become therapeutic options in the future. The role of these new agents will be clearer in the future as data regarding the relative efficacy, safety, and economic impact of these drugs become available. The preference for rate-control strategies over rhythm-control strategies could change if antiarrhythmic agents with improved tolerability are introduced.

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