

# Is There a Role for Maintaining Sinus Rhythm in Patients with Atrial Fibrillation?

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Recent studies have indicated that outcomes in patients with atrial fibrillation who are managed with rate control and anticoagulation are similar to those in patients who have maintenance of sinus rhythm. These studies did not include important groups of patients with atrial fibrillation in whom antiarrhythmic therapy may be appropriate. This perspective argues for the maintenance of sinus rhythm and for the use of antiarrhythmic therapy that in-

cludes medications, invasive procedures, and a combination of both in appropriate patients.

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Several studies have identified no morbidity or mortality advantage to the maintenance of sinus rhythm compared with appropriate rate control and anticoagulation. However, the patients in these studies were highly selected, and antiarrhythmic therapy was not uniformly applied. Antiarrhythmic therapy involves the use of medications, invasive procedures, or a combination of both. We believe that the careful use of these therapies to maintain sinus rhythm remains appropriate in some groups of patients. We discuss the arguments for antiarrhythmic therapy and propose strategies for their selection and use in appropriate patient populations.

## BACKGROUND

Four randomized studies have compared rate control with maintenance of sinus rhythm, the 2 largest of which had mortality end points (1-4) (Table 1). In each study, rate control was associated with survival equivalent to that of maintenance of sinus rhythm. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, the largest of the reported trials, randomly assigned 4060 patients with atrial fibrillation and risk for stroke to rate control or rhythm control (1). The average patient age was 69.7 years, 38% of patients were women, and approximately one third of patients were enrolled after their first episode of atrial fibrillation. The long-term use of anticoagulation was mandated for patients in the rate-control group but not for those in the rhythm-control group (in the latter group, anticoagulation was mandated for 1 month after restoration of sinus rhythm). At the 5-year visit, 35% of the rate-control group was in sinus rhythm and 15% had crossed over to the rhythm-control strategy. Symptoms, including heart failure, were the most common reasons for switching from rate to rhythm control (1). In the rhythm-control group, most patients were initially treated with sotalol or amiodarone. At the end of the study, 63% of patients in the rhythm-control group had undergone at least 1 trial of amiodarone. Sinus rhythm was present in 62% of patients in the rhythm-control group at the 5-year visit. Anticoagulation

was prescribed and maintained to the termination of the study in 85% of the rate-control group and 70% of the rhythm-control group. Occurrence of stroke did not significantly differ between strategies, and most strokes occurred in patients who had discontinued warfarin therapy or had subtherapeutic international normalized ratios. There was a nonsignificant trend toward an increased risk for death in the rhythm-control group (1). Further analysis indicated that antiarrhythmic drug use was associated with an increased risk for noncardiovascular (pulmonary disease and malignant conditions) but not cardiovascular mortality (5). The presence of sinus rhythm, independent of antiarrhythmic drugs, was associated with a significant reduction in the risk for death (6).

AFFIRM and the other randomized, controlled trials have failed to define a survival advantage associated with the use of antiarrhythmic drugs to maintain sinus rhythm compared with rate control. They have further defined the high rate of recurrence during therapy with antiarrhythmic medications, and this probably contributes to the stroke risk associated with rhythm control. Thus, this study and others have brought to light the importance of maintaining anticoagulation in patients with atrial fibrillation-related stroke risk independent of the use of antiarrhythmic drugs. In addition, AFFIRM has shown that while antiarrhythmic drugs may be associated with increased mortality, the overall maintenance of sinus rhythm (with or without drugs) is associated with improved survival compared with persistent atrial fibrillation (6). This observation supports the long-recognized mortality risk associated with atrial fibrillation and mandates the development of new and safer methods to maintain sinus rhythm (7).

## PATIENTS WHO ARE CANDIDATES FOR MAINTENANCE OF SINUS RHYTHM

The equivalent status of rate control and anticoagulation compared with antiarrhythmic drug use cannot be generalized to all patients with atrial fibrillation. The studies described in the preceding section enrolled patients with risk factors for stroke and an average age ( $\pm$ SD) of

**Table 1. Randomized Trials of Maintenance of Sinus Rhythm Compared with Rate Control\***

Study (Reference)	Patients, n	Mean Age ± SD, y	Mean Follow-up, y	Patients Receiving Amiodarone, %	Patients Receiving Warfarin, %	Patients Having Thromboembolic Complications, %	Mortality Rate, %
<b>AFFIRM (1)</b>							
Rate control	2027	70 ± 9	3.5	10	85	6	21.3/5 y
Rhythm control	2033	70 ± 9		70	70	7.5	23.8/5 y
<b>RACE (2)</b>							
Rate control	256	68 ± 9	2.3	NR	96–99	5.5	17.2/2.3 y
Rhythm control	266	68 ± 9		NR	86–99	7.9	12.6/2.3 y
<b>STAF (3)</b>							
Rate control	100	65 ± 9	1.8	0	NR	0.6	4.9
Rhythm control	100	66 ± 8		0	NR	3.1	2.5
<b>PIAF (4)</b>							
Rate control	125	61 ± 9	1	0	NR	NR	NR
Rhythm control	127	60 ± 10		100	NR	NR	NR

\* AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; NR = not reported; PIAF = Pharmacological Intervention in Atrial Fibrillation; RACE = Rate Control Versus Electrical Cardioversion Study; STAF = The Strategies of Treatment of Atrial Fibrillation.

69 ± 10 years. These trials did not include important groups of patients, including younger individuals with lone atrial fibrillation, patients with highly symptomatic atrial fibrillation who might not be candidates for rate control, and patients with severe congestive heart failure. The elderly, particularly those older than 80 years of age with contraindications to anticoagulation, were also not included. Population estimates suggest that patients with lone atrial fibrillation represent approximately 15% of patients with atrial fibrillation (8–10). Patients older than 80 years of age, who are traditionally not represented in clinical trials, account for 35% of the atrial fibrillation population (10). Therefore, the aforementioned trials will not reflect nearly 50% of the estimated 3.3 million adults who will have atrial fibrillation by the year 2025. Specific circumstances in which the maintenance of sinus rhythm is reasonable include the following (Table 2):

1. *Symptoms despite rate control.* As noted in AFFIRM, some patients continue to experience intolerable symptoms regardless of adequate control of the ventricular response. In particular, patients with diminished diastolic compliance (for example, long-standing hypertension and hypertrophic cardiomyopathy) may not tolerate loss of atrial function and benefit immensely from maintenance of sinus rhythm (8, 11). Patients who cannot determine or articulate the presence of symptoms related to atrial fibrillation may subconsciously adjust their lifestyle to the limitations imposed by atrial fibrillation. Patients who undergo a trial of restoration and maintenance of sinus rhythm may begin to recognize symptoms related to atrial fibrillation that they could not previously appreciate.

2. *Difficulty achieving rate control.* Inadequate rate control is associated with the development of tachycardia-induced cardiomyopathy (12). Antiarrhythmic drugs are indicated for patients who cannot achieve adequate rate control with atrioventricular nodal blocking drugs or do

not tolerate the doses of these medications that are required for adequate rate control. Radiofrequency ablation of the atrioventricular junction with complete reliance on permanent ventricular pacing can also be used when medications do not achieve adequate rate control (12). However, recent data suggest that mandatory ventricular pacing may sometimes result in impaired ventricular function, congestive heart failure, and recurrence of atrial fibrillation (13, 14).

3. *Patients who are not candidates for anticoagulation.* Amiodarone has been convincingly demonstrated to better suppress atrial fibrillation compared with other antiarrhythmic drugs (15, 16). A more comprehensive use of amiodarone in the aforementioned studies may have lessened the rate of stroke in the rhythm-control groups. The Canadian Trial of Atrial Fibrillation showed this reduction in stroke rate with amiodarone therapy (16). Many patients with atrial fibrillation will have warfarin therapy withheld or discontinued because of the risk for falls or other bleeding risks. A common scenario is the elderly pa-

**Table 2. Indications for a Sinus Rhythm Strategy or Rate Control**

<b>Maintenance of sinus rhythm</b>
Strong indications
Patients who have symptoms despite adequate rate control
Patients who are unable to obtain adequate rate control
Possible indications
Patients who are not candidates for anticoagulation
Patients who wish to remain candidates for curative therapies for atrial fibrillation
<b>Rate control and anticoagulation*</b>
Patients with ≥1 risk factor for stroke and minimal symptoms associated with atrial fibrillation

\*Patients for whom randomized, controlled trials support a strategy of rate control and anticoagulation as equivalent to rhythm control.

**Table 3. Antiarrhythmic Drugs: Cardiac and Noncardiac Toxicity\***

Drug	Dose/24 h	Ion-Channel Blocker	Cardiac Toxicity	Noncardiac Toxicity
Amiodarone	200–400 mg	K Ca Na	Bradycardia Torsades de pointes (rare) Increases in plasma concentrations of warfarin and digoxin	Pulmonary toxicity† Photosensitivity Hepatic toxicity† GI upset Thyroid dysfunction†
Disopyramide	400–750 mg	Na K	Torsades de pointes Heart failure	Urinary retention Dry mouth Contraindicated if patient has glaucoma
Dofetilide‡§	500–1000 mg	K	QT prolongation/torsades de pointes	–
Flecainide	200–300 mg	Na	Ventricular tachycardia Atrial flutter with 1:1 conduction	Dizziness Blurred vision
Procainamide	1000–4000 mg	Na	QT prolongation/torsades de pointes Cimetidine and trimethoprim may increase plasma levels of procainamide	Lupus-like syndrome GI upset Agranulocytosis
Propafenone	450–900 mg	Na	Ventricular tachycardia Atrial flutter with 1:1 conduction Increases in serum levels of digoxin Possible increases in plasma concentration of warfarin	Metallic taste Wheezing Dizziness
Quinidine	600–1500 mg	Na K	QT prolongation/torsades de pointes Enhanced atrioventricular nodal conduction Increases in serum levels of digoxin	Nausea Diarrhea Cinchonism
Sotalol‡§	160–320 mg	K	QT prolongation/torsades de pointes   Bradycardia Avoid in patients with severe renal deficiency	COPD or asthma exacerbation

\* Ca = calcium; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; K = potassium; Na = sodium.

† Usually occurs with long-term (>1 mo) therapy

‡ Adjust dose for renal function.

§ Avoid using with other drugs that prolong the QT interval (e.g., phenothiazines, tricyclic antidepressants, cisapride, certain macrolide antibiotics).

|| Dose-related risk for torsades de pointes.

tient who begins receiving warfarin at the time of atrial fibrillation diagnosis and later has this therapy discontinued because of gait instability and concern for traumatic falls. The maintenance of sinus rhythm with amiodarone may help reduce stroke risk in patients who develop an absolute contraindication to warfarin. The correct dose of amiodarone remains unknown. Whether or not early recurrences (during loading) or late recurrences mean total failure that necessitates discontinuation of drug therapy is debatable.

4. *Prevention of atrial remodeling and allowing patient to remain a candidate for new therapies.* Longer durations of atrial fibrillation associated with lower likelihoods of restoration and maintenance of sinus rhythm are probably the result of atrial electrical and mechanical remodeling (17, 18). Failure to restore and maintain sinus rhythm may relegate patients to lifelong atrial fibrillation and disqualify them from receiving therapies for atrial fibrillation suppression or cure.

**RISKS ASSOCIATED WITH ANTIARRHYTHMIC DRUGS**

The major toxicities of antiarrhythmic drugs include proarrhythmia and noncardiovascular abnormalities. The noncardiovascular toxicities are specific to the individual

drugs and range from a metallic taste to life-threatening pulmonary or liver toxicity (Table 3).

Most antiarrhythmic drugs alter cardiac sodium-channel or potassium-channel function. These medications prevent or terminate atrial fibrillation by prolonging the refractory period (potassium-channel blockers) or slowing the conduction (sodium-channel blockers) of atrial cells. Prolongation of the refractory period (prolongation of repolarization) may result in QT prolongation, whereas prolongation in conduction can cause QRS prolongation. QT prolongation with potassium-channel blockers may result in the life-threatening arrhythmia torsades de pointes (15). Drugs that block the delayed rectifier potassium channel ( $I_{kr}$  or  $I_{ks}$ ) may cause torsades de pointes in up to 5% of patients (19–21).

Factors that promote the development of torsades de pointes in conjunction with antiarrhythmic drugs include female sex, slow heart rates, hypokalemia or hypomagnesemia, congenitally prolonged QT intervals, and pauses associated with the conversion of atrial fibrillation to sinus rhythm (19–23). The concomitant use of medications that interfere with the hepatic metabolism of antiarrhythmic drugs may also result in QT prolongation (24). Similarly, reduced urinary clearance of renally excreted medications

may result in toxicity (as can occur with sotalol). The risk for torsades de pointes is sometimes dose-related (as with sotalol and dofetilide) and sometimes idiosyncratic and not dose-related (as with quinidine) (19). In the case of procainamide, the metabolite *N*-acetyl procainamide prolongs the QT interval, whereas the parent compound has little effect on repolarization. Rapid acetylators of procainamide develop more *N*-acetyl procainamide and are more prone to torsades de pointes. Slow acetylators produce less *N*-acetyl procainamide and have a lower risk for torsades de pointes (25).

Other tachyarrhythmias that may result from use of antiarrhythmic agents include ventricular tachycardia, particularly in patients taking type 1C medications (flecainide, propafenone) who have underlying previous myocardial infarction and impaired ventricular function (26). Atrial flutter with a prolonged QRS duration and severe hemodynamic intolerance may also occur, particularly with class 1C drugs (27). This latter complication can generally be avoided by adding atrioventricular nodal blocking medications.

Bradyarrhythmias result from sinus node suppression or slowing of conduction through the atrioventricular node. Both of these complications are more frequent in elderly patients with underlying sick sinus syndrome (28). In most instances, ambulatory monitoring (see following section) and appropriate dose reduction or discontinuation of therapy can prevent serious consequences (29, 30).

## MINIMIZING PATIENT RISK WITH ANTIARRHYTHMIC DRUGS

### Choice of Drug

The toxicity of antiarrhythmic drugs can be reduced by selecting the appropriate agent according to patient characteristics (8) (Table 4). Type 1C drugs should be avoided in patients with structural heart disease, such as previous myocardial infarction, idiopathic dilated cardiomyopathy, or congestive heart failure, but can be the first-line agents in patients with lone atrial fibrillation. Sotalol should be avoided in patients with renal insufficiency but

may be a preferred medication for patients with coronary artery disease and preserved left ventricular function.

### Initiation and Monitoring of Antiarrhythmic Drugs

The toxicity of antiarrhythmic drugs can also be reduced with appropriate dosing and monitoring of medications during the loading phase. For example, one may choose to initiate a small loading dose of amiodarone (for example, 400 mg/d for 2 weeks) in an elderly patient with the sick sinus syndrome to avoid significant bradycardia. QT prolongation is expected with amiodarone and is not generally associated with a significant risk for torsades de pointes (<1%) unless the corrected QT interval is markedly prolonged (>500 msec) (31). Other life-threatening toxicities include hepatic damage that necessitates twice-yearly evaluation of aminotransferase levels. Pulmonary toxicity can be an early complication but most often occurs after months of therapy. No defined screening process is available to identify pulmonary toxicity. One approach involves pulmonary function tests (including diffusing capacity) and chest radiography at initiation, followed by yearly chest radiography thereafter. Cough and dyspnea are the most common symptoms (>70% of patients) and should prompt an evaluation that includes radiographic imaging and pulmonary function testing (with reassessment of diffusion capacity) (32).

As noted above, several factors increase the risk for torsades de pointes in patients taking antiarrhythmic drugs. The need for in-hospital initiation of antiarrhythmic drug therapy that prolongs repolarization is somewhat controversial (29). In-hospital monitoring for 72 hours is mandatory for patients receiving dofetilide (33). In-hospital initiation of therapy with type 1C agents and amiodarone is generally not required. The pause associated with conversion of atrial fibrillation to sinus rhythm may promote the development of torsades de pointes. As a result, therapy with antiarrhythmic drugs that have the potential for torsades de pointes (type 1A, type 3) should be initiated during sinus rhythm. Considerable experience has confirmed the safety of outpatient initiation of amiodarone therapy during atrial fibrillation (30, 34–36). As noted, the con-

Table 4. Recommendations for Selection and Initiation of Therapy with Antiarrhythmic Drugs\*

Therapy Choice	Lone Atrial Fibrillation†	CHF or CAD: Low Ejection Fraction	CAD: Normal Ejection Fraction	Hypertrophic Myopathy
First-line	Flecainide‡ Propafenone‡	Amiodarone Dofetilide§	Sotalol Amiodarone	Amiodarone
Second-line	Sotalol Type 1A drugs   Amiodarone	Dofetilide‡ Type 1A drugs		Disopyramide Sotalol
Avoid		Flecainide Propafenone	Flecainide Propafenone	

\* CAD = coronary artery disease; CHF = congestive heart failure.

† Atrial fibrillation in the absence of hypertension, coronary artery disease, diabetes mellitus, congestive heart failure, or valvular disease.

‡ Consider concomitant use of atrioventricular nodal blocking agent.

§ Mandatory when therapy is initiated in the hospital.

|| Type 1A drugs are quinidine, procainamide, and disopyramide.

cern with type 1C agents is not torsades de pointes but rather the organization of atrial fibrillation into atrial flutter with prolonged conduction (QRS widening) and hemodynamic instability. For this reason, the concomitant use of atrioventricular nodal blocking agents from the onset of administration is recommended (8).

Our practice is to administer medications other than dofetilide in the ambulatory setting only if the patient does not have congestive heart failure and has had sinus rhythm restored. Amiodarone is the only agent we initiate in the outpatient setting while the patient is in atrial fibrillation. All patients use a continuous event recorder and transmit a single 30-second tracing each day to allow monitoring for bradycardia, QT prolongation, or tachyarrhythmias. This protocol is continued for 10 days (29, 30).

Patients must be made aware of circumstances that may render previously tolerated medications dangerous. For example, the new initiation of therapy with a diuretic or the development of a diarrheal illness leading to hypokalemia and hypomagnesemia can result in QT prolongation and torsades de pointes.

At present, most serious cases of proarrhythmia are believed to be related to antiarrhythmic drug blockade of one or both components of the delayed rectifier potassium channel ( $I_{kr}$  or  $I_{ks}$ ). Individuals who are susceptible to this acquired form of the long QT syndrome and resultant proarrhythmia may carry genetic mutations of this potassium channel that mildly affect ion channel function. Genetic screening before the initiation of antiarrhythmic drug therapy may some day identify patients at risk for proarrhythmia and allow safer selection of appropriate antiarrhythmic drug candidates (37–39). Continued research to develop effective antiarrhythmic medications with reduced toxicity is ongoing (40). Specifically, agents with ion channel effects limited to atrial tissue are under development and are hoped to limit ventricular proarrhythmia (41).

### NONPHARMACOLOGIC THERAPIES FOR THE MAINTENANCE OF SINUS RHYTHM

The percutaneous application of lesions around the orifices of the pulmonary veins is increasingly offered as an option for maintenance of sinus rhythm (42). Studies of percutaneous ablation for atrial fibrillation vary with regard to technique used, patient population studied, concomitant use of antiarrhythmic drugs, and rigor of follow-up (43–45). Currently, this therapy has proven most effective in patients with paroxysmal atrial fibrillation and relatively normal cardiac anatomy; success rates range from 60% to 85% (41–43). It is expected that the efficacy of this procedure will increase as catheter mapping and ablation technology improve. Major complications resulting from this procedure occur in 1% of cases and include pulmonary vein stenosis, stroke, cardiac perforation, and tamponade (46). A rare complication is esophageal fistula formation

presenting with air emboli (stroke) or gastrointestinal bleeding (47).

The surgical Maze surgery is an intraoperative procedure consisting of a series of lesions around the pulmonary veins and down to the mitral valve. The atrial appendage is also sutured closed. This procedure targets both the presumed areas of atrial fibrillation initiation (pulmonary veins) and tissue necessary to maintain sinus rhythm (left atrium). This procedure is generally performed as a component of a valve or coronary bypass operation but may be offered as a stand-alone procedure. The efficacy of this procedure approaches 80%, and the complications include those seen with percutaneous atrial fibrillation ablation procedures (48).

Single- or dual-site atrial pacing techniques have been studied as methods to prevent atrial fibrillation. Compared with asynchronous ventricular pacing (VVI mode), synchronized atrioventricular conduction facilitated through atrial pacing significantly reduces the frequency of atrial fibrillation (49–52).

Randomized studies of dual- or alternative-site atrial pacing to prevent atrial fibrillation have produced conflicting results, and no consensus currently exists for the efficacy of this approach as primary preventive therapy for atrial fibrillation (31, 53).

### HYBRID THERAPY

Antiarrhythmic medications are increasingly used in conjunction with invasive approaches such as radiofrequency ablation or cryoablation of atrial fibrillation and atrial flutter. Antiarrhythmic medications can convert atrial fibrillation to atrial flutter in up to 15% of cases (8, 19, 20). Radiofrequency ablation of atrial flutter has now become a routine, safe, and highly effective procedure (54). This hybrid approach with continuation of antiarrhythmic drug therapy after the procedure results in better outcomes than either intervention used alone (55, 56).

The combination of atrial pacing and antiarrhythmic medication is frequently used (28). Specifically, pacing therapies to maintain the continuous and homogenous electrical activation of the atria reduce the frequency of atrial fibrillation recurrence. This combination is extremely effective and is often necessary with amiodarone use in older patients (28).

New pacing devices allow antitachycardia pacing in the atria to terminate atrial tachyarrhythmias that might otherwise trigger atrial fibrillation. Once again, antiarrhythmic drugs may organize atrial fibrillation into atrial flutter or atrial tachycardia, which can then be pace-terminated by these devices.

Before using any of these antiarrhythmic therapies, the patient must fully understand the risks and benefits of each strategy. All strategies for maintenance of sinus rhythm must emphasize the necessity of thromboembolic prophylaxis based on stroke risk factors independent of the deci-

sion to maintain sinus rhythm or rate control. Maintenance of sinus rhythm may be achieved with antiarrhythmic drug use, catheter-based pulmonary vein ablation, operative Maze procedure, or a combination of the above.

## CONCLUSION

Maintenance of sinus rhythm with antiarrhythmic drugs does not confer a mortality advantage and does not reduce the thromboembolic risk compared with rate control. These medications remain important therapeutic options for certain patients, including those with symptoms not mitigated by rate control. The appropriate choice of antiarrhythmic medication made with attention to patient clinical characteristics and potential drug toxicity reduces the risk associated with these agents. New approaches to drug development and screening for risk for adverse events may ultimately reduce the toxicity of these agents. Rapid advances in pacing and ablation technologies either alone or in combination with antiarrhythmic drugs will also provide new options for maintenance of sinus rhythm.

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