Sinus Rhythm Restoration and Treatment Success: Insight From Recent Clinical Trials

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ABSTRACT

Atrial fibrillation (AF) is a common supraventricular tachyarrhythmia with substantial morbidity and mortality. This review briefly describes the mechanisms of AF development and progression, including electrical, structural, and contractile remodeling. In addition, the potential benefits of achieving and maintaining sinus rhythm are discussed. For example, rhythm control has been associated with improvements in left ventricular function, AF symptoms, exercise tolerance, the ability to perform activities of daily living, and quality of life. More recently, dronedarone, a noniodinated benzofuran derivative approved for use in the treatment of AF, was shown to significantly improve clinical outcomes including cardiovascular hospitalizations and death from any cause in A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter (ATHENA). The review concludes with an examination of AF treatment options and expectations. Evidence suggests that the complete absence of AF recurrence is not always achievable; however, complete restoration of sinus rhythm may not be necessary for patients to achieve clinically meaningful benefits.

Introduction

Atrial fibrillation (AF) is a common supraventricular tachyarrhythmia characterized by disorganized atrial activity, reduced cardiac function, and hemodynamic impairment.¹ As the population of the United States ages, the number of individuals with AF is expected to reach 5.6 million by 2050.

Clinicians have long recognized the importance of judicious management of AF to prevent negative cardiovascular sequelae. AF increases the risk of stroke approximately 5-fold and, in the United States, it is responsible for 25% of all strokes among the elderly.^{2,3} Other consequences of AF include worsening of congestive heart failure (CHF), increased risk of hospitalization, impaired quality of life, and increased mortality.⁴

Recently, there has been increasing interest not only in preventing the negative consequences of AF, but also in preventing progression of the disease itself. This interest reflects a better understanding of the mechanisms that cause AF and an increased awareness of the high prevalence of disease progression. Nearly 25% of patients who initially

present with paroxysmal disease eventually progress to persistent or permanent AF.⁵

Herein we describe current theories regarding the pathophysiology of AF and discuss arrhythmia-induced cardiac changes that are thought to sustain the arrhythmia and facilitate its progression. The potential benefits of achieving and maintaining sinus rhythm are explored, and treatment options and expectations are discussed.

Mechanisms of AF Development and Progression

The precise pathophysiology of AF development and progression remains incompletely understood. The principal electrophysiological mechanism responsible for AF development likely involves both focal activation (1 or more ectopic foci) and multiple wavelet re-entry.^{6–8} The progressive nature of AF has been attributed to changes in the electrical, structural, and contractile properties of atrial tissue that arise from the arrhythmia itself.⁸

Electrical remodeling typically begins soon after AF onset and is characterized by shortened action potentials and effective refractory periods and a loss of rate dependence.^{8,9} These irregularities reflect multiple abnormalities in ion channel expression and ion flow, including changes in the movement of calcium and sodium across atrial cell membranes. Specific changes include inactivation of I_{Ca} (short term) and downregulation of I_{Ca} expression (long term), in response to increased calcium

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influx associated with rapid firing, and downregulation of the fast sodium current.^{10–13} Electrical remodeling appears to be reversible upon restoration of sinus rhythm.¹¹

Structural remodeling is more insidious in onset (occurring over periods of weeks to months). Commonly observed changes in animal models include increased cell size, myolysis, and the accumulation of glycogen around the nucleus.¹¹ Fibrotic changes in peripulmonary vein tissue have been observed in patients with AF who undergo mitral valve surgery.¹⁴ Although the causes of these structural changes are not completely understood, they may include AF-induced changes in the expression of collagen and matrix metalloproteinase.^{15–17} Atrial stretch and compensatory elevations of catecholamine and angiotensin II concentrations, triggered by the loss of atrial systole and suboptimal ventricular filling, also may play a role.^{5,11,18} Changes in atrial structure presumably contribute to AF progression by altering refractoriness and conduction.¹⁹ Whereas some of these structural changes may be irreversible,⁸ the reversal of left ventricular dysfunction following ablation (proximal isolation of arrhythmogenic pulmonary veins and elimination of non-postventricular triggers) has been described, indicating that AF may trigger the development of a reversible cardiomyopathy in some patients.²⁰

Contractile remodeling likely arises in response to both electrical abnormalities (reduced release of systolic calcium) and structural atrial changes (myolysis).^{12,21} The resulting reduced contractility may lead to thrombus formation and atrial dilation. It also may facilitate disease progression by allowing the coexistence of multiple wavelets. Contractile remodeling typically begins early in the course of the disease and is reversible; however, recovery of contractile function may be slow because of the need to replace lost sarcomeres.^{8,12}

Potential Benefits of Rhythm Control

Antiarrhythmic drugs or left atrial radiofrequency ablation may be used to restore and maintain sinus rhythm, and atrioventricular nodal blocking drugs, pacemakers, or atrioventricular nodal ablation may be used to control the ventricular response. Antithrombotic therapy is commonly used to prevent thromboembolism, except in patients with lone AF or contraindications to antithrombotic agents.

The relative merits of rhythm control over rate control remain the subject of much discussion.^{4,22–24} The poor efficacy and tolerability profiles of available antiarrhythmic agents likely contributed to the lack of a mortality benefit for rhythm control (vs rate control) in several clinical studies.^{25–28} Inadequate control of AF is common, with up to 50% of patients treated with available antiarrhythmic drugs experiencing recurrence within 1 year.²⁹ Side effects also are a concern with existing treatments (eg, organ toxicity with amiodarone and proarrhythmia with membrane-active agents). In the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study (N = 4060), the absence of a greater benefit with rhythm control relative to rate control in the primary analysis was attributed to the incomplete suppression of AF and/or the negative impact of cardiac and noncardiac

side effects of antiarrhythmic therapies.^{30,31} Moreover, it was suggested that older patients had poorer outcomes on rhythm control because they may have been more vulnerable to drug toxicities than younger patients. Similarly, the lack of significant mortality benefits in other studies (eg, the Polish How to Treat Chronic Atrial Fibrillation [HOT CAFÉ; N = 205] and Rate Control vs Electrical Cardioversion [RACE; N = 522] studies) was attributed, at least in part, to drug toxicity.^{26,27} The results of these studies suggest that certain subsets of patients may derive greater survival benefits from available rhythm-control therapies than others, particularly younger patients and individuals with underlying structural heart disease (Table 1).^{25,28,30–35}

Data from the recently completed A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter (ATHENA; N = 4628) demonstrated that dronedarone, a noniodinated benzofuran derivative approved for use in the management of AF, reduced cardiovascular morbidity and mortality in a broad AF population (Table 2).^{36,37} The primary endpoint was the first occurrence of cardiovascular hospitalization or death from any cause. After a mean follow-up of 21 months, patients in the dronedarone (400 mg twice daily [bid]) group demonstrated a 24% reduced risk of cardiovascular hospitalizations or death from any cause (primary endpoint; $P < 0.001$).³⁷ Also observed were a 29% reduction in the risk of cardiovascular death ($P = 0.03$) and a 26% reduction in the risk of cardiovascular hospitalization ($P < 0.001$). The risk of all-cause mortality was reduced 16% with dronedarone therapy; however, this reduction was not statistically significant ($P = 0.18$).³⁷ In a post-hoc analysis, treatment with dronedarone was associated with a 34% reduction in adjusted risk of stroke and a 33% reduction in stroke or transient ischemic attack ($P = 0.027$ and $P = 0.020$, respectively, vs placebo).³⁶

These data are consistent with data from earlier studies that were designed to evaluate the effects of dronedarone on more traditional endpoints.^{38–41} However, these outcomes contrast with data from the Antiarrhythmic Trial With Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA),^{41,42} a non-AF study conducted in high-risk patients with severe heart failure (HF; with or without AF). In ANDROMEDA, dronedarone use in the high-risk population studied was associated with increased mortality. The reason for the excess deaths in ANDROMEDA is not known. It is likely that the differences in results from ATHENA and ANDROMEDA reflect the differences in the populations studied. Based on these findings, dronedarone should not be used in patients with advanced HF or HF with a recent decompensation requiring hospitalization.

Other potential benefits of restoring and maintaining sinus rhythm include improvements in left ventricular (LV) function,^{26,43} AF symptoms,⁴⁴ exercise tolerance,^{26,35,44–47} the ability to perform activities of daily living,⁴⁸ and quality of life.^{35,44–46,48–50} Among those patients who underwent echocardiography at baseline and after the first and second year of follow-up in the RACE study, both rhythm ($n = 175$) and rate ($n = 160$) control were associated with

Table 1. Summary of Studies Demonstrating Mortality Benefit of Rhythm Control

Study	Population	Mean Age, y	Selected Exclusions	Intervention	Study Duration	Key Findings
AFFIRM ^{25,30,31}	4060 adults with AF and high risk of stroke or death; 71% had hypertension, 38% had CAD, 23% had a history of CHF, 74% had normal LVEF, 35% had normal left atrial size	70	Not specified	Rhythm: amiodarone, disopyramide, dofetilide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, or a combination of these drugs; cardioversion was used as necessary. Rate: β -blockers, calcium-channel blockers (verapamil or diltiazem), digoxin, or a combination of these drugs	3.5 y (mean follow-up); maximum follow-up, 6 y	No overall survival benefit with rhythm vs rate control. ³¹ Presence of sinus rhythm was associated with improved survival ($P < 0.0001$). ³⁰ Patients age <65 y and those with history of CHF responded better to rhythm control. ²⁵
DIAMOND ³⁴	506 adults with CHF (NYHA class I, II, III, or IV) or MI and AF or AFL at baseline; 56% had class III or IV HF; AF/AFL history was not described	72	Heart rate <50 bpm (awake); 2nd- or 3rd-degree AV block not treated with a pacemaker; history of drug-induced proarrhythmia; corrected QT interval >460 ms (500 mg in BB); diastolic or systolic BP >115 or <80 mm Hg; CrCl <20 mL/min	Dofetilide 250 μ g bid (qd for patients with CrCl <40 mL/min) or placebo	Not specified; study closure at 12 months after randomization of final patient	Restoration and maintenance of sinus rhythm improved survival ($P < 0.0001$)
STAF ²⁸	200 adults with moderate to high risk of arrhythmic recurrence (≥ 1 of the following): persistent AF (duration >4 wk but <2 y); left atrial size >45 mm; heart failure (NYHA class $\geq$ II); LVEF $<45\%$; ≥ 1 prior cardioversion with arrhythmia recurrence	65 (rhythm), 66 (rate)	History of paroxysmal AF; left atrial size >70 mm; LVEF $<20\%$; Wolff-Parkinson-White syndrome; history of AV node ablation or modification; unsuccessful cardioversion within 4 wk prior to study entry	Rhythm: cardioversion followed by class I antiarrhythmic agents or sotalol in the absence of CHD; β -blocker and/or amiodarone in patients with impaired LV function. Rate: β -blockers, digitalis, calcium antagonists, or AV node ablation/ modification with or without pacemaker implantation	19.6 months (mean follow-up); maximum follow-up, 36 months	Total mortality ~ 2 -fold lower with rhythm vs rate control

Table 1. Continued

Study	Population	Mean Age, y	Selected Exclusions	Intervention	Study Duration	Key Findings
CRRAFT ³⁵	144 adults with chronic rheumatic AF (mean $\pm$ SD AF duration, 6.1 ± 5.4 y); mean $\pm$ SD left atrial size, 4.7 ± 0.6 cm; all had heart failure (NYHA class I, II, or III); 73% had valvular interventions performed	39	AF duration <3 mo; Left atrial size >6.0 cm; valvular heart disease with hemodynamic compromise; valvular surgery or balloon valvotomy within prior 2 mo	Rhythm: amiodarone (maintenance dose 200 mg daily) or placebo; with electrical conversion wherever required Rate: diltiazem (90 mg bid)	Up to 12 mo	Relative risk of death $12.4 \times$ higher with rate vs rhythm control
CHF-STAT ³³	103 adults with AF and heart failure; AF at baseline evaluation heart failure (NYHA class II, III, or IV for ≥ 3 mo); mean LVEF: 25% for amiodarone, 26% for placebo	67	MI or revascularization within 3 mo; heart failure due to uncorrected primary valvular disease or restrictive or infiltrative cardiomyopathy; history of aborted sudden death; symptomatic ventricular arrhythmia; QRS duration ≥ 180 ms; symptomatic hypotension or systolic BP <90 mm Hg	Amiodarone (maintenance dose, 300 mg daily) or placebo	Up to 4.5 y	Restoration and maintenance of sinus rhythm improved survival ($P = 0.04$)

Abbreviations: AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; AFL, atrial flutter; AV, atrioventricular; BBB, bundle branch block; bid, twice daily; BP, blood pressure; bpm, beats per minute; CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CHF-STAT, Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy; CRRAFT, Control of Rate Versus Rhythm in Rheumatic Atrial Fibrillation Trial; CrCl, creatinine clearance; DIAMOND, Danish Investigations of Arrhythmia and Mortality on Dofetilide; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; qd, once daily; SD, standard deviation; STAF, Strategies of Treatment of Atrial Fibrillation.

Table 2. Summary of ATHENA^{36,37}

No. of patients	4628
Mean age, y	72
Female, %	47
Comorbidities, %	Structural heart disease, 60; CHD, 30; CHF NYHA class II/III, 21 ^a ; LVEF <45%, 12
Mean duration of follow-up, mo	21
Primary outcome (first CV hospitalization or death from any cause), HR for dronedarone vs placebo	0.76 ($P < 0.001$)
Secondary outcomes, hazard ratios for dronedarone vs placebo	
All-cause mortality	0.84 ($P = \text{NS}$)
CV mortality	0.71 ($P = 0.03$)
CV hospitalization	0.74 ($P < 0.001$)
Death from cardiac arrhythmia	0.55 ($P = 0.01$)
Cardiac nonarrhythmic death	0.95 ($P = \text{NS}$)
Post-hoc analysis, HR for dronedarone vs placebo	
Stroke	0.66 ($P = 0.027$)
Stroke or TIA	0.67 ($P = 0.020$)
Abbreviations: 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; CHD, coronary heart disease; CHF, congestive heart failure; CV, cardiovascular; HR, hazard ratio; LVEF, left ventricular ejection fraction; NS, not significant; NYHA, New York Heart Association; TIA, transient ischemic attack.	
^a Individuals with NYHA class IV heart failure were excluded from study participation.	

improved ventricular function (LV fractional shortening) at 2 years.⁴³ Multivariate analysis showed that sinus rhythm at study endpoint was a significant predictor of this response ($P < 0.05$). Quality of life was similar for both groups at the end of the study⁴⁹; however, multivariate analysis showed the presence of sinus rhythm at study end to be a significant determinant of relative improvement on various subscales of the Short-Form Health Survey (SF-36), including physical function, role physical, and vitality.

Similarly, in the HOT CAFÉ study, patients in the rhythm-control group ($n = 104$) experienced significant improvement in LV fractional shortening at follow-up (mean duration, 1.7 years) relative to baseline (29.9% to 34.5%; $P < .0001$), but those in the rate-control group ($n = 101$) did not (32.8% to 35.6%; $P = \text{NS}$).²⁶ (A limitation of this study is that response was analyzed based on strategy allocation, not on actual achievement of desired response.)

Quality-of-life assessments also showed improvement after rhythm control in both the Pharmacological Intervention in Atrial Fibrillation (PIAF) trial (rate vs rhythm control; $n = 159$) and the Canadian Trial of Atrial Fibrillation (CTAF) study of amiodarone, sotalol, and propafenone ($N = 264$).^{47,50}

In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), patients with sustained sinus rhythm at

1 year ($n = 304$) had greater improvements in both exercise tolerance and quality of life relative to patients with persistent AF ($n = 174$).⁴⁵ Similar benefits were observed in a subsequent post-hoc analysis of quality of life and exercise performance.⁴⁶

Following on from early studies in catheter ablation in AF, a recent prospective study involving patients with CHF ($n = 58$) and without CHF ($n = 58$; $\geq$ New York Heart Association [NYHA] Class II; left ventricular ejection fraction <45%) experienced improvements in symptoms, exercise capacity, and quality of life following the procedure (mean follow-up, 12 months).⁴⁴ The majority of patients were in sinus rhythm at the end of the follow-up period (78% of the CHF group, 84% of the control group).

Together, these findings indicate that the restoration and maintenance of sinus rhythm can positively impact clinical outcomes. Additional data from the HOT CAFÉ, RACE, and Paroxysmal Atrial Fibrillation 2 (PAF-2) studies demonstrate that rhythm control also may prevent atrial remodeling and associated disease progression. In the HOT CAFÉ study, patients treated with rhythm-control therapy demonstrated significant reductions in both left ($P < 0.02$) and right ($P < 0.01$) atrial size during follow-up (mean duration, 1.7 years) whereas those in the rate-control arm had significant increases ($P < 0.05$ and $P < 0.001$, respectively).²⁶ In the RACE study, patients in normal sinus rhythm at Month 24 demonstrated numerical reductions in left atrial size and statistically significant reductions in right atrial size relative to baseline ($P < 0.05$).⁴³ In contrast, patients who did not attain sinus rhythm experienced significant increases in both parameters at this time point ($P < 0.05$). In the PAF-2 trial, the risk of progression from paroxysmal to permanent AF was reduced by 57% with pharmacologic rhythm-control therapy ($P = 0.02$).⁵¹

Limitations of Available Rhythm-Control Therapies

In light of these study results, the restoration and maintenance of sinus rhythm appears to be a reasonable management goal. Unfortunately, clinicians have only limited rhythm-control options, many with suboptimal efficacy and/or safety profiles.

Ablation

Ablation procedures are designed to eliminate AF triggers and/or to disrupt AF perpetuation in the atria (left atrial ablation) or to control the ventricular response in patients in whom sinus rhythm cannot be restored (atrioventricular nodal ablation). Because ectopic triggers most commonly originate in the pulmonary veins (>90%),⁵² pulmonary vein isolation is the most common contemporary ablation strategy employed to restore sinus rhythm.⁵³ This approach is believed to both eliminate the ectopic trigger and alter the arrhythmogenic substrate for re-entry.⁵³ Atrioventricular nodal ablation for the control of ventricular response is typically reserved for patients in whom sinus rhythm cannot be restored and rate control is inadequate with pharmacologic therapy.⁵⁴

Current guidelines describe catheter-directed, left atrial ablation as a second-line option for the treatment of

paroxysmal or persistent AF—one that is typically reserved for patients who are highly symptomatic or who have failed trials of pharmacologic therapies.^{53,54} Because fewer patients are candidates for surgical ablation, which is highly invasive, surgical procedures are not discussed here. Some patients appear to be more likely to derive benefit from catheter-directed, left atrial ablation than others. Those who are age <70 years of age with highly symptomatic paroxysmal AF that has never cardioverted; have failed ≥ 1 antiarrhythmic drug trial; have a left atrial size of <5 cm and an LVEF >40%; and lack significant cardiac comorbidities may be good candidates for ablation procedures.⁵⁵ Notably, ablation should not be performed in the presence of left atrial thrombus.⁵³

A general lack of data from large, well-designed, clinical trials has created uncertainty regarding the benefits and limitations of catheter-directed left atrial ablation that has impeded widespread acceptance and use.⁵⁶ However, systematic review of data from 63 published radiofrequency catheter ablation studies demonstrated high rates of success (disappearance of the arrhythmia; 57% [single procedure] to 71% [multiple or uncertain number of procedures] when used in the absence of antiarrhythmic drug therapy, and 72% [single procedure] to 77% [multiple or uncertain number of procedures] when used with antiarrhythmic drugs).⁵⁷ Another meta-analysis of data from 5 randomized, controlled trials comparing pulmonary vein isolation with medical therapy for the maintenance of sinus rhythm in patients with paroxysmal AF demonstrated greater likelihood of freedom from AF at 12 months with pulmonary vein isolation versus medical therapy (odds ratio [95% confidence interval CI]: 15.78 [10.07, 24.73]).⁵⁸

A number of factors likely influence the efficacy of catheter-directed left atrial ablation, including the duration of AF before the procedure. Because longstanding AF results in deleterious electrical and mechanical remodeling,⁵⁹ ablation is less likely to restore sinus rhythm in patients with persistent or permanent AF versus paroxysmal AF.⁵³ Patient variables (eg, age, concomitant cardiac conditions, left atrial size); the concomitant use of antiarrhythmic drug therapy; the extent/duration of follow-up; experience and technique; and the criteria used to define success also have the potential to influence outcome.⁵³ In one 2005 survey, 48% (range among centers, 23.5% to 85.5%) of patients who underwent catheter-directed AF ablation in the absence of antiarrhythmic drugs continued to experience AF during a mean follow-up period of 11.6 months.⁶⁰ Success rates were higher in higher-volume treatment centers and when follow-up was of intermediate duration (between 7 and 18 months).

Data regarding the impact of left atrial ablation on symptoms and quality of life are also limited; however, beneficial effects have been reported,^{48,53,61} including in patients with recurrences.⁶² In one study, conducted in patients with AF and congestive heart failure, catheter-directed AF ablation was associated with improvements in cardiac function and exercise capacity as well as in symptoms and quality of life.⁴⁴

Data available to date suggest that mortality and stroke/transient ischemic attack rates with catheter-directed, left atrial ablation and antiarrhythmic drug

therapy are comparable. Meta-analysis of data from 8 randomized comparisons demonstrated a risk difference for mortality of 0.003 (95% CI: -0.018, 0.013; $P = 0.74$) and a risk difference for stroke/transient ischemic attack of 0.004 (95% CI: -0.010, 0.018; $P = 0.54$).⁶³ It is anticipated that the ongoing Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, with its estimated enrollment of 3000 AF patients, will provide some much-needed insight into the relative risks and benefits of this approach, including more information regarding the impact of AF ablation on morbidity and mortality.^{64,65}

Common concerns regarding ablation use include its inherent invasiveness and potential for serious complications. In the systematic review of 63 published radiofrequency catheter ablation studies introduced above, the most common complication of catheter-directed ablation was pulmonary vein stenosis (1.6%).⁵⁷ Cardiac tamponade (0.7%), pericardial effusion (0.6%), periprocedural stroke (0.3%), and periprocedural transient ischemic attack (0.2%) were less common. In a worldwide survey demonstrative of “real-world” experience ($N = 8745$), major complications associated with curative ablation for AF occurred in 524 (6%) patients and included 107 episodes of cardiac tamponade, 47 transient ischemic attacks, 20 strokes, and 4 deaths.⁶⁰ Of course, experience and technique likely influence this risk.⁵³ An additional concern is the potential to render AF asymptomatic, resulting in a risk of thromboembolic complications for patients not receiving anticoagulation therapy.⁵³ In light of this potential risk, current guidelines recommend continued risk-based anticoagulation following ablation procedures.⁵³

Atrioventricular nodal ablation may be appropriate in patients with a rapid ventricular response to AF in whom sinus rhythm cannot be restored with antiarrhythmic drug therapy.⁵⁴ Potential benefits include improved exercise duration, LVEF, symptoms, and quality of life, and reduced health care use.⁶⁶ Disadvantages include the need for permanent pacing and long-term anticoagulation.⁵⁴ A detailed review of atrioventricular nodal ablation is beyond the scope of this review.

Cardioversion

Cardioversion should be performed for patients with persistent AF in whom the arrhythmia is the main factor responsible for acute heart failure, hypotension, or worsening of angina pectoris in the presence of coronary artery disease.⁵⁴ Restoration of sinus rhythm can be achieved either electrically or pharmacologically.

Direct-current cardioversion is highly effective but requires conscious sedation or anesthesia.⁶⁷ The likelihood of successful conversion may be enhanced by pretreatment with appropriate antiarrhythmic drugs, which can reduce the cardioversion threshold.⁶⁷ Risks associated with direct-current cardioversion of AF include thromboembolism and proarrhythmia. Further, AF recurrence is common, particularly if concomitant antiarrhythmic drug therapy is not initiated. Immediate direct-current cardioversion is the recommended approach for patients with AF involving pre-excitation when very rapid tachycardia or hemodynamic

instability is present.⁵⁴ Moreover, it may be considered when pharmacologic measures fail to promptly correct a rapid ventricular response in patients with ongoing myocardial ischemia, symptomatic hypotension, angina, or heart failure, and in patients for whom AF symptoms are perceived as unacceptable.

Pharmacologic cardioversion is simple to administer and most effective when performed within 7 days of AF onset.⁵⁴ Current guidelines describe dofetilide, flecainide, ibutilide, propafenone, and amiodarone as “agents with proven efficacy” for pharmacologic cardioversion of AF present for up to 7 days and dofetilide, amiodarone, and ibutilide as “agents with proven efficacy” for pharmacologic cardioversion of AF present for more than 7 days (Table 3).⁵⁴ However, the use of these agents for pharmacologic conversion is limited at least somewhat by the risk for potentially serious side effects, including the potential of amiodarone, dofetilide, and ibutilide to prolong the QT interval and trigger torsades de pointes.⁵⁴ If this approach is taken, appropriate monitoring is therefore required to aid the timely detection of any drug toxicity.

A “pill-in-pocket” approach may be appropriate for some patients with infrequent AF.^{54,68} Patients utilizing this approach self-administer a single dose of a class 1C agent upon the onset of AF symptoms. This may terminate the episode and/or prevent recurrence in patients with paroxysmal AF and prevent the need for or facilitate direct-current cardioversion in patients with persistent AF. This approach is associated with limited side effects in patients with no structural heart disease, but should be used with caution in those with underlying structural heart disease, which could contribute to conduction abnormalities and proarrhythmia.

Maintenance of Sinus Rhythm

Numerous clinical trials have evaluated the efficacy of antiarrhythmic drugs in maintaining sinus rhythm in patients with recurrent or persistent AF. In a 2006 meta-analysis of randomized controlled trials, several class IA, IC, and III agents significantly reduced AF recurrence; however, class IA agents were associated with increased mortality, and all agents were associated with discontinuation due to side effects.⁶⁹ The 2006 practice guidelines of the American College of Cardiology/American Heart Association/European Society of Cardiology provide a consensus decision-tree approach for the optimal use of antiarrhythmic drugs in patients with recurrent paroxysmal or persistent AF (Figure 1).⁵⁴ The guidelines recommend that any reversible precipitants of AF be corrected prior to antiarrhythmic administration. They also emphasize that subsequent selection of pharmacologic therapy be based first on safety, with consideration to underlying heart disease and the number and pattern of previous AF episodes. Lastly, they characterize catheter-directed left atrial ablation as a second-line treatment approach—one typically reserved for patients who fail to maintain sinus rhythm with antiarrhythmic drug therapy. Future guidelines will undoubtedly change based on the outcomes of major clinical trials and the approval of new AF therapies.

Table 3. Antiarrhythmic Drugs for Pharmacologic Cardioversion of Atrial Fibrillation Present for >7 Days, and Their Usual Dosages and Routes of Administration

Drug	Route of Administration	Dose
Agents with proven efficacy		
Dofetilide	PO	Dependent on CrCl: >60 mL/min: 500 µg bid; 40–60 mL/min: 250 µg bid; 20–40 mL/min: 125 µg bid; <20 mL/min: contraindicated
Amiodarone ^a	PO	Inpatient: 1.2–1.8 g/d in divided dose until 10 g total, then 200–400 mg/d maintenance or 30 mg/kg as a single dose. Outpatient: 600–800 mg/d in divided doses until 10 g total, then 200–400 mg/d maintenance
	IV/PO	5–7 mg/kg over 30 to 60 min, then 1.2–1.8 g/d continuous IV or in divided oral doses until 10 g total, then 200–400 mg/d maintenance
Ibutilide	IV	1 mg over 10 min; repeat 1 mg when necessary
Less-effective or incompletely studied agents		
Disopyramide	IV	No dose recommendation provided in guidelines
Flecainide	PO IV	200–300 mg ^b 1.5–3.0 mg/kg over 10 to 20 min ^b
Procainamide	IV	No dose recommendation provided in guidelines
Propafenone	PO IV	600 mg 1.5–2.0 mg/kg over 10 to 20 min ^b
Quinidine	PO	0.75–1.5 g in divided doses over 6 to 12 h, usually with a rate-slowing drug ^c
Abbreviations: AF, atrial fibrillation; bid, twice daily; CrCl, creatinine clearance; IV, intravenous; LV, left ventricular; PO, oral. Modified with permission from Fuster et al. ⁵⁴ ^a Amiodarone is not approved for this indication. ^b Should be used cautiously in patients with ischemic heart disease or impaired LV function because insufficient data are available upon which to base specific recommendations for these groups. ^c The use of quinidine loading to achieve pharmacologic conversion of AF is controversial, and safer methods are available with the alternative agents listed in the table. Quinidine should be used with caution.		

The typical doses and side effects of recommended agents are summarized in Table 4. To minimize the risk for proarrhythmia (risk is significantly increased for all drugs except amiodarone and propafenone),⁶⁹ therapies are commonly initiated at relatively low doses,

Figure 1. Algorithm of antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Abbreviations: LVH, left ventricular hypertrophy. Reprinted with permission from Fuster et al.⁵⁴

often while the patient is hospitalized. Doses should be titrated to heart rate and electrocardiographic response and doses of concomitant therapies also should be evaluated. Combination therapy may be considered if monotherapy fails.

Among the various agents currently in use, amiodarone appears to be more effective than Class I antiarrhythmic agents or sotalol. In an AFFIRM substudy, amiodarone proved more effective at 1 year than either class I agents (62% vs 23% in sinus rhythm with no cardioversions, respectively; $P < 0.001$) or sotalol (60% vs 38%, respectively; $P = 0.002$).⁷⁰ The class I agents used included quinidine, procainamide, disopyramide, moricizine, propafenone, and flecainide. Note: Moricizine is not available in the United States). Similarly, in the SAFE-T study of amiodarone and sotalol in 665 patients with persistent AF, the 2 drugs were equally effective in converting AF to sinus rhythm, but amiodarone was superior for maintaining it (median time to recurrence of AF was 487 days and 74 days, respectively; $P < 0.001$).⁴⁵ However, the potential of amiodarone to cause serious adverse effects in the long term might preclude its use as a first-choice drug. In this regard, the potential for amiodarone to cause pulmonary toxicity may have been a factor in the significantly higher noncardiovascular death rate (including pulmonary deaths) reported for the rhythm-control arm of the AFFIRM study.³¹ Although only 3 of the 169 noncardiovascular deaths in this group were considered related to amiodarone pulmonary toxicity, it is believed that other pulmonary deaths ($n = 36$) might have been caused by less-recognizable forms of amiodarone toxicity.

Whichever drug is administered, ongoing antiarrhythmic therapy should be monitored closely via reporting of symptoms, examining electrocardiographic parameters for possible drug-induced prolongation of QRS duration or QT interval, and monitoring cardiac output, plasma potassium

and magnesium levels, and renal function. Since any drug that appears safe initially can become proarrhythmic if coronary disease or heart failure occurs, patients should be alerted to the potential significance of symptoms such as syncope, angina, or dyspnea.

Many other therapies, with diverse mechanisms of action are in earlier stages of development for the treatment of patients with AF. These include atrial-selective agents (eg, vernakalant, tertiapin, and diphenylphosphine oxide-1), novel class III agents (eg, azimilide, tedisamil, and ersentilide), gap-junction modulators (eg, rotigaptide or AAP10; both connexin modulators), adenosine A1 agonists (eg, tecadenoson and seladenoson), and molecules that work via other mechanisms (eg, GsMTx4, a stretch-receptor antagonist; KB-R7943, a sodium/calcium exchange inhibitor; or cariporide, a sodium/hydrogen exchange inhibitor). Finally, investigation is also underway into some nonantiarrhythmics in AF (eg, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and omega-3 fatty acids/fish oil). Although the evidence to date is favorable for these new agents, data are not yet sufficient to critically and fully examine their potential benefits or long-term toxicity.

Treatment Expectations: Defining Treatment Goals

The benefits of effective AF management are widely accepted; however, no definitive measure of efficacy has been used consistently in clinical studies of AF therapies. Rhythm-control therapies have largely been judged by their ability to restore sinus rhythm/suppress recurrence. Numerous studies have demonstrated that complete restoration of sinus rhythm (100% absence of recurrence) often is unachievable. Average 1-year recurrence rates may be as high as 35% with amiodarone and 50% with other available antiarrhythmic drug therapies.²⁹ However, complete restoration of sinus rhythm may not be

Table 4. Antiarrhythmic Agents Used to Maintain Sinus Rhythm in Patients With Atrial Fibrillation

Drug ^a	Daily Dose	Potential Adverse Effects
Amiodarone ^b	100–400 mg	Photosensitivity, pulmonary toxicity, polyneuropathy, gastrointestinal upset, bradycardia, torsades de pointes (rare), hepatic toxicity, thyroid dysfunction, eye complications
Disopyramide	400–750 mg	Torsades de pointes, heart failure, glaucoma, urinary retention, dry mouth
Dofetilide ^c	500–1000 µg	Torsades de pointes
Flecainide	200–300 mg	Ventricular tachycardia, heart failure, conversion to atrial flutter with rapid conduction through the atrioventricular node
Propafenone	450–900 mg	Ventricular tachycardia, heart failure, conversion to atrial flutter with rapid conduction through the atrioventricular node
Sotalol ^c	160–320 mg	Torsades de pointes, heart failure, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease

Modified with permission from Fuster et al.⁵⁴

The presence of factors known to predispose patients to ventricular proarrhythmia should be assessed before initiation of antiarrhythmic therapy, eg, long QT interval, wide QRS duration, structural heart disease, depressed left ventricular function, hypokalemia/hypomagnesemia, female gender, renal dysfunction, bradycardia, previous proarrhythmia, concomitant ventricular tachycardia or rapid ventricular response rate, and concomitant therapy with diuretics, drugs that prolong the QT interval, or other drugs associated with torsades de pointes.

^aDrugs are listed alphabetically.

^bA loading dose of 600 mg/d is usually given for 1 mo, or 1000 mg/d for 1 wk. Doses of digoxin and warfarin typically should be reduced prior to amiodarone initiation because concomitant administration often is associated with increases in serum digoxin levels and international normalized ratio, respectively.

^cDose should be adjusted for renal function and QT-interval response during in-hospital initiation phase.

necessary to confer clinically meaningful benefit. For example, improvements in quality of life and symptom frequency and severity are commonly associated with catheter ablation, even among patients in whom AF recurs.^{61,62} Although improvements in patients who experienced recurrence were generally of smaller magnitude than in those who remained in sinus rhythm, they were perceptible to patients. Similar findings have been reported with

antiarrhythmic drug use. In the STAF study, scores on the SF-36 physical role function and mental health domains significantly improved from baseline to follow up (mean duration, 19.5 months) in the rhythm-control group (both $P < 0.05$), despite the fact that only 70% of patients were in sinus rhythm after cardioversion and only 23% at 36 months.²⁸ In the PIAF study, SF-36 scores for physical functioning, physical role function, vitality, and social functioning improved significantly from baseline to Month 12 in the rhythm-control group (all $P < 0.05$), despite the fact that only 56% of patients in this group remained in sinus rhythm at the 12-month timepoint.⁴⁷

In patients with AF and CHF, improvements in LV function have been described even for patients who did not achieve 100% suppression of AF. In a catheter ablation study, significant ($P = 0.03$) improvements in LV function were observed in 4 of 12 patients who achieved conversion of permanent AF to paroxysmal AF.⁴⁴ Such improvements reflected increases in LVEF of $\geq 20\%$ or to a value $\geq 55\%$.

Improvements in AF recurrence, quality of life, symptom frequency/severity etc., as described above, are important in AF management. However, moving forward, the results of ATHENA (Table 2) should dictate a greater emphasis on improving clinical outcomes (eg, cardiovascular hospitalizations/mortality) in the AF population.

Conclusion

Early implementation of rhythm control, with a focus on early restoration and maintenance of sinus rhythm, may be beneficial in preventing the progression of AF and associated morbidity and mortality. Therefore, it should be a high priority among treatment goals. The clinical benefits of optimal rhythm control are well established, and include relief of symptoms and improvements in exercise tolerance, hemodynamics, LV function, and quality of life. However, use of currently available procedures and agents is limited due to poor efficacy and/or tolerability concerns as well as the need for additional outcomes data. As observed in ATHENA, effective and well-tolerated AF therapies may reduce cardiovascular hospitalization and mortality and the risk of stroke, even in moderate-to-high-risk patients (eg, elderly patients are likely to be unable to tolerate available antiarrhythmic drugs). These results are likely to change future clinical research and AF management such that measurable clinical outcomes become the primary focus.

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