

Review

Treatment of Atrial Fibrillation

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IMPORTANCE Atrial fibrillation is a common arrhythmia that affects more than 2.5 million people in the United States and causes substantial morbidity and mortality, especially regarding the increased risk of stroke.

OBJECTIVE To summarize atrial fibrillation treatment exclusive of stroke prevention.

EVIDENCE REVIEW An Ovid MEDLINE comprehensive literature search was performed on atrial fibrillation therapy excluding anticoagulation and emphasizing studies published within the last 5 years through April 2015 (N = 5044 references). The 2014 atrial fibrillation guideline from the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society also was reviewed.

FINDINGS Reversible causes of atrial fibrillation should be identified. Risk factor modification, including weight loss and treatment of hypertension, diabetes, and obstructive sleep apnea can reduce atrial fibrillation episodes. Appropriate anticoagulation is necessary for patients at substantial stroke risk regardless of rate or rhythm treatment strategy. Sinus rhythm is often needed to control symptoms; however, an alternative strategy for atrial fibrillation is appropriate rate control. Rate control is safe in older patients (those who are about age ≥ 65 years) followed up for a few years, but no such safety data exist for patients younger than 60 years or for those followed up for longer periods. Thus, selection of therapy is individualized, taking into account present and future medical problems for the patient. Choice of an antiarrhythmic drug is based on safety first vs efficacy. Catheter ablation is an effective nonpharmacological alternative that is often, but not always, the second-line treatment. Reduction of the frequency and duration of atrial fibrillation episodes that result in a significant improvement in quality of life is a good marker of drug treatment success and complete elimination of atrial fibrillation is not required in many patients. Rate control is usually achieved with a β -blocker or non-dihydropyridine calcium channel blockers. It is important to assess adequate rate control during both rest and activity. If the ventricular rate goes uncontrolled for a prolonged period, tachycardia-mediated cardiomyopathy can occur.

CONCLUSIONS AND RELEVANCE Therapy for atrial fibrillation includes prevention and modification of inciting causes and appropriate anticoagulation. Rate control is necessary for all patients. Maintenance of sinus rhythm with drugs or catheter ablation should be considered based on the individual needs of each patient.

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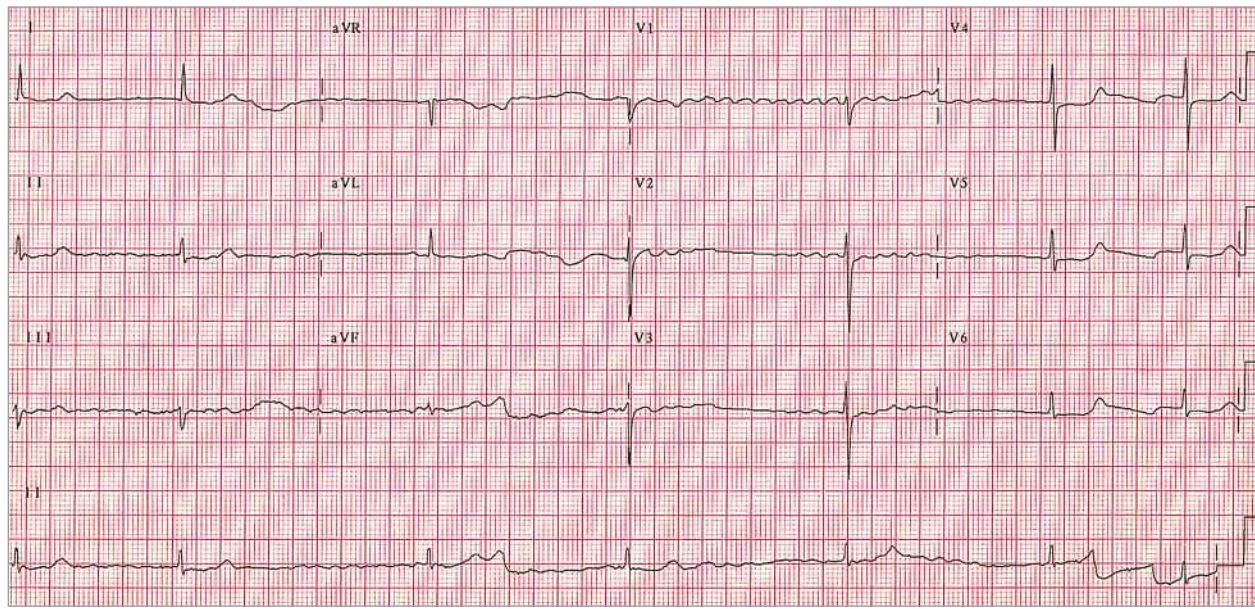
Atrial fibrillation (AF) is a common arrhythmia affecting more than 2.5 million people in the United States.^{1,2} Its incidence increases with age and the presence of concomitant heart disease. An electrocardiogram of AF shows a characteristic pattern of rapid atrial fibrillatory waves that change morphology (Figure 1). Intracardiac atrial activation varies both temporally and spatially, resulting in uncoordinated atrial contractility. In the absence of heart block, the ventricular response is characterized by an irregular R-R interval.

Atrial fibrillation used to be classified as paroxysmal or chronic. It is now viewed as paroxysmal, persistent, long-standing

persistent, or permanent AF.² Paroxysmal AF resolves spontaneously within 7 days of onset and persistent AF lasts longer than 7 days. Long-standing persistent AF lasts more than 12 months. Permanent AF occurs when the patient or physician decide not to seek restoration and maintenance of sinus rhythm.

Atrial fibrillation may be asymptomatic, especially in older individuals (aged ≥ 65 years). When symptoms occur, they include palpitations (often expressed as a fluttering or an uneasy sensation in the chest), shortness of breath, fatigue, dizziness, and syncope. Atrial fibrillation is associated with morbidity and increased risk of mortality.² Stroke is a complication of AF,

Figure 1. Electrocardiogram of Atrial Fibrillation



Atrial activation is rapid and irregular and often noted best in lead V1. The ventricular rate is irregularly irregular.

and its risk is associated with several clinical factors summarized by the CHA₂DS₂-VASc scoring system (components include congestive heart failure, hypertension, age \geq 75 years, diabetes, stroke or transient ischemic attack, vascular disease, age of 65-74 years, and female sex).³

Patients experiencing persistent rapid ventricular responses from AF can develop tachycardia-mediated cardiomyopathy; however, ventricular function can improve to normal levels following rate or rhythm control.^{1,2} Duration of tachycardia resulting in cardiomyopathy was 6 months to 6 years (mean of 2 years) with rates of greater than 120 beats/min in one study⁴ and a median of 4.2 years in another.⁵ The minimal rate and duration of tachycardia to cause cardiomyopathy is unknown.

We review the mechanisms of AF, rate and rhythm control strategies, including drugs and nonpharmacological therapies and cardioversion.

Literature Review

An Ovid MEDLINE comprehensive literature search was performed on treatment of AF, including rate and rhythm control strategies, antiarrhythmic and rate control drugs, catheter ablation, and electrical cardioversion but not anticoagulation, with an emphasis on studies published within the last 5 years through April 2015 (N = 5044 references). A focus was original research, especially randomized clinical trials and systematic reviews. In addition, the 2014 guideline² for management of AF from the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society was reviewed and pertinent articles individually read.

Mechanisms of AF

Atrial fibrillation is caused by atrial electrophysiological abnormalities, structural abnormalities, or a combination of these. Extrinsic factors, such as the autonomic nervous system, often are involved as well.^{1,2,6-8} The pathophysiology of AF is not entirely understood. One hypothesis explaining AF is that there are ectopic foci or triggers that are rapidly firing with fibrillatory conduction,⁹ both of which are complex patterns of atrial activation representing AF on the electrocardiogram.

The most common location for triggers are the pulmonary veins; however, several other sites (eg, the superior vena cava or coronary sinus musculature) have been identified.^{1,2,7,10,11} Triggers most likely explain briefer episodes of AF. Longer duration AF (several hours) probably requires abnormal atrial tissue. Abnormal atrial tissue can result in multiple reentrant wavelets responsible for sustained AF.^{12,13} More recently, rotors or spiral wave reentrant circuits have been recognized in humans to maintain AF.^{2,7,14,15}

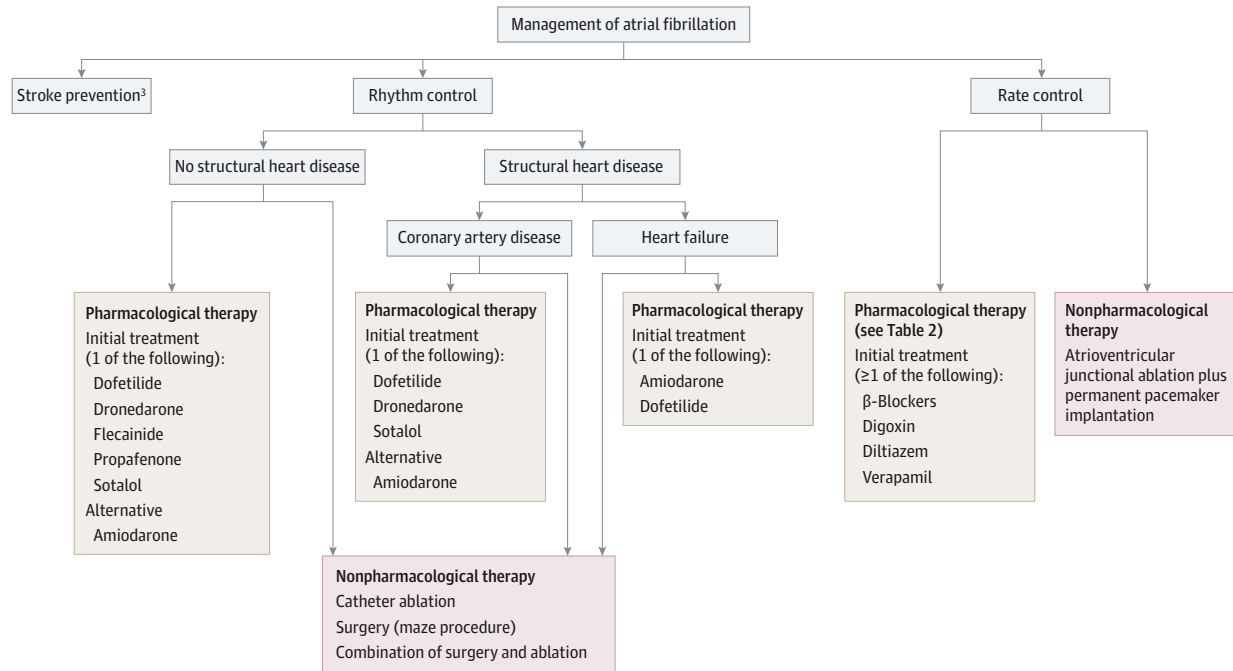
The pathophysiology of AF represents an intricate interaction of triggers and substrate and autonomic influences.^{1,2,13} Atrial fibrillation can result in structural and electrical remodeling and changes in the autonomic nervous system.¹³ These adverse changes may eventually preclude restoration and maintenance of sinus rhythm using antiarrhythmic drugs or catheter ablation.^{1,2}

Treatment of AF

Maintenance of Sinus Rhythm vs Rate Control

Potential reversible causes of AF should be identified and treated if possible.² Atrial fibrillation related to hyperthyroidism or acute

Figure 2. Overview of Management of Atrial Fibrillation



General overview for atrial fibrillation management. See Figure 4 for proposed treatment algorithm.

Table 1. Antiarrhythmic Drugs for Maintenance of Sinus Rhythm

Antiarrhythmic Drug Name	Typical Dose	Timing	Potential Significant Adverse Effects
Flecainide	50-200 mg	Every 12 h	Sinus node or atrioventricular node dysfunction Atrial flutter with 1:1 ventricular response
Propafenone	150-300 mg (immediate release) 225-425 mg (extended release)	Every 8 h Every 12 h	Sinus node or atrioventricular node dysfunction Atrial flutter with 1:1 ventricular response
Amiodarone	Loading dose: 400-600 mg/d Maintenance dose: 200-300 mg	For 4 wk Daily	Sinus node or atrioventricular node dysfunction Lung, liver, or thyroid toxicity Prolonged QT interval (torsade de pointes ventricular tachycardia rare)
Dofetilide	125-500 µg	Every 12 h ^a	Prolonged QT interval with torsade de pointes ventricular tachycardia
Dronedaronone	400 mg	Every 12 h	Sinus node or atrioventricular node dysfunction Prolonged QT interval (torsade de pointes ventricular tachycardia rare)
Sotalol	40-160 mg	Every 12 h ^b	Sinus node or atrioventricular node dysfunction Prolonged QT interval (torsade de pointes ventricular tachycardia rare)

^a Indicates renal-based dosing.

^b Renal dosing may require dosing every 24 hours instead.

pulmonary problems may not recur after these conditions resolve. Modification of AF risk factors (eg, obstructive sleep apnea, hypertension, and obesity) can result in substantial improvement in symptom burden but typically not long-term elimination of AF.¹⁶⁻¹⁸

The 3 major treatment strategies for AF are maintenance of sinus rhythm, heart rate control during AF, and prevention of stroke (Figure 2). Maintenance of sinus rhythm requires the use of an antiarrhythmic drug or tissue ablation. Total elimination of AF is typically not achievable using antiarrhythmic drugs. However, complete elimination of AF does not need to be a treat-

ment goal because recurrence is not considered a treatment failure if it only occurs occasionally without disabling symptoms. For example, a person with frequent episodes of symptomatic AF before treatment who later has few AF episodes after therapy likely will still experience a marked improvement in quality of life.

Antiarrhythmic drugs are only modestly effective as first-line therapy for AF.² Even though antiarrhythmic drugs (Table 1) may be chosen as the primary strategy, AF recurrences may require the addition of a rate controlling agent (Table 2). Comparative trials of catheter ablation vs antiarrhythmic drugs typically

demonstrate superiority of ablation to maintain sinus rhythm² (Table 3).

A rate control strategy is used when sinus rhythm is not necessary and the goal is to minimize symptoms during AF. Rate control is required even if the patient is asymptomatic during AF because prolonged periods of rapid ventricular rates can lead to tachycardia-mediated cardiomyopathy and heart failure.^{1,2,4,5}

Several studies have compared the safety and efficacy of rate and rhythm control approaches in patients with AF.²⁶⁻²⁸ Two of the largest were the Atrial Fibrillation Follow-up Investigation of Rhythm Management²⁶ (AFFIRM) study and the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation²⁷ (RACE) study.

The AFFIRM trial enrolled 4060 patients assigned to either strategy.²⁶ The mean (SD) age was 69.7 (9) years and the mean follow-up time was 3.5 years. Patients had to be at least 65 years old or have other risk factors for death or stroke. Women accounted for 39.3% of patients. Hypertension was present in 70.8% of patients and coronary artery disease in 38.2%. Amiodarone or sotalol were used in more than two-thirds of patients in the rhythm control group. Mortality was the primary end point and was not different between treatment groups. Five-year mortality was 23.8% in the rhythm control group and 21.3% in the rate control group (hazard ratio [HR], 1.15; 95% CI, 0.99-1.34; $P = .08$).

The RACE trial enrolled 522 patients randomized to maintenance of sinus rhythm compared with rate control.²⁷ The mean age was 68 years and the mean (SD) follow-up was 2.3 (0.6) years. Patients had to have recurrent persistent AF or flutter not lasting longer than 1 year. Women accounted for about 36% of patients. Hypertension occurred significantly more often in the rhythm control group than in the rate control group (55% vs 43%, respectively; $P = .007$). The composite of death and morbidity from cardiovascular causes (primary end point) occurred in 17.2% of the rate control group and 22.6% of the rhythm control group (HR, 0.73; 90% CI, 0.53-1.01; $P = .11$).

A recent meta-analysis²⁹ of 10 studies comparing rate vs rhythm control strategies using drug therapy showed no difference in any clinical outcomes (risk ratio [RR] for all-cause mortality, 1.15; 95% CI, 0.88-1.50; $P = .31$). An exploratory subanalysis in patients

younger than 65 years demonstrated an advantage of rhythm control over rate control in the prevention of all-cause mortality (RR, 3.03; 95% CI, 1.59-5.75; $P < .001$).²⁹

Follow-up was less than 4 years in the AFFIRM and RACE trials. Ionescu-Iltu et al³⁰ reported findings from a large population-based database of patients treated with rhythm control or rate control drugs. Crude rates for mortality after 5 years of follow-up were 41.7% in the rhythm control group and 46.3% in

Table 2. Drugs for Rate Control

	Dose
β-Adrenergic Blockers	
Atenolol	25-100 mg/d
Bisoprolol	2.5-10.0 mg/d
Carvedilol	3.125-25.0 mg ^a
Metoprolol succinate	50-400 mg/d ^b
Metoprolol tartrate	25-100 mg ^a
Nadolol	10-240 mg/d
Propranolol	10-40 mg ^c
Calcium Channel Antagonists	
Diltiazem	120-360 mg/d ^d
Verapamil	120-480 mg/d ^d
Digoxin	0.125-0.250 mg/d
Intravenous Agents	
Digoxin	0.25 mg initial ^e
Diltiazem	0.25 mg/kg ^{f,g}
Esmolol	500 μg/kg ^h
Verapamil	0.075-0.150 mg/kg ^{f,i}

^a Twice per day

^b May be divided into 2 doses per day.

^c Three or 4 times per day.

^d May be in divided doses and in extended-release formulation.

^e Additional doses allowed but 1.5 mg maximum within 24-hour period.

^f Bolus over 2 minutes.

^g Dose range: 5 to 15 mg per hour.

^h Bolus over 1 min; then 50 to 300 μg/kg/min.

ⁱ If no response, an additional 10 mg after 30 minutes and then a 0.005-mg/kg/min infusion.

Table 3. Results From Randomized Trials of Catheter Ablation vs Antiarrhythmic Drug Therapy in Atrial Fibrillation

Source	No. of Patients	End Point	AF Recurrence, % ^a	
			Catheter Ablation	Antiarrhythmic Drugs
Catheter Ablation vs Antiarrhythmic Drugs in First-Line Therapy				
Wazni et al, ¹⁹ 2005	70	1-y AF recurrence	13	63
Cosedis Nielsen et al, ²³ 2012	294	Cumulative AF burden ^b	13	19
Morillo et al, ²⁵ 2014	127	2-y AF recurrence	54.5	72.1
Catheter Ablation vs Antiarrhythmic Drugs in Second-Line Therapy				
Jaïs et al, ²⁰ 2008	112	1-y AF recurrence	11	77
Wilber et al, ²¹ 2010	167	9-mo AF recurrence	34	84
Packer et al, ²² 2013	245	1-y AF recurrence	30.1	92.7
Mont et al, ²⁴ 2014 ^c	146	1-y AF recurrence	29.6	56.3

Abbreviation: AF, atrial fibrillation.

^a The difference in outcome was statistically significant for all comparisons of catheter ablation vs antiarrhythmic drugs except Cosedis Nielsen.²³

^b AF burden was expressed as % of time in AF, 90th percentile.

^c Patients in this study were diagnosed with persistent AF.

the rate control group. There appeared to be no difference in mortality during the first 4 years; however, in those surviving more than 5 years, mortality was lower in the rhythm control group (HR, 0.88; 95% CI, 0.78-1.00).

Even though stroke is the most feared complication of AF, there are other reported neurological consequences (eg, cognitive impairment, silent cerebral infarcts, memory impairment, Alzheimer disease, and myocardial infarction).³¹⁻³³ Future studies are needed to evaluate the safety and efficacy of a rhythm control vs rate control approach on these outcomes.

Atrial fibrillation can worsen symptoms in patients with heart failure.¹⁻³ Maintenance of sinus rhythm has a salutary effect by providing an atrial contraction contribution to cardiac output, regularization, and physiological control of the heart rate. Quality of life is also impaired in patients who have both heart failure and AF.³⁴ In one study,³⁵ rhythm control using antiarrhythmic drugs was not superior to rate control in patients with heart failure. Beneficial effects of sinus rhythm obtained using catheter ablation are much more promising,³⁴ and some studies showed a substantial improvement in left ventricular function after catheter ablation.^{36,37}

Summary

Choice of rhythm control or rate control therapy should be individualized for each patient and the physician should be flexible in modifying the strategy if the clinical situation changes.^{38,39} Years of persistent AF can cause mechanical and electrical atrial remodeling with the possible consequence that restoration and maintenance of sinus rhythm may not be possible.³⁸ Thus, it is important the clinician factor this possible consequence into the decision-making process when selecting a treatment strategy.

Rate control in patients older than 65 years appears safe and appropriate as an initial therapy.²⁶ If symptoms persist, rhythm control should be considered, remembering that symptoms can be subtle (eg, fatigue or a generalized lack of energy).^{38,39} For patients younger than 65 years, preliminary data²⁹ suggest a survival advantage of sinus rhythm, which may favor rhythm control as the initial approach.

Maintenance of Sinus Rhythm

Antiarrhythmic Drug Therapy

Antiarrhythmic drugs are usually necessary to maintain sinus rhythm.^{1,2} Table 1 lists the antiarrhythmic agents with their typical doses and potential significant adverse effects. Elimination of all episodes of AF is an ideal but unrealistic goal for most patients; therefore, a reasonable end point is marked reduction in symptoms and in the frequency and duration of recurrent episodes of AF.

Selection of the optimal agent for pharmacological maintenance of sinus rhythm is based primarily on the drug's safety and then by its efficacy.^{1,2,40,41} For example, amiodarone has been shown in several randomized trials to be superior to the comparative antiarrhythmic agent for maintaining sinus rhythm²; however, it has a substantial adverse effect profile including liver, lung, and thyroid toxicity. Drugs such as flecainide and propafenone should be avoided in patients who have heart failure or coronary artery disease.

To improve the safety of drug use for patients with AF, an algorithm was proposed that directed selection of an agent based on the presence or absence of other clinical factors that might increase the risk of adverse events for a particular drug.⁴¹ A guiding principle of therapy is to eliminate any specific etiologic factor (eg, thyrotoxicosis or alcohol abuse) before considering drug treatment. In a few patients, the clinical history may direct the choice of therapy; for example, a β -blocker may be selected first in patients with AF only occurring during exercise.

Certain caveats should be considered when selecting an initial agent for maintenance of sinus rhythm.^{1,2} Both dofetilide and sotalol can increase the QT interval and should be used with caution in patients at risk for torsade de pointes ventricular tachycardia. Dronedaron and amiodarone also can increase the QT interval but the risk of torsade de pointes ventricular tachycardia is very low.¹ In the presence of substantial left ventricular hypertrophy (wall thickness >1.5 cm), dofetilide, flecainide, propafenone, and sotalol are not recommended.^{2,38} Calcium channel blockers or β -blockers should be given in conjunction with propafenone and flecainide because the latter drugs may alter the atrial electrophysiological properties, resulting in atrial flutter, which if slow enough can lead to 1:1 atrioventricular node conduction and a rapid ventricular rate (often >200 beats/min).¹⁻³

Hospital admission to monitor efficacy and safety during initiation of antiarrhythmic drug therapy is inconvenient for patients and costly for the medical system. Based on the available evidence, these drugs should be started while a patient is in the hospital if there is any significant concern for patient safety. However, outpatient initiation of therapy is often reasonable and safe for patients.¹⁻³

Patients in sinus rhythm without heart disease, who have normal electrolyte status and are taking an atrioventricular nodal blocking agent, may have flecainide and propafenone initiated on an outpatient basis, typically starting with a lower dose and monitoring each drug's effect on the electrocardiogram within several days after drug initiation and uptitration. Amiodarone and dronedaron may be started in patients in sinus rhythm or with AF; however, careful monitoring of their electrocardiogram status is recommended with either an event recorder or an electrocardiogram taken in the office. Both drugs slow conduction over the atrioventricular node and a blocking agent for the atrioventricular node may not be needed.

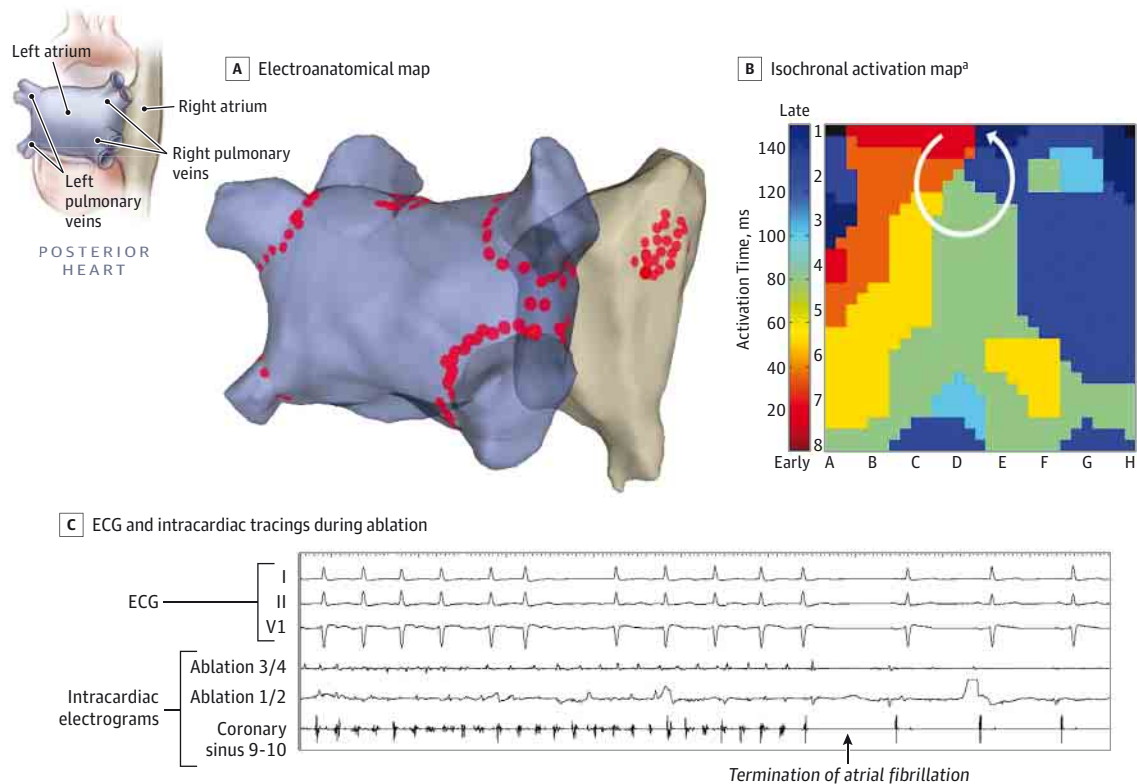
Dofetilide can only be started in the hospital setting. Sotalol can prolong the QT interval and cause torsade de pointes ventricular tachycardia; therefore, some advocate that it always be started in the hospital setting. However, sotalol can be administered without hospitalization to selected patients who are in sinus rhythm and have normal electrolyte levels and QT intervals, starting at a relatively low dose with follow-up electrocardiograms to determine the drug's effect on the QT interval.^{1,38} If the dose is titrated upward, the QT interval is again evaluated within 2 to 3 days of the dose increase. If the initial drug chosen is ineffective or causes troubling adverse effects, another first-line agent may be chosen or amiodarone or catheter ablation are reasonable alternatives.

Catheter Ablation

Patient Selection

In general, catheter ablation is recommended for patients with symptomatic paroxysmal or persistent AF who are refractory to intoler-

Figure 3. Radiofrequency Catheter Ablation to Isolate the Pulmonary Veins and Rotor Mapping and Ablation



A, 3-dimensional electroanatomical map of the left (blue) and right (gray) atria. The red dots represent ablation lesions. Ablations are seen circumferentially around the ostia of the pulmonary veins to accomplish isolation of the pulmonary veins. B, A rotor from the right atrium is shown and the arrow identifies the atrial activation sequence. C, Ablation in the right atrium (red dots)

resulted in sudden termination of atrial fibrillation into sinus rhythm. ECG indicates electrocardiogram.

^a The numbers and letters surrounding the map represent electrode positions on the basket mapping catheter.

ant to at least 1 antiarrhythmic drug.^{2,42} A number of clinical factors should also be considered in deciding to pursue ablation. Persistent AF (especially long-standing persistent AF) responds less favorably to ablation than paroxysmal AF.² Procedure-related complications, patient preferences, age, degree of symptoms, and presence of structural heart disease are also important factors to consider. In selected patients, catheter ablation may be the preferred first-line treatment.^{2,42,43}

Catheter Ablation of AF

Seminal observations by Haissaguerre et al¹¹ in 1998 demonstrated that rapidly firing atrial impulses in the pulmonary veins could lead to AF, and ablation of these triggers often prevented AF. This finding led to a sea change in the ablation approach to AF in which the focus was on electrical pulmonary vein isolation (PVI). Although PVI had reasonably good success to cure patients with paroxysmal AF, it demonstrated limited efficacy in patients with persistent AF. Other mechanisms of initiation and maintenance of AF have been demonstrated including triggers from nonpulmonary vein sources, rotors, and cardiac autonomic ganglia activity.^{6,7,15,26,44,45} These diverse mechanisms have led to varied approaches, including linear atrial ablation lines and ablation of complex fractionated atrial electrograms and ganglionic plexi.^{7,46,47}

Recent reports have indicated that AF may be sustained by a small number of rotors (spiral waves) that may be located in the left or right atrium.^{14,15,48} Ablation of these rotors improved outcomes of AF compared with PVI alone. This concept of AF maintenance by focal drivers was further validated with ablation guided by noninvasive techniques of mapping.⁴⁹

Ablation using PVI can be performed at or near the pulmonary vein ostium (venoatrial junction) and results in the elimination or dissociation of pulmonary vein potentials (Figure 3). More commonly, a wider area around the pulmonary veins is ablated to avoid pulmonary vein stenosis and achieve better success rates. The most common energy source used is radiofrequency energy delivered through the platinum-iridium tip of an ablation catheter. Cryoablation is another effective method to achieve circumferential pulmonary vein lesions.²²

Meta-analysis data demonstrated short-term and long-term efficacy of catheter ablation of AF.⁵⁰⁻⁵² At long-term follow-up, the rate of freedom from atrial arrhythmia with a single procedure was 54.1% in patients with paroxysmal AF and 41.8% in patients with nonparoxysmal AF. With multiple procedures, the long-term success rate improved to 79.8%.⁵² Collective data from a number of randomized clinical trials comparing medical therapy with catheter ablation^{19-25,43,53} have shown the superiority of ablation in eliminating clinical AF episodes and symptoms (Table 3).

Ablation as first-line therapy was addressed in 2 studies. The second Radiofrequency Ablation vs Antiarrhythmic Drugs for Atrial Fibrillation Treatment²⁵ (RAAFT-2) study showed a higher 1-year freedom from AF in the ablation group (45% vs 28% in the drug therapy group; $P = .02$). In the Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation²³ (MANTRA-PAF) trial, no significant differences were noted between the groups for the cumulative burden of AF during a period of 2 years; however, symptomatic AF was significantly lower in the ablation group than in the drug therapy group (93% vs 84%, respectively; $P = .01$).

An important unanswered question regarding AF ablation is whether it improves survival and the long-term risk of stroke. The ongoing Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation⁵⁴ (CABANA) trial is addressing the issue of whether ablative therapies could improve outcomes of stroke and survival compared with antiarrhythmic drug therapy. The ongoing Early Treatment of Atrial Fibrillation for Stroke Prevention Trial⁵⁵ (EAST) is addressing the issue of whether early use of rhythm control (ablation, antiarrhythmic drugs, or both) can improve the end points of stroke or cardiovascular death compared with usual care.

Atrial fibrillation ablation is associated with a variety of complications and these were assessed in a worldwide survey of 85 institutions performing 20 825 radiofrequency catheter ablations.⁵⁶ Major complications occurred in 4.5% of the ablations and the rate of procedure-related deaths was 0.15%. Other major events included a 0.94% rate of stroke or transient ischemic attack, 1.3% rate of cardiac tamponade, and a 0.04% rate of atrial-esophageal fistula.

Summary

Catheter ablation is a reasonable alternative to antiarrhythmic drug therapy in treating patients with symptomatic AF.^{2,42} Ablation in experienced centers may be performed as first-line treatment in symptomatic patients with paroxysmal AF.^{2,42}

Cardioversion

Cardioversion refers to the acute termination of sustained AF using direct current shock or antiarrhythmic drugs. Direct current cardioversion results in sinus rhythm immediately, whereas antiarrhythmic drugs take variable amounts of time to terminate AF. In situations in which urgent cardioversion is needed, the direct current approach is preferred. Cardioversion is performed in patients in whom restoration of sinus rhythm is considered a necessary or desired outcome.

Direct Current Cardioversion

A direct current shock synchronized to the QRS complex is delivered externally through electrode pads placed on the chest. Because shocks on the T waves can induce ventricular fibrillation, synchronization should be obtained by selecting an electrocardiogram lead that has a prominent QRS without sensing of T waves. Adhesive gel electrode pads may be placed anteriorly over the sternum (with the upper edge at the sternal angle) and posteriorly (just to the left of the spine) to maximize the atrial tissue in the path of the

direct current shock.⁵⁷ Alternate pad positions, such as right anterior-lateral configuration and applying local pressure on 1 or both pads for better contact, may improve efficacy in some patients.

Biphasic waveforms improve defibrillation efficacy at all energy settings compared with monophasic shocks.^{58,59} Ibutilide pretreatment has been shown to improve the efficacy of direct current cardioversion of AF.⁶⁰ An initial high-energy shock (≥ 200 J) is generally recommended because it may avoid the need for repeat shocks and prolonged sedation.⁶¹ Complications associated with direct current cardioversion include risks related to general anesthesia, induction of ventricular fibrillation by shock on T wave, thromboembolic events, and postcardioversion arrhythmias.

Pharmacological Cardioversion

Cardioversion with class Ic (flecainide, propafenone) and class III (ibutilide, dofetilide) antiarrhythmic agents are less effective than direct current cardioversion.² Pharmacological cardioversion is advantageous in avoiding the need for anesthesia and shock, but there is potential for proarrhythmia related to the drugs used. A single oral loading dose of propafenone (450-600 mg) or flecainide (200-300 mg) can be useful to convert recent-onset AF.²

A pill in the pocket approach to achieve out of hospital conversion of AF (using flecainide or propafenone) appeared to be safe and effective in 1 study,⁶² but should be used only after it is observed to be safe in a monitored setting. Because propafenone and flecainide can convert AF to slow atrial flutter resulting in 1:1 atrioventricular nodal conduction and very rapid ventricular rates, an atrioventricular nodal blocking agent should be administered concomitantly.² Oral dofetilide and intravenous ibutilide are always administered in the hospital due to risk of QT prolongation and torsade de pointes ventricular tachycardia.

Role of Anticoagulation

Conversion of AF to sinus rhythm is associated with an increased risk of stroke not only at the time of the event but also for the ensuing weeks.² Patients may be at continued risk of left atrial thrombus formation and stroke during this period; therefore, anticoagulation is recommended for at least 3 weeks before and 4 weeks after cardioversion. Patients at low overall stroke risk and who have AF that has been present for less than 48 hours can receive cardioversion without prior anticoagulation.² However, there are no randomized clinical trial data to support this, and although rare, systemic emboli may occur in this situation.⁶³

Furthermore, it is often not possible to know precisely when AF started, and if there is uncertainty, the episode should be considered as being present for longer than 48 hours. Anticoagulation therapy is essential when AF duration is longer than 48 hours. Two strategies of anticoagulation are available.¹ The first is warfarin (with an international normalized ratio of ≥ 2.0) for 3 weeks before and 4 weeks after cardioversion.² The second is transesophageal echocardiography and combination treatment with an anticoagulant using heparin, enoxaparin, or 1 of the newer oral non-vitamin K antagonists immediately before cardioversion followed by warfarin or a non-vitamin K antagonist for 4 weeks.² In patients without risk factors for stroke, anticoagulation can be discontinued 4 weeks after cardioversion. If the patient has risk factors for stroke, long-term anticoagulation should be continued after cardioversion.²

Rate Control Treatment Strategy

Pharmacological Approaches

In general, the pharmacological agents fit into 4 categories: β -adrenergic blocking drugs, non-dihydropyridine calcium channel antagonists (Table 2), digitalis glycosides, and primary antiarrhythmic drugs, most notably amiodarone. All of these agents act by slowing conduction over the atrioventricular node. The specific choice of agent depends on the clinical circumstances and patient comorbidities.

β -Adrenergic Blockers

β -Adrenergic blocking agents are the most commonly used drugs to control the ventricular rate during AF.⁶⁴ By reducing sympathetic tone, conduction over the atrioventricular node is slowed and atrioventricular nodal refractoriness is increased. Multiple agents are available and there are few data comparing one agent with another. In a patient with an acute situation, metoprolol, propranolol, and esmolol can be administered intravenously; however, hypotension and bradycardia are important adverse effects.

β -Blockers are the preferred drugs for rate control during AF in patients with coronary artery disease, especially in those who have had a myocardial infarction, and in patients with congestive heart failure.^{2,65} A recent meta-analysis showed no survival benefit of β -blockers in patients with AF and heart failure.⁶⁶ However, there was also no harm compared with placebo. Thus, in patients with heart failure and depressed left ventricular function, β -blockers are preferred over verapamil or diltiazem.² β -Blockers should be used cautiously in patients with chronic obstructive pulmonary disease and a history of bronchospasm.

Calcium Antagonists

The non-dihydropyridine calcium channel blockers verapamil and diltiazem have direct effects in slowing atrioventricular node conduction and both are available in intravenous and oral forms (Table 2). For the acute control of the ventricular response during AF, intravenous diltiazem is commonly used and is administered with a loading bolus followed by a titratable infusion. Calcium antagonists should generally be avoided in patients with congestive heart failure and left ventricular dysfunction due to their negative inotropic effects; however, use of these drugs may be reasonable in patients with AF and heart failure with preserved left ventricular ejection fraction.^{2,65} For patients with chronic obstructive pulmonary disease and asthma, non-dihydropyridine calcium channel blockers are first-line therapy. Caution should be used in older patients who may be more prone to adverse effects, including constipation and leg edema. Intravenous diltiazem and verapamil are contraindicated in patients with Wolff-Parkinson-White syndrome and preexcited AF.²

Digoxin

Digoxin acts indirectly on the atrioventricular node by enhancing parasympathetic tone. As such, it may be effective in slowing the ventricular rate during AF in the patient at rest. However, the ability of digoxin to slow the ventricular rate is less during states of exertion when there is vagal withdrawal and enhanced sympathetic tone. It is often used as a combination therapy with a β -blocker or calcium channel antagonist^{2,65} because the effects on slowing the

ventricular rate can be synergistic. In particular, the combination of carvedilol and digoxin can be useful in patients with AF and a reduced left ventricular ejection fraction.⁶⁷

It should be noted that a recent study from the US Department of Veterans Affairs⁶⁸ documented increased mortality in patients with AF who were treated with digoxin compared with patients who did not receive digoxin. This retrospective and nonrandomized study raises important concerns regarding the use of this drug. β -Blockers and non-dihydropyridine calcium channel blockers have a class I recommendation, whereas the use of digoxin received no recommendation.² Prospective studies will likely be needed to better define the role of digoxin in patients with AF.

Antiarrhythmic Drugs

Amiodarone is an antiarrhythmic agent with multiple mechanisms of action. In addition to its class III antiarrhythmic activity, it also exhibits β -adrenergic and calcium channel blockade. Consequently, it can be useful to control the ventricular rate during atrial fibrillation. Intravenous amiodarone should not be used in patients with AF and ventricular preexcitation. Although not common, amiodarone use can result in the cardioversion of AF to sinus rhythm, and thus full anticoagulation is important to minimize the risk of stroke. Amiodarone has multiple long-term toxic effects and should not be used unless other rate control measures are not effective, not tolerated, or contraindicated.^{1,2}

Nonpharmacological Approaches

Atrioventricular junctional ablation and placement of a pacemaker is an effective strategy to control the ventricular rate during AF (ablate and pace strategy).² It is most often useful in patients who are refractory to pharmacological approaches to rate control and who are not considered candidates for a rhythm control strategy. By slowing and regularizing the rate, symptoms can significantly improve. In a meta-analysis of 21 studies, Wood et al⁶⁹ reported that quality of life, exercise duration, left ventricular ejection fraction, and health care use all significantly improved with the use of this strategy. Ideally, after atrioventricular junction ablation, patients will have a junctional escape rhythm.

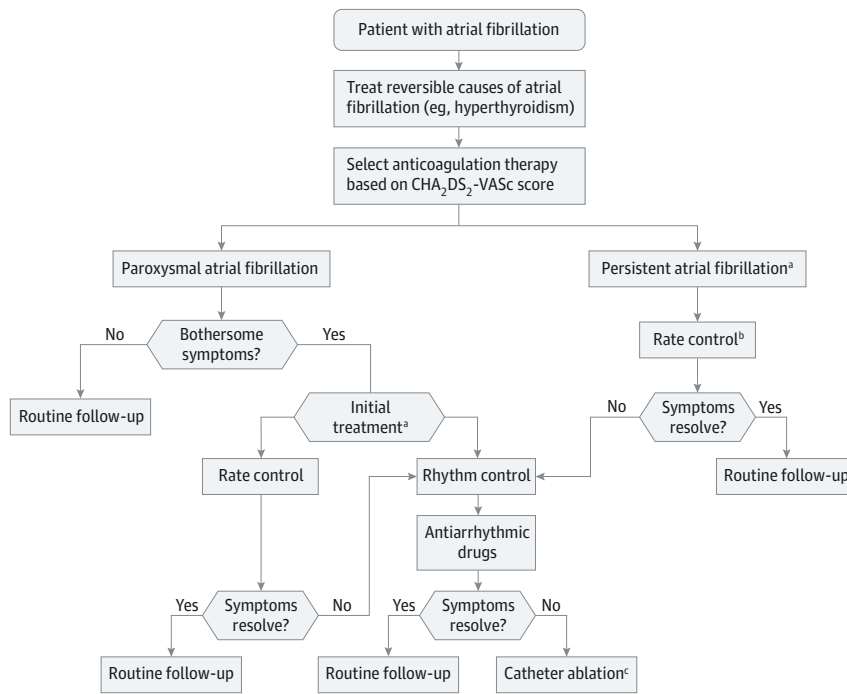
However, this is inconsistent and many patients become dependent on a pacemaker. An important potential downside to this approach is the development of right-ventricular pacing-induced cardiomyopathy.^{2,70} Some investigators have advocated the use of biventricular pacing in an ablate and pace strategy, especially when the baseline left ventricular ejection fraction is reduced. Brignole et al⁷¹ reported that the incidence of death from heart failure, hospitalization due to heart failure, and worsening heart failure occurred less often in patients with cardiac resynchronization (biventricular pacing) compared with only right ventricular pacing after atrioventricular junctional ablation.

An upgrade to a biventricular device should be considered in patients who develop pacing-induced cardiomyopathy. In addition, there appears to be a minimally increased incidence of sudden cardiac death and torsade de pointes ventricular tachycardia after atrioventricular junctional ablation, the mechanism of which is not clear.⁷²

Assessment and Target Heart Rates

The principal goals of a rate control strategy are to improve symptoms and prevent the development of tachycardia-induced cardi-

Figure 4. Proposed Treatment Algorithm for Paroxysmal and Persistent Atrial Fibrillation



CHA₂DS₂-VASc scoring system: components include congestive heart failure, hypertension, age of 75 years or older, diabetes, stroke or transient ischemic attack, vascular disease, age of 65 to 74 years, and female sex.

^a The choice of rate control or rhythm control as initial treatment is a shared decision between the patient and physician based on many factors.

^b Use of drugs to slow the ventricular rate during atrial fibrillation (see Table 2).

^c Use of intracardiac catheters to eliminate atrial triggers or modify atrial substrate.

omyopathy. The latter may occur when the ventricular rate is greater than about 120 beats/min for a prolonged duration and may be completely reversible when adequate heart rate control is achieved.^{4,5,65,73} However, the degree of rate slowing necessary to prevent or reverse this complication is uncertain. Historically, optimal heart rate control during AF has been suggested as a resting rate of less than 80 beats/min and a heart rate of less than 110 beats/min during a 6-minute walk.³⁸

Importantly, an isolated resting heart rate of less than 80 beats/min in the office setting is not sufficient evidence of adequate rate control. It is important to measure heart rate during activity over the course of the day (eg, by using a 24-hour ambulatory monitor). For an assessment of the heart rate during moderate exertion, either a formal 6-minute walk test or a brief walk in the office hallway can be sufficient.

The AFFIRM investigators²⁶ used a rate control target of less than 80 beats/min at rest, and defined adequate heart control as less than 110 beats/min during a 6-minute walk test or a mean heart rate of less than 100 beats/min on a 24-hour Holter monitor. In contrast, the RACE investigators²⁷ used a more lenient approach to rate control, targeting only a resting rate of less than 100 beats/min. In a subsequent retrospective analysis of both trials, Van Gelder et al⁷⁴ concluded that although the mean heart rate was lower in the AFFIRM trial (76.1 beats/min vs 83.4 beats/min in the RACE trial), there were no important differences between a lenient and stricter rate control strategy.

Subsequently, the RACE II investigators⁷⁵ prospectively addressed this issue and found that a lenient rate control strategy was as effective as a strict rate control strategy. After an analysis of all these data, the current guideline² from the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society stated a heart rate control strategy targeting a resting heart

rate of less than 80 beats/min for the symptomatic management of AF was a class IIa recommendation, and a lenient rate control strategy with a resting heart rate of less than 110 beats/min was a class IIb recommendation when patients are asymptomatic and left ventricular systolic function is preserved.

Summary

Rate control is important to minimize symptoms during AF and to prevent tachycardia-mediated cardiomyopathy. β-Blockers and non-dihydropyridine calcium channel blockers are the preferred agents and the selection of a specific drug depends on patient characteristics.^{2,65} Effectiveness of therapy should be evaluated at rest and during activity.

Figure 4 shows an overall possible approach for patients with AF. Depending upon symptoms, patients who have paroxysmal AF might require no therapy or treatment directed toward rate or rhythm control. Rhythm control typically begins with antiarrhythmic drugs; however, if drugs are ineffective, catheter ablation should be considered. Patients who present with persistent AF should have their heart rate controlled during AF. If symptoms do not resolve, a rhythm control strategy should be undertaken. Antiarrhythmic drugs are recommended as a first-line therapy. If antiarrhythmic drugs do not provide success, catheter ablation may be considered.

Conclusions

Therapy for atrial fibrillation includes prevention and modification of inciting causes and appropriate anticoagulation. Rate control is necessary for all patients. Maintenance of sinus rhythm with drugs or catheter ablation should be considered based on the individual needs of each patient.

ARTICLE INFORMATION

Author Contributions: Dr Prystowsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: Prystowsky.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: All authors.

Study supervision: Prystowsky.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Prystowsky reported receiving personal fees for serving on the board of directors for Stereotaxis; previously serving on the board of directors for CardioNet; owning stock in Stereotaxis; previously owning stock in CardioNet and Topera; receiving personal fees for serving as a consultant to Abbott, EP/Topera, CardioNet, Stereotaxis, and Medtronic; receiving institutional grant support from Boston Scientific, Medtronic, and St Jude; and holding a patent with CardioNet but not receiving royalties. Dr Padanilam reported owning stock in Topera. No other disclosures were reported.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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