Atrial Fibrillation: Beyond Rate Control

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Learning Objectives: On completion of this article, you should be able to (1) understand indications for pursuing a rhythm control approach; (2) describe the advantages and disadvantages of various antiarrhythmic drugs; and (3) identify common drug-drug interactions encountered in the primary care setting.

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Abstract

Atrial fibrillation is the most common cardiac dysrhythmia encountered in the primary care setting. Although a rate control strategy is pursued by physicians for the initial treatment of atrial fibrillation, the efficacy of a rhythm control approach is often undervalued despite offering effective treatment options. There are many pharmacological therapies available to patients, with drug choice often dictated by safety concerns (toxicities and proarrhythmic adverse effects) as well as patient characteristics and comorbidities. This article presents a simplified approach to understanding the rhythm control strategy, including the advantages and disadvantages of various antiarrhythmic drugs and common drug-drug interactions encountered in the primary care setting.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an estimated prevalence of 33.5 million individuals globally. It has reached epidemic proportions as the number of individuals affected with AF is expected to double in the next several decades because of an increasingly older population, underscoring the need for cost-effective outpatient management of AF.[1] Aside from addressing the role of thromboembolism prophylaxis when AF is detected, the primary care physician is faced with a wealth of treatment options that often fall into 2 broad overlapping categories: rate or rhythm control.

Rate control involves the use of negatively chronotropic drugs (eg, β-blockers or calcium

channel blockers) to reduce the rapid ventricular rate frequently found in AF. Conversely, rhythm control involves the use of pharmacological, electrical, or surgical cardioversion to convert AF to normal sinus rhythm. The aim of these options is to reduce symptoms, including dizziness, shortness of breath, and palpitations, as well as prevent complications, such as heart failure. Some studies have also suggested that catheter ablation (CA) of AF is associated with a decreased risk of stroke and mortality in patients with a high CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-75 years, sex category [female]).[2]

Most commonly, a rate control strategy is pursued by physicians for the initial treatment of AF. Rhythm control is typically initiated when adequate rate control is not achieved or when patients have a high degree of symptoms despite achieving rate control. However, the efficacy of a rhythm control approach is often undervalued despite offering effective treatment options. It is important to understand the rhythm control approach, who the "ideal" patient is for this approach, and how to manage these patients, especially in the primary care setting. Additionally, modifiable risk factor management has emerged as an important pillar in AF treatment. Studies have found that improved management of both established and independent risk factors, including obesity, sleep apnea, hypertension, diabetes, excessive alcohol consumption, and a sedentary lifestyle, likely reduce AF burden. Furthermore, eating heart-healthy foods and incorporating dietary modifications may also reduce the risk of development of AF.[3]

PHARMACOLOGICAL THERAPY FOR AF

There are many pharmacological therapies available to patients, and drug choice is often dictated by safety concerns (toxicities and proarrhythmic adverse effects) as well as patient characteristics and comorbidities. For example, a patient with severe left ventricular (LV) hypertrophy, heart failure, and coronary artery disease would have more restricted options in terms of antiarrhythmic drug (AAD) therapy than a younger patient without these comorbidities. Furthermore, the presence of hepatic or renal dysfunction also plays an important role in drug consideration.

UPSTREAM THERAPY

Although this article largely focuses on antiarrhythmic therapy, it is worthwhile mentioning upstream therapies. Upstream therapy refers to the use of non-AADs that modify the atrial substrate— or target-specific mechanisms to prevent the occurrence or recurrence of AF. These drugs include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, or omega-3 polyunsaturated fatty acids. Animal studies have provided reasonable data on the benefit of upstream therapy, but translation to humans has been limited and largely insufficient to suggest widespread use of these agents for AF prevention.[4-6]

AAD THERAPY

Historically, AADs have been classified according to the Vaughan-Williams classification scheme by their mechanism of action: sodium channel blockers (class I), β-blockers (class II), potassium channel blockers (class III), and calcium channel blockers (class IV). Furthermore, class I drugs are subdivided into class IA, class IB, and class IC on the basis of drug affinity for sodium channels. After deciding on a rhythm approach, it is important to realize there is no "one size fits all" choice, and the selection of the AAD will depend on several factors (Figure 1). The following AADs are available for treatment of AF.

Class IA Agents

Quinidine, procainamide, and disopyramide are class IA antiarrhythmic agents. Historically, quinidine was one of the most commonly used antiarrhythmics for AF. Although effective in maintaining sinus rhythm, it has been surpassed by other AADs given its unfavorable safety profile, in particular the increased mortality associated with its use in patients with heart failure.[7] Although it is especially useful in the treatment of Brugada syndrome, worldwide supplies are unfortunately limited.[8,9] Disopyramide can also be used for AF rhythm control, but its use is rare. Like quinidine, disopyramide should be avoided in those with heart failure because of its negative inotropic effect. However, disopyramide in combination with

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β-blockers, diltiazem, or verapamil has been found to be effective in minimizing the frequency of AF in patients with hypertrophic cardiomyopathy. It can also produce strong anticholinergic effects, and because of the frequency with which it can induce urinary retention, its use is limited in men, especially those with prostatic hyperplasia. Procainamide is a drug rarely used for management of AF in the United States given its adverse effect profile, including a lupuslike syndrome and potentially severe bone marrow toxicity. However, the intravenous form is a first-line therapy for management of emergency department patients with symptomatic AF in the Ottawa Aggressive Protocol.[10] Among these patients, the use of intravenous procainamide was associated with a 60% conversion to normal sinus rhythm, decreased duration of hospital stay, and fewer hospital admissions.

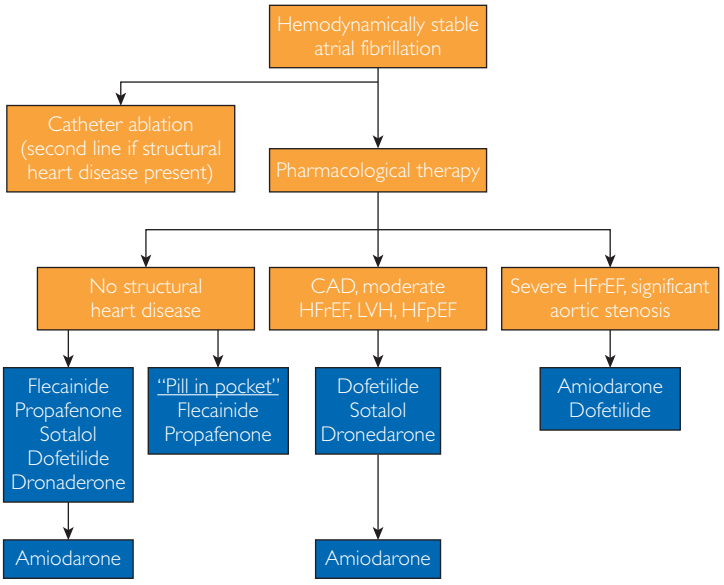

FIGURE 1. Flow diagram for initiation of rhythm or catheter ablation in symptomatic patients with atrial fibrillation. Catheter ablation as a first-line therapy is typically for patients with heart failure and tachycardiomyopathy. Catheter ablation may also be performed if pharmacotherapy is initiated but fails. CAD = coronary artery disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVH = left ventricular hypertrophy.

Class IB Agents

Lidocaine, phenytoin, and mexiletine are generally used for treatment of ventricular tachyarrhythmias and are rarely used for supraventricular tachyarrhythmias. Thus, they are not prescribed as rhythm options for AF.

Class IC Agents

Flecainide and propafenone are effective agents for rhythm control in AF but have certain noteworthy limitations of which clinicians should be aware. These drugs should be avoided in patients with known conduction system disease and in patients with ischemic heart disease because previous research has found increased mortality in patients with previous acute coronary syndrome (Cardiac Arrhythmia Suppression Trial).[11,12] Additionally, both of these agents are negative inotropes and should be avoided in patients with LV dysfunction. Thus, class IC agents are most appropriate for patients with paroxysmal AF who have no known structural heart disease and have a history of good compliance.

A "pill in the pocket" strategy involving the use of class IC agents may be used for patients who have infrequent episodes of paroxysmal AF. This approach involves self-administration of a single dose of oral propafenone (450-600 mg) or oral flecainide (200-300 mg) to restore sinus rhythm. In this approach, the patient should take a β-blocker or diltiazem (if they are not receiving long-term atrioventricular nodal blocker therapy already) roughly 30 minutes before administration of flecainide or propafenone to prevent a rapid ventricular rate if conversion to atrial flutter were to occur. Importantly, the first dose of a class IC agent utilized for this strategy should be administered under monitored conditions.

Class II Agents

By antagonizing β-adrenergic receptors, class II agents slow the sinus rhythm and atrioventricular nodal conduction. Thus, these agents can be useful in the treatment of arrhythmias such as sinus tachycardia, atrioventricular nodal reentry tachycardia, and AF.

Class III Agents

These agents act via potassium channel blockade and lengthen the action potential. Thus, the QT interval must be monitored in these patients, and these drugs are contraindicated in patients with a baseline corrected QT interval greater than 500 ms. Class III agents are more often used in patients who have

persistent AF, have structural heart disease (coronary artery disease or mild LV dysfunction), and have a creatinine clearance greater than 20 mL/min because this class of drugs is renally cleared. Sotalol and dofetilide have limited efficacy for conversion of AF to sinus rhythm but may be used for recurrent AF prevention. Studies have found the efficacy in maintaining sinus rhythm using sotalol and dofetilide to be 30% to 50% and 58%, respectively, at 1 year after drug initiation.[13] For initiation or dose escalation of sotalol and dofetilide, patients must be in an inpatient setting with electrocardiographic monitoring, ideally under the care of an electrophysiologist given the risk of excessive QT prolongation that can cause torsades de pointes. Follow-up visits should include electrocardiography to measure the QT interval and ensure there are no electrolyte abnormalities of serum potassium and magnesium.[11]

Although typically used as a second-line agent because of numerous extracardiac adverse effects, amiodarone continues to have widespread use and is currently the most widely prescribed antiarrhythmic medication in the United States, representing 45% of all prescribed antiarrhythmics, because of its high efficacy in the management of both supraventricular and ventricular arrhythmias.[14] Amiodarone, which has class IC and III properties, is effective in patients with severe heart failure, poor renal function, and failure of other agents. However, amiodarone carries a black box warning and thus should only be used in patients with life-threatening arrhythmias because of several potentially fatal toxicities, the most important of which is pulmonary toxicity (seen in 10%-17% of patients).[14]

Dronedarone is a structural analogue of amiodarone but does not have the iodine moieties seen in amiodarone. Although it has fewer extracardiac adverse effects compared with amiodarone, it is also less efficacious.[15] Given that prior studies have found it increases mortality in patients with depressed ejection fraction,[16] it is contraindicated in patients with New York Heart Association class III or IV heart failure or those who have had an episode of decompensated heart failure in the preceding 4 weeks.[11]

Class IV Agents

This class includes the calcium channel blockers verapamil and diltiazem that selectively block conduction through the atrioventricular node. These agents are typically used in a rate control strategy as opposed to a rhythm control approach because of their negative chronotropic effect.

DRUG INTERACTIONS

When patients are taking antiarrhythmics, it is important that clinicians consider drug-drug interactions, which could both alter the efficacy of the drug and potentially cause toxicity. The Table highlights drugs commonly encountered in the primary care setting that could interact with antiarrhythmics.[17]

CATHETER ABLATION

Catheter ablation is a procedure that uses radiofrequency energy to form nonconducting scar tissue in the heart that is triggering AF. Most commonly, the responsible area is around the pulmonary veins.[18] Thus, electrophysiologists seek to form complete linear lesions around the circumference of the pulmonary veins with a goal of forming a nonconducting scar around the pulmonary vein, thereby blocking electrical signals from exiting and entering the veins (Figure 2).[19] This procedure results in isolation of the pulmonary vein from the left atrium, preventing initiation and propagation of AF.

Indications for CA

Shared decision making between the physician and patient is an important element before pursuing CA. The role of CA as a first-line therapy, before a trial of a class I or III antiarrhythmic agent, is an appropriate indication in patients with symptomatic paroxysmal or persistent AF.[20] Selected asymptomatic patients with paroxysmal or persistent AF may also be candidates for AF ablation after a discussion of the risks and benefits with an experienced electrophysiologist.[20] Most studies assessing the efficacy of CA enrolled patients who were young, healthy, and had symptomatic paroxysmal AF refractory to one or more AADs. Thus, the role of CA is less well established for other patient groups, specifically elderly patients, those with severe heart failure, and those with long-standing AF. Nevertheless, the indications for AF ablation are not altered by the presence of heart failure or elderly age (>70 years).

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TABLE. Interactions of Antiarrhythmic and Commonly Prescribed Drugs[17]

	Class IA			Class IC		Class III		Class IC & III
Variable	Quinidine	Procainamide	Disopyramide	Flecainide	Propafenone	Sotalol	Dofetilide	Amiodarone
Cardiovascular								
Warfarin	Level C	Level A	Level A	Level A	Level C	Level A	Level A	Level D
Lisinopril	Level A	Level A	Level B	Level A	Level A	Level C	Level A	Level C
Amlodipine	Level C	Level A	Level A	Level A	Level A	Level C	Level C	Level C
Hydrochlorothiazide	Level C	Level A	Level C	Level A	Level A	Level C	Level X	Level C
Furosemide	Level A	Level A	Level A	Level A	Level A	Level C	Level C	Level C
Spironolactone	Level C	Level A	Level A	Level A	Level A	Level C	Level A	Level C
Losartan	Level A	Level A	Level A	Level A	Level A	Level C	Level A	Level C
Metoprolol	Level D	Level A	Level C	Level A	Level C	Level C	Level A	Level C
Carvedilol	Level D	Level A	Level C	Level A	Level C	Level C	Level A	Level C
Labetalol	Level A	Level A	Level C	Level A	Level C	Level C	Level A	Level C
Atorvastatin	Level C	Level A	Level A	Level A	Level C	Level A	Level C	Level C
Rosuvastatin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level B
Pravastatin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level A
Simvastatin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level D
Pulmonary								
Albuterol	Level D	Level D	Level D	Level C	Level C	Level X	Level D	Level D
Ipratropium (nasal)	Level C	Level A	Level C	Level A	Level A	Level A	Level A	Level A
Tiotropium	Level X	Level A	Level X	Level A	Level A	Level A	Level A	Level A
Psychiatric								
Fluoxetine	Level X	Level X	Level X	Level X	Level X	Level X	Level X	Level X
Escitalopram	Level X	Level X	Level X	Level D	Level D	Level X	Level X	Level X
Paroxetine	Level D	Level D	Level D	Level D	Level C	Level D	Level D	Level D
Sertraline	Level D	Level D	Level D	Level C	Level C	Level D	Level D	Level D
Fluvoxamine	Level C	Level A	Level C	Level A	Level C	Level A	Level C	Level A
Wellbutrin	Level A	Level C	Level A	Level C	Level C	Level A	Level A	Level A
Endocrine								
Insulin	Level A	Level A	Level C	Level A	Level A	Level C	Level A	Level A
Metformin	Level A	Level A	Level C	Level A	Level A	Level A	Level C	Level A
Levothyroxine	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level C
Neurologic								
Pregabalin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level A
Gabapentin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level A
Lisdexamfetamine	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level A
Opioid analgesics	Level C	Level A	Level C	Level A	Level A	Level A	Level A	Level A

Key:
- Level A: No known drug interaction.
- Level B: No action needed; the agents may interact but there is little to no evidence of clinical concern.
- Level C: Monitor therapy; appropriate monitoring therapy should be implemented; possible dose adjustment.
- Level D: Consider therapy modification; aggressive monitoring, possible dose change, or choose alternative agents.
- Level X: Avoid combination.

Outcomes and Complications of CA for AF

To date, few studies have independently assessed the effect of CA on long-term outcomes. Although some studies have reported a low thromboembolic risk in patients who discontinued oral anticoagulation after successful AF ablation, only a minority of patients included in the studies had a CHA_2DS_2-VASc score of 2 or more. A recent propensity-matched retrospective cohort documented that CA is associated with a decreased risk of stroke or transient ischemic attack and mortality among patients with a high CHA_2DS_2-VASc score.[2] Two prior randomized controlled trials compared CA to AADs as a first-line therapy for rhythm control.[21,22] Although patients who underwent CA had more complications requiring

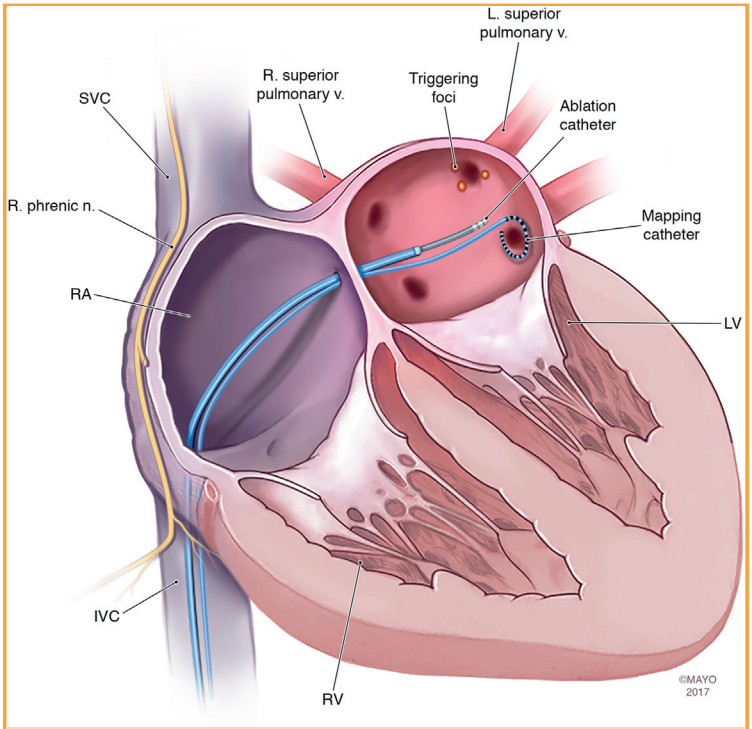

FIGURE 2. Catheter ablation of triggering foci around the pulmonic veins. IVC = inferior vena cava; L. = left; LV = left ventricle; n. = nerve; R. = right; RA = right atrium; RV = right ventricle; SVC = superior vena cava; v. = vein.

intervention compared with patients who were given AADs, more patients who underwent CA were free from AF at 24-month follow-up.

An individual's rhythm outcome after CA is difficult to predict, and patients require on average 1.5 CA procedures to achieve symptomatic relief.[23] The highest success rates have been found in younger patients with paroxysmal AF in the absence of structural heart disease. Maintenance of sinus rhythm without major symptomatic recurrence of AF after CA has been reported to be 70% in those with paroxysmal AF and 50% in those with persistent AF.[24] Recurrences of AF after CA are common in the first 3 months postprocedure; for patients with an early recurrence of AF, a pharmacological rhythm approach may be pursued.[20] However, AF recurrence 3 months postablation or later could represent recovery of pulmonary vein conduction, which may be responsive to repeated ablation.[25]

About 5% to 7% of patients have severe complications after CA, and 2% to 3% have life-threatening, but manageable, complications.[26] The potential risks of a complication are similar in younger and older patients; the most common complications include:

- Death (0.1%-0.5%)
- Heart block requiring permanent pacemaker (1%-2%)
- Stroke/thromboembolism (<1%)
- Vascular complications including bleeding, infection, and hematoma (2%-4%)
- Cardiac trauma (including myocardial perforation, tamponade, and infarction) (1%-2%)

Follow-up After CA

Physicians should be aware of some potential delayed complications of CA for AF during follow-up of the patient. Pulmonary vein stenosis is a feared complication in which patients can present with a wide range of symptoms, with the most common being dyspnea (67%), cough (45%), fatigue (45%), and decreased exercise tolerance (45%).[27] Another potential complication that can cause unexplained dyspnea is phrenic nerve injury.[27] This injury can occur when ablating the right superior pulmonary vein (close to the right phrenic nerve) or within the left atrial appendage (close to the left phrenic nerve). Atrial esophageal fistula is a rare but devastating complication. It usually occurs 2 to 4 weeks after the procedure, and patients may present with neurologic deficits, fever, chest pain, hematemesis, and altered mental status.[28] Lastly, there is growing recognition of upper gastrointestinal tract motility issues including gastroesophageal reflux, pyloric spasm, and gastric hypomotility as a result of AF ablation, with the proposed mechanism involving damage to the vagus nerve.[29] Although asymptomatic and symptomatic AF recurrences postablation are common, the likelihood of having an asymptomatic AF recurrence compared with a symptomatic AF recurrence is considerably increased postablation. Thus, primary care physicians should be cautious of discontinuing thromboembolism prophylaxis even if patients are asymptomatic postablation. Patients should ideally be seen for follow-up at a minimum of 3 months postablation by a cardiologist and on annual basis thereafter by some type of physician.[20]

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Periablation Anticoagulation

Patients with AF are at increased risk of thromboembolism during, immediately after, and several months after their ablation.[30] Thus, many physicians initiate therapeutic anticoagulation at least 3 weeks before ablation in patients with a CHA_2DS_2-VASc score of 2 or greater. Several clinical trials have found that AF ablation can be safely performed on patients receiving uninterrupted warfarin, dabigatran, or rivaroxiban. Because of reduced atrial contraction, endothelial damage, and a thrombotic state postablation, patients should receive warfarin or a novel oral anticoagulant for at least 2 months postablation regardless of their CHA_2DS_2-VASc score or rhythm status.[20]

SURGICAL AND HYBRID APPROACH TO AF MANAGEMENT

The Cox maze procedure is based on the existence of numerous connected electrical pathways in atrial substrate that propagate and sustain AF. The goal of the maze procedure is to create scar tissue to form a pathway from the sinoatrial node to the atrioventricular node and also interrupt aberrant electrical depolarization, thereby terminating AF. Although typically highly effective at terminating AF, a stand-alone operation for correction of AF is performed infrequently because of the highly invasive nature of a surgical approach. Thus, surgical ablation for AF is typically performed in patients undergoing concomitant cardiac surgery.

Previous work found that 93% of patients who underwent the Cox maze IV procedure had sustained sinus rhythm at 6 months postprocedure while receiving AAD therapy.[31] Atrial fibrillation surgical ablation is reasonable for selected patients with AF undergoing cardiac surgery for other indications (American College of Cardiology/American Heart Association class IIa recommendation), but a stand-alone AF surgical ablation may be reasonable for selected patients who are highly symptomatic and are not well managed with other approaches (American College of Cardiology/American Heart Association class IIb recommendation).[11]

CONCLUSION

This concise review provides an approach to the management of AF with a focus on rhythm control. With this review, we believe physicians will be better able to understand the rhythm control approach and to identify which patients and what pharmacological or interventional approach is most appropriate.

Abbreviations and Acronyms: **AF** = atrial fibrillation; **CA** = catheter ablation; **AAD** = antiarrhythmic drug; **LV** = left ventricle

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