

Clinical Management of Atrial Fibrillation

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- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

Karen Majorowicz, RN, is currently employed in the Cardiac Intermediate Care Unit at Shands Healthcare at the University of Florida, Gainesville. She received her Master's in Medical-Surgical Nursing in 1978 from the University of Maryland. Karen has created numerous instructional manuals on Medicare and has conducted educational programs on cardiovascular assessment.

Faculty Disclosure

Contributing faculty, Karen Majorowicz, RN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners

John M. Leonard, MD

Jane C. Norman, RN, MSN, CNE, PhD

Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, nurses, and other healthcare professionals working in an adult healthcare setting, where they are likely to encounter patients who are (or should be) receiving medical intervention for control of atrial fibrillation.

Accreditations & Approvals



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NetCE designates this continuing education activity for 10 ANCC contact hours.



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Disclosure Statement

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Course Objective

The purpose of this course is to provide a basic review of current treatment options for the management of atrial fibrillation and indications for use, risks, and criteria for evaluating the treatment's efficacy.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe cardiac conduction and the components of an ECG waveform.
2. Use your knowledge of the pathophysiology of atrial fibrillation, including key defining characteristics, to differentiate it from other arrhythmias and predict impact on normal functioning.
3. Outline common cardiac and noncardiac causes of atrial fibrillation.
4. List key clinical data, including subjective symptoms, past medical history, physical assessment findings, and diagnostic/laboratory tests, important to obtain when assessing a patient with atrial fibrillation.
5. Identify key components that should be considered in the development of the medical plan of care, including the issue of generic drug substitution.
6. Compare and contrast antiarrhythmic medications appropriate to use for acute and chronic rate control for patients with atrial fibrillation.
7. Outline the use of pharmacologic therapy in the restoration of normal sinus rhythm, including indications for use and procedure for administration.
8. Describe electrical cardioversion, including indications and pre- and postprocedure care.
9. Discuss antiarrhythmic medications that may be used to maintain normal sinus rhythm in a patient following successful spontaneous, electrical, or pharmacologic cardioversion.
10. Select appropriate pharmacologic measures that may be used to reduce risk of thromboembolic events in persons with atrial fibrillation.
11. Discuss the use of radiofrequency ablation of the atrioventricular (AV) node in the clinical management of atrial fibrillation.
12. Describe the causes and recommended management of atrial fibrillation in adult patients following coronary artery bypass graft surgery and in patients with Wolff-Parkinson-White syndrome.
13. Using simulated case study data, develop a best practice strategy for the clinical management of atrial fibrillation.



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Atrial fibrillation is one of the most commonly sustained arrhythmias seen in medical practice and affects an estimated 2.7 to 6.1 million people in the United States [1; 2]. Consider the following statistics [3; 4; 5; 6; 7; 8; 9]:

- Increasing age is a major risk factor for the development of atrial fibrillation. As the American population continues to age, increasing numbers of elderly individuals will require medical care for the management of atrial fibrillation.
- Atrial fibrillation is associated with increased morbidity and mortality, especially in the elderly population.
- Elderly individuals who develop atrial fibrillation and also have a history of congestive heart failure, myocardial infarction, and/or left ventricular dysfunction are at increased risk for poor outcomes and complications.
- Atrial fibrillation is a major independent risk factor for thromboembolic cerebrovascular accidents (CVAs). CVAs may result in death or serious disability.
- Hospital stays for management of atrial fibrillation are longer than hospital stays for the treatment of other arrhythmias.

The clinical management of atrial fibrillation presents a complex challenge to the clinician. A wide variety of pharmacologic and nonpharmacologic therapies is available for the treatment of atrial fibrillation. Therapy should be individualized to each specific patient. Carefully assess the patient's status and past medical history with an emphasis on the patient's specific pattern of atrial fibrillation, including its onset, duration, and precipitating factors, the symptoms experienced during atrial fibrillation, the impact of the arrhythmia on the patient's activities of daily living, risk factors for atrial fibrillation, findings from laboratory and diagnostic tests, and history of cardiovascular disease.

It is important to match patient assessment data with an appropriate medical management plan. Common goals seen in the management of atrial fibrillation include rate control, restoration of normal sinus rhythm, maintenance of normal sinus rhythm, and prevention of thromboembolic complications.

The selection of appropriate pharmacologic and nonpharmacologic therapies for the patient should be based on the identified goal(s) and patient assessment data. A wide range of antiarrhythmic medications is available with varying effects on the electrical conduction system in the heart. Some are contraindicated in the presence of concurrent illnesses, such as hypertension and asthma. Non-pharmacologic therapies include direct current (electrical) cardioversion, radiofrequency ablation, and atrial or dual chamber pacemakers.

Regular follow-up is required to monitor the effectiveness of the therapy in meeting the identified medical goals. Evaluation criteria include a rate that is controlled within desired parameters, increased ability to perform activities of daily living, reduction in severity of attacks of atrial fibrillation, absence of undesired side effects of prescribed antiarrhythmic medications, and absence of any thromboembolic complications.

A BRIEF REVIEW OF NORMAL ELECTRICAL CONDUCTION

In the normal heart, the heart beat is initiated by the sinoatrial (SA) node. From the SA node, the electrical impulse travels through both the right and left atria, causing depolarization of the atria. Atrial depolarization is followed by atrial contraction and atrial repolarization. The electrical impulse travels from the atria to the atrioventricular (AV) node located in the inferior wall of the right atrium. The speed of conduction slows in the AV node to allow time for the atria to depolarize, contract, and complete ventricular filling. From the AV node, the electrical impulse travels through the bundle of His located in the septum of the heart. The bundle of His divides into the right and left bundle branches.

These branches divide further into the smaller fibers of the Purkinje system. Electrical conduction through the His-Purkinje system is rapid, causing rapid depolarization of both the right and left ventricles. Depolarization of the ventricular cells spreads from the apex of each ventricle to the base, and moves from the endocardium to the epicardium. Ventricular depolarization is followed by ventricular contraction and ventricular repolarization [10; 11; 12].

CELLULAR EVENTS IN NORMAL CARDIAC CONDUCTION (THE ACTION POTENTIAL)

When an electrical impulse stimulates a cardiac cell, a series of events is initiated that causes the cell to depolarize and repolarize. This generates an action potential that allows the electrical impulse to propagate, ultimately resulting in the contraction of the cells of the myocardium. The basic events that occur during the formation of the action potential are as follows:

- When an electrical impulse stimulates a cardiac cell, the cell depolarizes. Positively charged sodium ions from the extracellular space flood rapidly into the intracellular space. This increases the total number of positively charged ions in the intracellular space, and the charge in the intracellular space becomes less negative. The potential or voltage in the cell increases. This is phase 0 of the development of the action potential.
- The flood of sodium ions into the intracellular space stops very quickly. It is followed by a brief and incomplete period of repolarization. This period is mediated by a temporary movement of potassium ions from the intracellular to the extracellular space. This brief period of repolarization is referred to as phase 1 of the action potential.

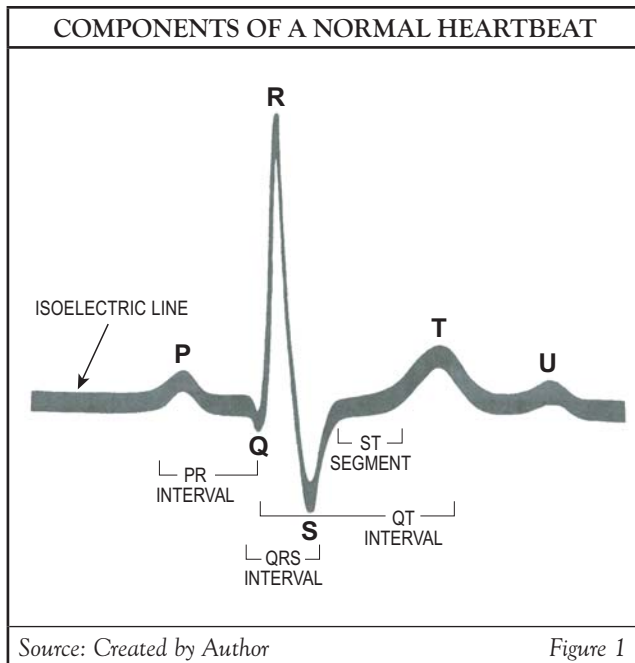
- Phase 2 of the action potential is characterized by a balance of inward and outward movement of ions. Calcium ions move slowly through select channels into the intracellular space while potassium ions move out through multiple channels into the extracellular space. This initiates a slow repolarization and creates a plateau in the action potential. Cardiac contraction is mediated by phase 2.
- In phase 3, the calcium channels close. The process of repolarization is accelerated.
- In phase 4, electrical diastole occurs. Except for the SA node, the heart rests. The SA node begins the process of initiating the next electrical impulse.

After the myocardial cell has depolarized, there is a period of time during which the cell cannot generate an action potential in response to another electrical impulse; this is referred to as the “absolute refractory period.” As the cell continues to repolarize, an “effective refractory period” occurs in which the cell can transiently depolarize in response to an electrical impulse but generally will not develop enough of an action potential to propagate the impulse to surrounding cells. As repolarization nears completion, the cell is said to be in a “relative refractory period.” In this period, a strong electrical stimulus can trigger the cell to depolarize and create another action potential [13; 14; 15].

A REVIEW OF ELECTROCARDIOGRAM WAVEFORM

The electrical events that occur in the heart are reflected in the electrocardiogram (ECG) waveform. The components of a normal beat are (**Figure 1**):

- The **P wave** represents atrial depolarization.
- The **PR interval** represents the amount of time the electrical impulse takes to travel from the SA node through the AV node. The normal PR interval is 0.12 to 0.20 seconds.



- The **QRS interval** represents the amount of time it takes the ventricles to depolarize. In normal conduction, ventricular depolarization occurs rapidly. This rapid conduction is reflected in a narrow QRS interval. The normal duration of a QRS interval is <0.10 seconds.
- The **T wave** represents ventricular repolarization.
- The **QT interval** represents the amount of time that it takes the ventricles to depolarize and repolarize; it is measured from the beginning of ventricular depolarization (i.e., the start of the QRS interval) to the end of repolarization (i.e., the end of the T wave). During the early part of the QT interval, the ventricles are completely refractory and unable to respond to another electrical impulse. During the latter part of the interval, the ventricles are only partially refractory and may respond to some impulses but not to others. The normal QT interval is <0.44 seconds.

ABNORMAL ECG WAVEFORM

When changes occur in the normal cardiac cycle, the normal ECG waveform is altered to reflect them. For example, prolonged repolarization is reflected in a prolonged QT interval. A slowing of conduction from the SA node through the AV node may be reflected in a prolonged PR interval. Abnormal conduction of the electrical impulse through the ventricles results in a QRS interval that is wider than usual or bizarre in shape. Careful analysis of the changes in a patient's ECG can provide valuable information in the diagnosis and treatment of the arrhythmia [7; 16].

ANTIARRHYTHMIC DRUGS AND CARDIAC ELECTROPHYSIOLOGY

Antiarrhythmic medications interrupt or prevent arrhythmias by altering electrical conduction in the heart. Some antiarrhythmic medications have a single mechanism of action, but many have multiple mechanisms. In general, antiarrhythmic medications may act by:

- Prolonging the normal development of the action potential
- Inhibiting or slowing the movement of sodium or calcium ions into the intracellular space
- Altering the movement of potassium ions out of the intracellular space
- Altering the speed at which the impulse is conducted through the AV node
- Prolonging ventricular repolarization and the refractory period

Because antiarrhythmic medications impact specific events in cardiac conduction, they run the risk of creating new arrhythmias or worsening existing arrhythmias. Arrhythmias caused by the administration of an antiarrhythmic medication are referred to as proarrhythmias. Proarrhythmias can range from mild to severe. Serious proarrhythmias include ventricular tachycardia, torsades de pointes, and ventricular fibrillation. We will look at the actions and properties of specific antiarrhythmic agents in more detail in later sections.

ATRIAL FIBRILLATION

PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

Atrial fibrillation is an arrhythmia characterized by rapid, disorganized electrical activity in the atria. Instead of the SA node depolarizing to initiate a heartbeat, ectopic (or abnormal) areas in the atria depolarize rapidly and irregularly, resulting in chaotic atrial activity. Because of the chaotic electrical activity, normal atrial depolarization does not occur. Patchy areas of the atria may attempt to contract, giving the atria a “quivering” appearance, but the unified contraction of both the right and left atria (needed to complete active filling of the ventricles) cannot occur. One theory suggests that the mechanism underlying atrial fibrillation is the development of multiple impulses or “wavelets” in the atria. These impulses wander around and through the atria, getting caught in a cycle that continuously circulates in the atria, triggering small, erratic areas of depolarization. In atrial fibrillation, atrial impulses may be generated at a rate as high as 300 impulses per minute. Atrial impulses bombard the AV node. However, because of its inherent characteristics, the AV node tends to limit ventricular response to the atrial stimulation. Because the AV node is less excitable than the nearby atrial or ventricular cells, it conducts impulses more slowly, and its refractory period (when it cannot respond to another electrical stimulus) is relatively prolonged.

Conduction in the AV node is also “decremental.” This means that, as the impulse is conducted through the AV node, the action potentials that are generated have less and less ability to stimulate new action potentials. In atrial fibrillation, some atrial impulses are “blocked” or lost in the AV node because the action potentials that are generated are insufficient to stimulate further electrical activity.

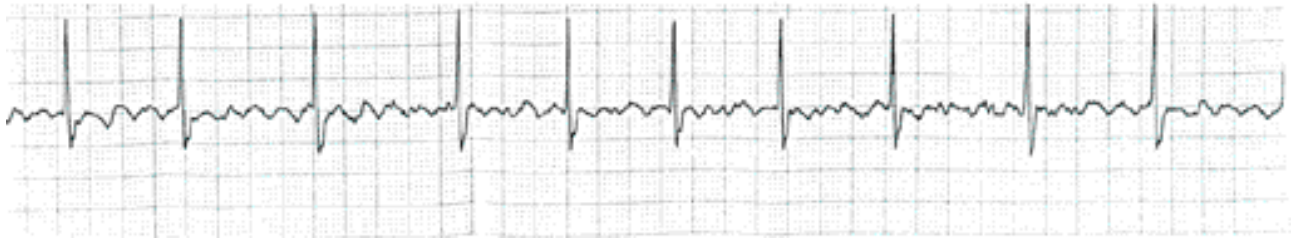
Finally, the AV node has the property of concealed conduction. An atrial impulse may enter the AV node, stimulate depolarization of initial cells in the node, and be blocked from further conduction.

Although the impulse is not sufficient to generate ventricular depolarization, it depolarizes enough cells in the AV node to create a refractory period. Subsequent impulses entering the AV node immediately following that impulse will be blocked. The AV node will be unable to accept or respond to them until repolarization has occurred. Due to the combination of slowed, decremental, and concealed conduction, the AV node can limit ventricular rate in atrial fibrillation to less than 200 beats per minute (bpm). It is important to note that these properties of the AV node create a relationship between atrial and ventricular rates in atrial fibrillation: when the atrial rate increases, the ventricular rate decreases. However, when the atrial rate slows, the ventricular rate may actually increase. At a slower rate, more atrial impulses are likely to stimulate the AV node at a time when the impulse can be conducted through the AV node to the ventricles [17; 18; 19].

Clinicians who work with patients who have atrial fibrillation are aware that the longer atrial fibrillation persists, the harder it becomes to terminate the arrhythmia and maintain normal sinus rhythm. Research suggests that atrial fibrillation triggers a process known as “atrial remodeling.” In atrial remodeling, electrical, histologic, anatomic, and autonomic nervous system changes occur in the atria that facilitate the continuation of atrial fibrillation and impair the heart’s ability to return to normal sinus rhythm [3; 20; 21; 22]. Changes that have been hypothesized include:

- Gradual enlargement of the atria through dilation and stretching. Atrial hypertrophy may increase the vulnerability of the atria to abnormal electrical impulses and may shorten the atrial refractory period. A shortened refractory period facilitates development of the continuous loop or cycle of impulses (also called a re-entry mechanism) that sustains atrial fibrillation.
- Alteration in the normal flow of one or more ions (especially calcium ions) across the cardiac cell membrane.

RHYTHM STRIP OF ATRIAL FIBRILLATION



Source: Created by Author

Figure 2

- Progressive shortening of the effective refractory period in the atria.
- Adrenergic activation may contribute to the initiation of ectopic activity

KEY DEFINING CHARACTERISTICS OF ATRIAL FIBRILLATION

The two key defining characteristics of atrial fibrillation are (**Figure 2**) [3; 6; 17; 19]:

- Total absence of normal sinus P waves. The absence of P waves indicates that the heart beat was not initiated in the SA node, or normal pacemaker, of the heart. The P waves are replaced by fibrillatory (fib) waves. These fib waves may be so fine that they are indiscernible or barely discernible; or, they may be very coarse and more clearly seen on the ECG tracing.
- An irregularly irregular ventricular response when conduction through the AV node is normal.

Additional characteristics associated with atrial fibrillation include:

- A variable ventricular rate. The rate may range from less than 60 bpm to as high as 160 bpm.
- A QRS interval that is usually (but not always) normal in configuration and duration.

TYPES OF ATRIAL FIBRILLATION

The types of atrial fibrillation may be described in terms of onset or duration of rate. Descriptions based on rate include the following [3; 17]:

- Rapid ventricular response: atrial fibrillation with a ventricular rate greater than 120 bpm.
- Controlled ventricular response: atrial fibrillation with a ventricular rate between 60 bpm and 110 bpm.
- Slow ventricular response: atrial fibrillation with a ventricular rate of less than 60 bpm.

Descriptions based on onset and duration have not been standardized throughout medical literature. Terms such as acute onset, chronic, and others have been used. In its published practice guidelines, the American College of Cardiology, the American Heart Association, and the European Society for Cardiology (ACC/AHA/ESC) Task Force recommends the following simplified terminology for episodes of atrial fibrillation that last more than 30 seconds and are not caused by another, reversible medical cause [3; 23]:

- First-detected: the first diagnosed or known episode of atrial fibrillation that a patient experiences. A first-detected episode may be symptomatic or asymptomatic; it may or may not be self-limited. It may or may not actually be the patient's first episode of atrial fibrillation; however, it is the first episode that is formally identified as atrial fibrillation.

- **Paroxysmal:** recurrent atrial fibrillation that spontaneously terminates or terminates with intervention within seven days of onset, and episodes may recur with variable frequency.
- **Persistent:** recurrent atrial fibrillation that is sustained beyond seven days; it may include atrial fibrillation that is terminated by electrical cardioversion or pharmacologic therapy. This category also includes cases of long-standing atrial fibrillation (e.g., longer than one year) that usually lead to permanent atrial fibrillation.
- **Permanent:** paroxysmal or persistent atrial fibrillation in which pharmacologic and/or electrical cardioversion is not attempted or is not successful.
- **Nonvalvular:** atrial fibrillation in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

DIFFERENTIATING ATRIAL FIBRILLATION FROM OTHER SUPRAVENTRICULAR TACHYCARDIAS

Atrial fibrillation is one of several arrhythmias in which the electrical impulse is initiated at or above the AV node. These arrhythmias are usually referred to using the umbrella term, supraventricular tachycardias (SVT). Other common SVTs include atrial flutter and AV nodal re-entrant tachycardia.

In atrial flutter, the heart beat originates in the atria somewhere outside the SA node. More organized than fib waves, atrial flutter (F) waves have a characteristic sawtooth appearance. Flutter waves occur at regular intervals and at rates between 240 and 400 bpm. One or more flutter waves may be present before each QRS interval. Conduction through the AV node is often regular (i.e., every second or third or fourth flutter wave is conducted). The most common pattern is 2:1 conduction, which results in a ventricular rate of 150 bpm. Flutter waves do not result in organized contraction of the atria, but they may increase atrial oxygen demands by triggering “near contractions.” Atrial flutter is generally

differentiated from atrial fibrillation by the presence of flutter waves that are more defined than fib waves and occur at regular intervals and regular ventricular rhythm [24].

In AV nodal re-entrant tachycardia (also referred to as paroxysmal supraventricular tachycardia or PSVT), the ventricular rate falls between 150 and 250 bpm. No evidence of atrial activity is present. The ventricular rhythm is regular. The arrhythmia has an abrupt onset and termination, with episodes lasting from seconds or minutes to days, and may occur in persons with no history of heart disease as well as in elderly persons with chronic heart disease. The arrhythmia may be differentiated from sinus tachycardia by rate; sinus tachycardia rarely exceeds a rate of 150 to 160 bpm in an adult at rest. It may also be differentiated from atrial fibrillation because the rhythm is regular. It may be differentiated from atrial flutter by rate; the usual rates associated with AV nodal re-entrant tachycardia are too slow for 1:1 (atrial to ventricular) conduction in atrial flutter and too fast for 2:1 conduction [3; 17; 25].

Differential diagnosis of atrial fibrillation is based on ECG analysis combined with patient history, description of symptoms, current medications, and past medical history. At a controlled rate, atrial fibrillation is usually readily recognizable because of the absence of sinus P waves and the irregularly irregular rhythm. However, at higher rates, identification of these key characteristics may become more difficult. The physician may choose to facilitate diagnosis through the use of intravenous adenosine. Adenosine is a medication that may be administered intravenously to aid in the differential diagnosis of a narrow complex SVT. Adenosine should not be administered in the presence of a wide QRS complex tachyarrhythmia, nor should it be administered if the arrhythmia’s underlying mechanism has already been identified. Adenosine has an immediate onset of action and an extremely short half-life (i.e., <10 seconds) [26]. Care should be taken to administer the medication rapidly enough to ensure that the medication reaches the systemic circulation before its half-life expires. Due to its extremely short half-

life, adenosine is not effective for pharmacologic cardioversion; as soon as the effects wear off, the original arrhythmia resumes. Adenosine acts by interrupting re-entry pathways and slowing conduction through the AV node; it slows the ventricular rate to permit analysis and identification of the exact arrhythmia. Side effects include bradycardia, a brief period of asystole that does not exceed 15 seconds, and a sense of flushing and lightheadedness. It is a potent vasodilator and may cause hypotension. The side effects may be uncomfortable for the patient but are usually short and self-limiting [13; 15; 19; 27]. In 2013, the U.S. Food and Drug Administration (FDA) issued a warning of a rare but serious risk of myocardial infarction and death with the use of adenosine [28]. Adenosine should be avoided in patients with unstable angina or cardiovascular instability. When administering adenosine, follow these tips [13; 15; 19; 26]:

- Make sure that the patient has a good IV access.
- Administer adenosine undiluted through a proximal IV access.
- Administer an initial dose of 6 mg over one to two seconds. Follow the medication quickly with a rapid normal saline flush to make sure that the entire dose reaches systemic circulation. Remember that the rapid administration rate is vital for effectiveness. If adenosine is administered too slowly, it may have the adverse effect of further increasing heart rate.
- Continuously monitor ECG and heart rate before, during, and after administration. Record a continuous strip during administration to assess the arrhythmia when the rate slows or the arrhythmia breaks and resumes.
- After one to two minutes, if the initial dose is ineffective, a second dose of 12 mg may be given as a rapid one- to two-second bolus. The second dose should also be followed with a rapid saline flush.

- Note that a single dose should not exceed 12 mg.
- If the second dose is ineffective, another 12 mg dose may be given after several minutes.

EFFECTS OF ATRIAL FIBRILLATION ON SYSTEMIC FUNCTIONING

Atrial fibrillation causes a drop in cardiac output. Atrial contraction does not occur, thereby reducing ventricular filling during mechanical diastole. Loss of atrial contraction (or “atrial kick”) may reduce cardiac output from 5% to 40%. Symptoms of decreased cardiac output may develop; how severe these symptoms are depends on multiple factors, including the person’s age, overall health, and presence of structural heart disease. If atrial fibrillation occurs at a rapid ventricular rate, cardiac output is reduced further. Any tachycardia reduces ventricular filling time. When ventricular filling is already reduced due to the loss of atrial kick, further reduction in filling time from a rapid heart rate may greatly exacerbate signs of reduced cardiac output. Over time, atrial fibrillation with a rapid ventricular response may cause a tachycardia-induced cardiomyopathy. This cardiomyopathy may be reversible when the heart rate is controlled [3; 17; 19]. Loss of atrial contraction also causes stasis of blood in the atria. Stasis of blood increases the risk of thrombus formation and can lead to the development of thromboembolic complications such as CVAs [17; 29].

CAUSES OF ATRIAL FIBRILLATION

The causes of atrial fibrillation may be grouped into three major categories [6; 30]:

- Primary arrhythmia in the absence of structural heart disease or other precipitating causes
- Secondary arrhythmia associated with a range of cardiovascular diseases
- Secondary arrhythmia in the absence of heart disease but in the presence of a systemic problem that precipitates the arrhythmia

Historically, atrial fibrillation, as a primary arrhythmia, was thought to develop in isolation, with no known precipitating cause. Called “lone atrial fibrillation,” this type of atrial fibrillation was defined as occurring in the presence of documented normal left ventricular function, typically in people 60 years of age or younger. It was characterized by a paroxysmal onset and termination and frequent recurrence. However, a Working Group of the American College of Cardiology suggests that the category of lone (idiopathic) atrial fibrillation is no longer mechanistically or clinically useful [2]. The Working Group posits several reasons for avoiding use of the term “lone atrial fibrillation,” including [2]:

- Outdated terminology, as the term “lone atrial fibrillation” predates current understanding of the many disorders that may contribute to the initiation of atrial fibrillation
- Broad definition of and variation in what investigators have termed “lone atrial fibrillation,” leading to confusion and diminished usefulness of the term
- Wide variation in the reported prevalence (0.2% to 68%) of lone atrial fibrillation
- No specificity in requirement for extensiveness and interval of baseline imaging to exclude heart disease
- Well-established heritability of atrial fibrillation not taken into account when classifying an individual as having lone atrial fibrillation
- Lack of unique pathophysiologic mechanisms attributed to lone atrial fibrillation

Instead, the term “paroxysmal atrial fibrillation” should be used.

As a secondary arrhythmia, atrial fibrillation may be caused by cardiac and noncardiac causes. Common cardiac causes include [30; 31; 32]:

- Hypertension
- Rheumatic heart disease

- Mitral valve disease (e.g., mitral stenosis, mitral valve prolapse, mitral valve annular calcification)
- Congestive cardiomyopathy/congestive heart failure
- Acute myocardial infarction
- Sick sinus syndrome
- Pericarditis
- Hypertrophic cardiomyopathy
- May occur following cardiac/coronary artery bypass graft (CABG) surgery

The persons at highest risk to develop atrial fibrillation are those with long-standing hypertension, valvular heart disease, left ventricular hypertrophy, depressed left ventricular function, and coronary artery disease. Atrial fibrillation associated with cardiovascular disease may initially have a paroxysmal onset; however, the arrhythmia can continue to progress to persistent or chronic atrial fibrillation. Noncardiac, systemic diseases may also cause atrial fibrillation. Diabetes mellitus is a major risk factor for the development of atrial fibrillation. Other noncardiac causes include [2; 30; 31; 32]:

- Hyperthyroidism
- Male sex
- Advancing age
- Obesity
- Obstructive sleep apnea
- Genetic factors
- Alcohol and drug use
- Noncardiac surgery
- Noncardiac diagnostic procedure
- Pulmonary conditions/hypoxemia caused by pulmonary conditions (e.g., pneumonia, chronic obstructive pulmonary disease [COPD])
- Pulmonary embolus
- Over-the-counter use of some herbs, such as ephedra or ginseng

Emerging risk factors for atrial fibrillation include [2]:

- Subclinical atherosclerosis
- Chronic kidney disease
- Inflammation
- Increased height, birth weight
- Smoking
- Caffeine intake
- Ethnicity

Atrial fibrillation caused by noncardiac causes is frequently reversible once the underlying condition is resolved. In some instances, the atrial fibrillation may spontaneously convert to normal sinus rhythm. In other cases, the arrhythmia responds well to pharmacologic or electrical cardioversion to restore normal sinus rhythm [30].

ASSESSMENT OF THE PATIENT WITH ATRIAL FIBRILLATION

CLINICAL SIGNS AND SYMPTOMS

Patients in atrial fibrillation can present with symptoms that range from asymptomatic to severely incapacitating. Consider these patient examples:

- Patient K is 68 years of age. He is found to be in controlled atrial fibrillation during a routine physical before surgery for a total knee repair. He reports that he has experienced no symptoms and has never before been told that he has an irregular heartbeat or arrhythmia.
- Patient J is 45 years of age. She presents to the emergency department with atrial fibrillation with rapid ventricular response. An ECG shows her heart rate to be 160 bpm. She complains of feeling palpitations and slightly short of breath. She gives a history of intermittent episodes of palpitations and dyspnea that start and stop abruptly. She reports feeling frightened and out of control because her symptoms occur without warning and without obvious precipitating cause.

- Patient W is 76 years of age. He presents to the emergency department with severe dyspnea and dizziness. His blood pressure is hypotensive at 85/50 mm Hg. His respirations are 32 breaths per minute, and he has rales in both lung bases. His oxygen saturation on room air is 87%. His ECG shows atrial fibrillation with rapid ventricular response at a rate of 140–160 bpm. Patient W gives a history of coronary artery disease, previous myocardial infarction, and long-standing hypertension. He reports that his symptoms started about a week earlier and have gradually grown worse.
- Patient C is 58 years of age. She makes an appointment to see her physician and reports that she has been experiencing a “pounding heart beat” intermittently for the last few days. She denies other symptoms but admits that she has been “more tired” than usual and that she has not “gotten as much done during the day as usual.” Patient C has a history of mitral valve disease and a mitral valve replacement several years earlier. She also has mild (Class I/II) congestive heart failure. An ECG shows Patient C to be in atrial fibrillation at a relatively controlled rate of 80–90 bpm.

As the simulated patient examples show, symptoms of atrial fibrillation may include one or more of the following [3; 30; 31; 32]:

- Palpitations
- Decreased blood pressure
- Fatigue
- Dizziness
- Shortness of breath
- Exacerbation of congestive heart failure
- Chest pain (angina)
- Syncope or near syncope
- Reduced exercise tolerance

Because of the unpredictable pattern of paroxysmal atrial fibrillation, patients with this type of atrial fibrillation may feel frightened and out of control. They may choose to curtail their usual level of activity in an attempt to prevent the arrhythmia from occurring. Depression and a sense of helplessness may occur.

Atrial high-rate episodes may be detected by a cardiac implantable electronic device. These cases should result in further evaluation to establish the diagnosis and guide treatment decisions [33].

PHYSICAL ASSESSMENT

Physical assessment findings in atrial fibrillation may include the following [3]:

- Rapid heart rate and irregularly irregular heart rhythm
- Irregular jugular venous pulsations
- Variable loudness of S1
- Variable pulse pressure. This results from the variable ventricular filling caused by the irregular conduction of atrial impulses through the AV node to the ventricles.
- A blood pressure that appears to vary widely. In atrial fibrillation with a controlled or slow ventricular response, there may be long pauses between some beats. When an electronic, noninvasive blood pressure device is used (or when the pressure is released too rapidly during manual auscultation of blood pressure), the systolic blood pressure reading may vary widely. Taking serial blood pressure readings and using an average of readings to estimate the patient's actual blood pressure may be needed.
- Hypotension, especially if cardiac output is significantly reduced
- Signs of congestive heart failure, such as decreased oxygen saturation and rales/crackles in lung fields
- Signs of poor peripheral perfusion, such as diminished peripheral pulses and impaired capillary filling

RELATED LABORATORY AND DIAGNOSTIC TESTS

Assessment of the patient with atrial fibrillation should include laboratory and diagnostic tests to identify any factors that may be contributing to the development of the arrhythmia as well as to rule out any noncardiac causes of the arrhythmia. Appropriate laboratory and diagnostic tests may include the following [3; 11; 23; 30; 31; 32]:

- Serial cardiac enzymes to evaluate for possible acute myocardial infarction
- Arterial blood gases to assess for hypoxia
- Thyroid function studies to evaluate for hyperthyroidism
- Serum electrolytes, particularly imbalances in sodium, potassium, or magnesium
- Complete blood count to evaluate hematocrit and hemoglobin. Anemia may aggravate angina and signs of decreased cardiac output.
- Chest x-ray to evaluate for signs of congestive heart failure or underlying pulmonary disease/pneumonia
- Ultrasound studies (i.e., echocardiography [ECHO]) to identify valvular disease and evaluate left ventricular function
- Transesophageal ECHO (TEE) to evaluate for presence of clots in atria
- 12-lead ECG to evaluate arrhythmia
- Continuous ambulatory ECG monitoring for patients who complain of symptoms associated with atrial fibrillation but are in normal rhythm upon presentation to healthcare system/emergency department
- Nuclear medicine cardiac studies

ASSESSING NON-ENGLISH-PROFICIENT PATIENTS

When a patient does not speak the same language as the clinician, a professional interpreter should be consulted to ensure accurate communication. A systematic review of the literature has shown that the use of professional interpreters provides better

clinical care than the use of “ad hoc” interpreters, with the former improving the quality of care for patients with limited English language skills to a level equal to that for patients with no language barriers [34; 35]. Use of professional interpreters has been associated with improvements in communication (errors and comprehension), utilization, clinical outcomes, and satisfaction with care [34; 35]. Individuals with limited English language skills have indicated a preference for professional interpreters rather than family members [36].

ESTABLISHING THE MEDICAL PLAN OF CARE

Effective clinical management of the patient with atrial fibrillation is based on evaluation of the patient’s status, identification of appropriate medical goals, and determination of which specific therapies will be most effective in assisting the patient to reach the identified goal(s).

Until the 2000s, no consensus existed about what therapy or combination of therapies is the most effective in the clinical management of atrial fibrillation. In 2001, the ACC/AHA/ESC task force was formed to make recommendations for the management of persons with atrial fibrillation. Through a process of rigorous and expert evaluation of published data, the Task Force derived specific guidelines that have been published in the *American Journal of Cardiology* and are available on the AHA website [37]. The Task Force updated these guidelines in 2014 and again in 2019 [23; 33]. Effective clinical management of the person with atrial fibrillation begins with a thorough history and assessment of the patient to identify the patient’s type and pattern of atrial fibrillation [23; 33]. Based on the patient’s type and pattern of atrial fibrillation, symptoms, and underlying cause, appropriate medical goals should be identified. Specific therapies are then selected based on the identified goals [38].

PATIENT FACTORS

Adequate patient assessment should focus on the patient’s symptoms, past medical history, any concurrent illnesses, and psychosocial issues. When assessing the patient, consider the following [3; 39]:

- What type of atrial fibrillation does the patient have? Is this a first detected episode? Does the patient have recurrent paroxysmal, recurrent persistent, or permanent atrial fibrillation?
- How often does the patient experience atrial fibrillation? How long does it last? What precipitates it? What terminates it?
- What specific symptoms does the patient have?
- What impact do the symptoms have on the patient’s ability to work? Take care of himself/herself? His/her activity tolerance? Does the patient feel frightened? Disabled by the symptoms?
- What impact is the atrial fibrillation having on any other medical problems that the patient has? Is it exacerbating his/her angina? Is it exacerbating his/her congestive heart failure?
- Does the patient have some type of cardiovascular disease? Coronary artery disease? Hypertension? Valvular heart disease? History of myocardial infarction? History of congestive heart failure?
- Does the patient have some other systemic problem that is precipitating the atrial fibrillation?
- Is the patient elderly?
- Has the patient been treated for atrial fibrillation? What treatment was prescribed? How effective was that treatment? Did the patient follow the prescribed treatment? Did it work? Did side effects develop?
- How will the patient pay for his/her medical care and medications? What medications and treatments will his/her insurance pay for?

- Is the patient able and willing to comply with prescribed medication therapy? Has the patient been compliant with medication therapy in the past?
- What is the patient's renal and hepatic function? Are these normal?

IDENTIFICATION OF APPROPRIATE MEDICAL GOALS

Based on a thorough evaluation of the patient's status and other factors, one or more medical goals should be identified. The initial goal for a patient who is hemodynamically unstable is the immediate restoration of normal sinus rhythm through electrical cardioversion. The initial goal for patients who present with atrial fibrillation with a rapid ventricular response is rate control. Once the patient's status has stabilized, long-term goals may be developed. When developing long-term goals, consider the following points [3; 17; 23; 33; 38; 39; 40; 41; 42]:

- Use of antiarrhythmic therapy may not be necessary for persons with asymptomatic paroxysmal atrial fibrillation.
- Use of antiarrhythmic therapy is indicated for persons who experience severe symptoms with paroxysmal atrial fibrillation.
- Long-term rate control is indicated for persons with persistent or permanent atrial fibrillation.
- Long-term rate control is also indicated for patients who have repeatedly reverted to atrial fibrillation following electrical or pharmacologic cardioversion. Ablation for symptomatic persistent atrial fibrillation and for severely symptomatic recurrent atrial fibrillation may be indicated.
- Catheter ablation performed in experienced centers may be indicated to maintain sinus rhythm in select patients with significantly symptomatic, paroxysmal atrial fibrillation who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease.

- Catheter ablation is indicated for symptomatic patients with atrial fibrillation who have Wolff-Parkinson-White (WPW) syndrome.
- Restoration of normal sinus rhythm is indicated for those who have persistent signs of decreased cardiac output during episodes of atrial fibrillation.
- Direct-current cardioversion may be indicated as part of a long-term management strategy to restore sinus rhythm in patients with atrial fibrillation.
- Maintenance of normal sinus rhythm may be indicated for persons who spontaneously convert from atrial fibrillation to sinus rhythm.
- Maintenance of normal sinus rhythm is indicated for persons who are successfully converted by pharmacologic or electrical means.
- Elimination or interruption of the arrhythmia through radiofrequency ablation (of the focal source of the arrhythmia or the AV node) is indicated for patients who cannot tolerate antiarrhythmic therapy, whose arrhythmia is not successfully controlled by optimal doses of antiarrhythmic therapy, or who cannot be successfully cardioverted through pharmacologic or electrical means.

To assist the clinician in selecting and prioritizing appropriate medical goals, the ACC/AHA/ESC Task Force established recommendations for the management of various types of atrial fibrillation. These recommendations are summarized in *Table 1*.

SELECTION OF SPECIFIC THERAPIES

Antiarrhythmic medications are the mainstay of treatment for atrial fibrillation. They may be used for acute and chronic rate control. They also may be used for pharmacologic cardioversion of atrial fibrillation to normal sinus rhythm and maintenance of normal sinus rhythm following successful conversion; however, their use for achieving rhythm control has decreased due to evidence of greater

RECOMMENDED MANAGEMENT FOR PERSONS WITH ATRIAL FIBRILLATION	
Type of Atrial Fibrillation	Recommended Management Strategy
First-detected, self-limiting	Assess severity of symptoms Therapy only indicated if symptoms are severe (e.g., hypotension, heart failure, angina pectoris) Consider anticoagulation on individual basis
First-detected, persistent	Assess symptoms Control ventricular rate Anticoagulate as needed Consider antiarrhythmic therapy Consider cardioversion to restore normal sinus rhythm Long-term antiarrhythmic drug therapy unnecessary
Recurrent paroxysmal	Assess symptoms Control rate and anticoagulate as needed If severely symptomatic, consider antiarrhythmic therapy to maintain normal sinus rhythm and decrease frequency of recurrent episodes of atrial fibrillation Consider ablation if antiarrhythmic treatment fails
Recurrent persistent	Assess severity of symptoms Control ventricular rate Anticoagulate as indicated For severe symptoms, consider antiarrhythmic therapy to restore or maintain normal sinus rhythm and electrical cardioversion to restore sinus rhythm Consider electrical cardioversion as needed Continue anticoagulation as needed and therapy to maintain sinus rhythm Consider ablation for severely symptomatic recurrent atrial fibrillation after failure of more than one antiarrhythmic drug plus rate control
Permanent	Pharmacologic therapy for rate control Anticoagulate as indicated If symptomatic with medication, consider more aggressive therapy
Source: [3; 20; 42]	

Table 1

safety and lower costs for hospitalization obtained from the use of rate-control strategies [23; 43]. The AHA/ACC/HRS recommends treating the precipitating or reversible causes of atrial fibrillation prior to initiating antiarrhythmic drug therapy [23]. Whatever the goal of treatment, selection of specific antiarrhythmic medications should be guided by the following [23; 43]:

- Patient characteristics (e.g., age, disease states, renal function, concurrent drug therapies)
- Effectiveness of the medication in meeting identified goals (i.e., controlling rate within desired parameters, limiting episodes of atrial fibrillation)
- Specific action of the medication on the cardiac cycle and its risk of proarrhythmias and other serious side effects
- Medical contraindications to the use of some antiarrhythmic medications in the presence of specific cardiovascular disorders
- Convenience of administration (i.e., dosing, frequency, schedule of doses)
- Cost and ready availability of the medication(s)

AN ISSUE IN THE SELECTION OF ANTIARRHYTHMIC MEDICATIONS: PRODUCT SUBSTITUTION

With the increasing emphasis on reduction of healthcare costs, there has been an increase in the use of generic (as opposed to proprietary) medications. Almost every state has passed regulations encouraging the substitution of less expensive drug products for more expensive proprietary products. State regulations may approve substitutions only for medications on an approved list, or the regulations may permit the substitution of any medication, except those specifically listed on a list of exclusions. On the national level, the FDA provides a specific list of approved drugs. This list is updated on a monthly basis [44].

When a pharmaceutical company develops a new drug, the company may apply for one or more patents for (1) the drug itself; (2) the manufacturing process; (3) how the drug is delivered to the bloodstream; or (4) how the medication is to be used. Although the patent gives the company exclusive rights to the new drug for 17 years, this period often involves at least 10 years of development. In reality, the company may have only seven years to exclusively sell the drug. A newly developed drug is given several names. The generic name, which is the medication's official name (derived from the drug's chemical name, structure, and/or formula), must be unique. Generic names are frequently difficult to pronounce, remember, and spell. The new drug is also given a trade name or proprietary name that signifies that the drug is the exclusive property of its company. Trade names are simpler, easier to remember, and often emphasize an attribute of the medication. Trade names must also be unique. After the patent on a specific drug has expired, other companies may manufacture and sell that drug under its generic name. Generics are frequently sold at a lower price than trade/proprietary drugs. Generic versions of a drug must meet FDA approval, specifically the following three points [44; 45]:

- The generic preparation must contain the same amount of active drug ingredient as the original proprietary preparation.

- The generic must be manufactured according to federal standards as defined in the Good Manufacturing Practices.
- In the human body, the generic medication must be released in equivalent fashion (i.e., same rate, to same extent) as the proprietary drug. This is referred to as "bioequivalence." Bioequivalence is established by a drug company through the use of small research studies. For time-release medications, the process of establishing bioequivalence is more strict, extensive, and time-consuming. Because there is more variation inherent in the use of time-release forms, more extensive testing is required to ensure bioequivalence. Because of the cost and extensiveness of the process, very few time-release generic drugs are available.

Proprietary and generic versions of a medication may vary in several respects [26; 45]:

- Appearance of the medication. By law the size, color, and shape of the generic must significantly differ from the proprietary. Patients will notice the difference.
- Different inactive ingredients. While the active ingredients must be the same, the inactive components may vary. Inactive ingredients are routinely used in medications to add bulk, to keep the tablet from crumbling/disintegrating until use, to help the medication dissolve, or to provide a pleasant taste. There have been instances in which the difference in inactive ingredients has changed the absorption of the active ingredients.
- Variable bioequivalence. Regulations permit as much as a 20% variation in bioequivalence. For medications, such as antiarrhythmic medications that may have a very narrow margin for therapeutic effect, this variation may alter how effective the generic medication is in managing the patient's arrhythmia.

Practically speaking, the use of a generic substitution means that the patient could experience different effectiveness with different preparations. Random switching from proprietary to generic or from one generic to another could increase side effects, decrease rate control, and cause more frequent relapse from normal sinus rhythm to atrial fibrillation. For that reason, any generic substitution of antiarrhythmic medications should be done very carefully. With many antiarrhythmic medications, very small variations in the serum blood level may influence the effectiveness of the medication in controlling the arrhythmia and significantly increase the risk of proarrhythmias and serious side effects. Physician groups have made the following recommendations regarding the use of generic antiarrhythmic medications [39]:

- Regardless of the preparation used, closely monitor the patient's status and serum drug levels. Adjust dosage as indicated by data.
- Avoid substitution of antiarrhythmic medications for patients with life-threatening arrhythmias, arrhythmias that cause loss of consciousness, or when a change in drug level (increase) can cause life-threatening proarrhythmias.
- Use a generic for less serious arrhythmias if an easy, reliable assay is available and a therapeutic drug level is stable and sustained over time.
- If generic substitution is necessary, give preference to generic medications that have only one preparation available, thus avoiding multiple switches from one generic product to another. Also give preference to a generic preparation that is widely available in hospital and outpatient pharmacies.
- If switching from a proprietary to a generic medication, re-establish effectiveness and proper dose with the new preparation.
- The physician may wish to specify on the prescription the exact preparation of a medication to be dispensed. Some states have regulations that limit the physician's ability to specify preparations. Also, specifying a proprietary medication may present a financial issue for the patient; insurance companies may not cover the higher cost preparation.

PHARMACOLOGIC THERAPY

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

A classification system for antiarrhythmic drugs was developed in the early 1970s. An antiarrhythmic medication was classified according to its specific effect on the normal cardiac cycle. When the classification system was developed, it was believed that each antiarrhythmic medication had only one action. Electrophysiologic research has shown that the mechanisms involved in the generation and spread of an electrical impulse throughout the heart are complex, and that antiarrhythmic medications may impact more than one of these mechanisms. Although the classification system does not reflect the advances in the understanding of electrophysiology, it is still in common use today. **Table 2** summarizes the classification system [46; 47].

SITE OF CARE DECISIONS FOR ANTIARRHYTHMIC THERAPY

When selecting and initiating (or changing) antiarrhythmic therapy, the site of care should be considered. Sites of care may include the patient's home, a physician's office, an outpatient clinic, or an inpatient setting. Some antiarrhythmics, such as dofetilide, can only be initiated in an inpatient setting. For others, inpatient initiation is strongly recommended if risk of proarrhythmia is high. Proarrhythmic risk is increased in persons with structural heart disease, congestive heart failure, and those who already have a prolonged QT interval. Persons who have no structural heart disease and whose QT interval is normal are considered to be at low risk for development of proarrhythmias. In these cases, antiarrhythmic therapy may be initiated in outpatient settings. If antiarrhythmic therapy is initiated outside the hospital setting, transtelephone monitoring may be used to intermittently assess the patient's heart rate and rhythm for any undesired changes [3; 48].

CLASSIFICATION OF ANTIARRHYTHMIC MEDICATIONS			
Class	Action/Properties	Class Proarrhythmic Effects	Specific Agents
Ia	Blocks the rapid influx of sodium Slows rate of development of phase 0 of the action potential Slows conduction velocity; QRS complex widens Prolongs repolarization; QT interval lengthens	Torsades de pointes (quinidine) Ventricular fibrillation or asystole Second-degree heart block	Quinidine Procainamide Disopyramide
Ib	Sodium channel blocker Shortens action potential duration Shortens repolarization Used only for management of ventricular arrhythmias	Increased premature ventricular contractions (rare) AV block/conduction disturbances	Lidocaine Mexiletine
Ic	Significant block of sodium channel Slows conduction velocity; QRS complex widens Has no effect on repolarization; QT interval unaffected	Re-entry arrhythmias	Flecainide Propafenone
II	Beta adrenergic blockers Slows AV node conduction Slows sinus rate Decreases myocardial oxygen consumption	Sinus bradycardia AV block	Metoprolol Acebutolol Propranolol Esmolol
III	Blocks outward movement of potassium ions in phase 3 of the action potential Prolongs repolarization; lengthens QT interval Prolongs cardiac action potential and effective refractory period At increased heart rates, has reduced ability to affect/slow the cardiac action potential	Sinus bradycardia Torsades de pointes	Amiodarone Sotalol Dofetilide Ibutilide
IV	Calcium channel blockers Blocks slow inward movement of calcium ions into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period	Sinus bradycardia AV block	Verapamil Diltiazem
AV = atrioventricular; SA = sinoatrial.			
Source: [46; 47]			Table 2

DRUG INTERACTIONS

When selecting antiarrhythmic agents, potential drug interactions should be considered. Serious interactions may occur between two antiarrhythmic medications, between an antiarrhythmic and other cardiovascular medications, and between antiarrhythmics and noncardiac medications. Interactions that may occur include the following [13; 15; 19; 26; 45]:

- Other drugs may potentiate or inhibit the effectiveness of antiarrhythmic drugs.
- Other drugs may interfere with the normal absorption of antiarrhythmic drugs, thus reducing the serum level and the drug's effectiveness in controlling an arrhythmia.
- Other drugs may interfere with the normal metabolism or excretion of another medication, thus increasing the serum levels and increasing the risk of toxicity.

- Antiarrhythmic drugs may potentiate or inhibit the therapeutic effects of other medications.
- Antiarrhythmic drugs may interfere with the normal absorption, metabolism, or excretion of another medication, thus reducing the serum level and the drug's effectiveness.
- When given concurrently with other antiarrhythmic drugs, an antiarrhythmic drug may have cumulative effects on heart rate and blood pressure.

Table 3 lists some common drug to drug interactions.

PHARMACOLOGIC THERAPY FOR RATE CONTROL

ACUTE INTERVENTION

When a person presents with uncontrolled atrial fibrillation, his/her ventricular rate may reach 160 bpm. The immediate goal of medical therapy is to control the heart rate to decrease acute symptoms, relieve hypotension, reduce signs of ischemia, and reduce or prevent signs of congestive heart failure from developing. No single agent has been found to be more effective than others in controlling rapid rates. For acute rate control, the administration route of choice is intravenous. Antiarrhythmic drugs commonly prescribed for acute rate control include diltiazem, verapamil, esmolol, metoprolol, and digoxin [3; 42].

Diltiazem

Diltiazem acts by blocking calcium transport into the myocardial and vascular smooth muscle cells. As a result, conduction through the SA and AV nodes is slowed, and the refractory period of the AV node is prolonged. Ventricular rate is slowed, but the underlying atrial arrhythmia is not corrected. Diltiazem should be administered initially as an IV bolus. The

usual dose is a 0.25 mg/kg bolus administered over a two-minute period. Diltiazem has a rapid onset of action. If effective, it should slow the patient's heart rate within three to seven minutes of administration. If the initial dose is ineffective in slowing the patient's heart rate, the bolus may be repeated at a higher dose of 0.35 mg/kg over two minutes. The patient's heart rate and rhythm and blood pressure should be monitored during administration. Bradycardia, bradyarrhythmias such as heart block, and hypotension may occur. To achieve or maintain rate control, a continuous infusion may be started following bolus administration. The infusion may be started at 10 mg/hour and increased in increments of 5 mg/hour to achieve rate control if no undesirable side effects occur. Diltiazem should be used with caution in patients with congestive heart failure, known pre-existing conduction defects, and significant hypotension [3; 26; 54].

Verapamil

Verapamil, another calcium channel blocker, also slows ventricular rate by slowing conduction through the AV node and prolonging the refractory period of the AV node. Revised guidelines published by the AHA/ACC/HRS recommend a loading or bolus dose of 0.075–0.15 mg/kg administered over two minutes; no maintenance or continuous drip is included in the recommendations [23]. If ineffective in achieving rate control and if no untoward effects occur, the bolus may be repeated at a higher dosage of 10 mg administered 30 minutes after the initial dose [23]. Verapamil should not be used for patients with atrial fibrillation secondary to WPW syndrome or patients who have a wide QRS complex tachyarrhythmia. Verapamil should be used with caution for persons with pre-existing conduction disturbances or left ventricular dysfunction. The patient's heart rate and rhythm and blood pressure should be monitored during and following administration. Bradycardia, heart block, and hypotension may occur [26; 55].

COMMON DRUG TO DRUG INTERACTIONS OF ANTIARRHYTHMIC DRUGS (AADs)					
AAD	AAD Increases the Level of Action	AAD Inhibits the Action	AAD Serum Levels Increased	AAD Serum Levels Decreased	Other Considerations and Comments
Amiodarone	Warfarin sodium Quinidine Procainamide Disopyramide Cyclosporine Flecainide Digoxin	—	Cyclosporine Flecainide Digoxin	—	Additive effects on heart rate, blood pressure, force of cardiac contraction can occur when administered concurrently with calcium channel blockers, beta blockers Significant drug-food interaction when administered with grapefruit juice
Digoxin	—	—	Erythromycin Tetracycline Quinidine Amiodarone Diltiazem Verapamil Propafenone Itraconazole Alprazolam Spironolactone Nicardipine Indomethacin Rifampin	Cholestyramine Antacids Bismuth Neomycin Sulfasalazine Select anticancer drugs Metoclopramide	Concurrent administration of medications such as thiazide diuretics, ticarcillin, or amphotericin B that cause hypokalemia can increase risk of digitalis toxicity
Diltiazem	Digoxin Cyclosporine	—	Cimetidine Propranolol Carbamazepine	Phenytoin Phenobarbital	Additive effects on heart rate, blood pressure, force of cardiac contraction can occur with administration concurrently with calcium channel blockers, or beta blockers
Disopyramide	Warfarin	—	Quinidine Cimetidine Erythromycin	Phenobarbital Phenytoin Rifampin Quinidine	Additive effects on heart rate, blood pressure, force of cardiac contraction can occur when administered concurrently with calcium channel blockers, beta blockers, or flecainide Should not be administered within 48 hrs before or 24 hrs after administration of verapamil
Dofetilide	—	—	Cimetidine Ketoconazole Trimethoprim Verapamil	—	Significant risk of dangerously prolonged QT intervals when administered concurrently with other medications that prolong QT intervals (e.g., hydrochlorothiazide) Significant drug-food interaction when administered with grapefruit juice
Esmolol	Succinylcholine	Theophylline	Digoxin	Thyroid preparations	Potentiates effect on heart rate, AV conduction, blood pressure and risk for heart failure when given concurrently with negative inotropes, calcium channel blockers, or digoxin IV preparation physically incompatible with IV sodium bicarbonate, furosemide, or diazepam

Table 3 continues on next page.

COMMON DRUG TO DRUG INTERACTIONS OF ANTIARRHYTHMIC DRUGS (AADs) (Continued)					
AAD	AAD Increases the Level of Action	AAD Inhibits the Action	AAD Serum Levels Increased	AAD Serum Levels Decreased	Other Considerations and Comments
Flecainide	Digoxin	—	Cimetidine Amiodarone Propranolol	—	Additive effects on heart rate, blood pressure, force of cardiac contraction when given concurrently with beta blockers or calcium channel blockers Neither disopyramide nor verapamil should be coadministered unless the benefit is judged to outweigh the risk
Ibutilide	—	—	—	—	Significant risk of dangerously prolonged QT intervals when administered concurrently with other medications that prolong QT interval
Metoprolol	May alter effectiveness of insulin and oral hypoglycemic agents	Theophylline Negates positive action of dopamine, dobutamine	—	Thyroid preparations	Additive myocardial depression possible when administered concurrently with general anesthesia, IV phenytoin, or verapamil Concomitant use with beta blockers can increase the risk of bradycardia
Procainamide	—	—	Cimetidine Amiodarone Ranitidine	Cimetidine Amiodarone Ranitidine	Additive effect if administered with other AADs
Propafenone	Warfarin Cyclosporine Digoxin	—	Cimetidine Desipramine Imipramine Haloperidol Venlafaxine Propranolol	Etravirine	Concomitant use of propafenone and quinidine is not recommended Concomitant administration of propafenone and amiodarone can affect conduction and repolarization and is not recommended
Propranolol	May alter effectiveness of insulin and oral hypoglycemic agents	Theophylline Negates positive action of dopamine, dobutamine	—	Thyroid preparations	Additive myocardial depression possible when administered concurrently with general anesthesia, IV phenytoin, or verapamil
Quinidine	Warfarin Digoxin	—	Cimetidine Ranitidine Amiodarone	Dilantin Phenobarbital Rifampin Nifedipine Sodium bicarbonate Thiazide diuretics	—
Source: [13; 20; 26; 38; 49; 50; 51; 52; 53]					Table 3

Esmolol

Esmolol is a short-acting beta adrenergic blocker that slows ventricular rate in atrial fibrillation by slowing conduction through the AV node. Initial administration is an IV bolus dose/loading dose of 0.5 mg/kg administered over one minute. The bolus should be followed with an infusion of 0.05 mg/kg/min for four minutes. If the desired rate control is achieved, the infusion should be continued at that rate. If adequate rate control is not achieved at that dose, the bolus should be repeated followed by an infusion of 0.1 mg/min for four minutes. The total dose should not exceed 200 mcg/kg/min. This procedure may be repeated until rate control is achieved or undesirable side effects occur. The patient's heart rate, ECG rhythm, and blood pressure should be monitored during the administration. Hypotension may occur. Once rate control is achieved, the infusion should be reduced to 0.025 mg/kg/min. Because esmolol has a short half-life, the therapeutic effects and side effects usually reverse within 10 to 20 minutes after the infusion is stopped. Because the therapeutic effects wear off quickly, care should be taken when switching the patient to an oral preparation to prevent relapse/loss of rate control. To transition the patient to oral medication, the first dose of the oral medication should be administered while the patient is still receiving esmolol. Thirty minutes after the first oral dose is given, the esmolol infusion should be reduced by one-half. The second dose of the oral agent should be administered at its scheduled time. One hour after the scheduled administration of the second oral dose, assess the patient's heart rate, ECG rhythm, and blood pressure. If rate control is maintained, the esmolol infusion may be discontinued. Note: Esmolol has no oral preparation; long-term control by oral agent requires a different agent [3; 26].

Metoprolol

Metoprolol is a longer acting beta adrenergic blocking agent that decreases conduction through the AV node. Although metoprolol is not labeled for use in the management of atrial arrhythmias, it is used by some clinicians to control/slow ventricular rate in atrial fibrillation with a rapid ventricular response.

For acute rate control, an IV bolus of 2.5–5 mg may be given over two minutes and repeated every two to five minutes up to a total of 15 mg in a 10- to 15-minute period. The patient's heart rate, ECG rhythm, and blood pressure should be monitored closely. Bradycardia, bradyarrhythmias, heart block, and hypotension may occur. Use of metoprolol is contraindicated for persons with bradycardia, AV conduction problems, uncompensated congestive heart failure, or asthma [3; 26; 56].

Digoxin

Digoxin is an older agent that may be used to control ventricular rate in some patients. Once considered a leading treatment for rate control in atrial fibrillation, digoxin is primarily recommended for persons with atrial fibrillation who also have congestive heart failure caused by systolic dysfunction. Digoxin acts by prolonging the refractory period of the AV node as well as slowing conduction through SA and AV nodes. Digoxin therapy is initiated by either an oral or intravenous loading dose protocol. Intravenous administration should be used in an acute situation. The revised AHA/ACC/HRS guideline notes that one-half the total digitalizing dose (TDD) of 9–12 mcg/kg may be administered over five minutes with the remaining portion as 25% fractions at four- to eight-hour intervals or 0.25 mg may be given intravenously every two hours up to a total of 1.5 mg over 24 hours followed by an oral maintenance regimen [23]. These doses should be given at six- to eight-hour intervals. The usual protocol for an oral loading dose is 0.75–1.5 mg given in three to four doses every six to eight hours. The maintenance oral dose is 0.125–0.25 mg once daily [23]. Careful monitoring of serum digoxin levels is recommended. For digoxin to achieve a therapeutic effect, the serum digoxin level must fall within the therapeutic level of 0.5–2 ng/mL. The therapeutic range for digoxin is very narrow. Serum levels in excess of 2 ng/mL are considered toxic and may cause tachyarrhythmias, bradycardia, heart block and bradyarrhythmias, and other symptoms [3; 13; 15; 19; 26; 30; 40; 57; 58]. **Table 4** summarizes information about antiarrhythmic medications used for acute rate control.

PHARMACOLOGIC THERAPY FOR ACUTE RATE CONTROL IN ATRIAL FIBRILLATION					
Agent	Class	Action	Dosage/Route	Side Effects	Comments
Diltiazem	IV	Inhibits transport of calcium into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period Slows ventricular rate Controls ventricular rate in atrial fibrillation	IV: 0.25 mg/kg bolus over 2 mins If needed, may repeat after 15 mins with dose of 0.35 mg/kg IV over 2 mins May be followed by continuous infusion at 10 mg/hour May increase to 15 mg/hour	Bradycardia Heart block CHF Hypotension Flushing Angina Syncope Insomnia Nausea	Rapid onset of action Onset: 3 to 7 mins Duration of IV bolus may last more than 30 mins
Verapamil	IV	Inhibits transport of calcium into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period Slows ventricular rate May reduce atrial electrophysiologic remodeling	IV loading dose: 0.075–0.15 mg/kg over 2 mins	AV block Hypotension Bradycardia Heart failure Dizziness Fatigue CHF	Use with caution for patients with conduction disturbances Negative inotrope; may make left ventricular dysfunction worse Should not be used for patients with accessory conduction pathways Rapid onset of action (3 to 5 mins) Duration of IV bolus may last more than 30 mins
Esmolol	II	Beta adrenergic blocker Decreases AV nodal conduction Can rapidly slow ventricular response in atrial fibrillation	IV dosing only: Administer loading dose of 0.5 mg/kg over 1 min Follow with infusion at rate of 0.05 mg/kg/min for 4 mins; if adequate rate control is achieved, continue at the same rate. If adequate rate control is not achieved, repeat the same procedure, increasing the rate by 0.05 mg/kg/min every 4 mins until the rate control is achieved (or side effects occur). Maximum: 200 mcg/kg/min When the rate control is achieved, omit loading dose and reduce infusion rate to 0.025 mg/kg/min. Begin transition to another antiarrhythmic: administer first dose; 30 mins later, reduce infusion rate by one-half. Administer 2nd dose of new agent when scheduled. If rate control is maintained 1 hour after 2nd dose, stop infusion.	Hypotension Dizziness Diaphoresis Nausea and vomiting Fatigue	Short half-life (9 mins) Contraindicated for patients with bradycardia, uncompensated CHF, and conduction problems

Table 4 continues on next page.

PHARMACOLOGIC THERAPY FOR ACUTE RATE CONTROL IN ATRIAL FIBRILLATION (<i>Continued</i>)					
Agent	Class	Action	Dosage/Route	Side Effects	Comments
Metoprolol	II	Beta adrenergic blocker Decreases AV nodal conduction Slows ventricular rate in atrial fibrillation	IV loading dose: 2.5–5 mg over 2 mins and repeated every 2 to 5 mins up to a total dose of 15 mg in a 10- to 15-min period	Bradycardia Heart block CHF Hypotension Flushing Angina Syncope Insomnia Nausea	Rapid onset of action Onset: 5 mins Duration of IV bolus may last more than 30 mins Contraindicated for patients with bradycardia, AV conduction abnormalities, uncompensated CHF, and asthma
Digitalis (Digoxin)	None	Prolongs AV node refractory period Slows conduction through the SA and AV nodes Slows ventricular rate in atrial fibrillation	IV loading dose 0.25 mg IV every 2 hours up to total dose of 1.5 mg Oral loading dose: 0.75–1.5 mg every 6 to 8 hours Oral maintenance dose: 0.125–0.375 mg/day	Bradycardia AV block Signs of dig toxicity: Multiple tachyarrhythmias Bradyarrhythmias Visual disturbances Anorexia Nausea and vomiting Malaise Headache Weakness Seizures	Onset: 2 hours Consider as first line of treatment for patients with CHF secondary to systolic dysfunction Serum digoxin levels should be periodically monitored; therapeutic level is 0.5–2 ng/mL Dig toxicity often occurs with dig levels >2 ng/mL Dig toxicity is more likely to occur with hypokalemia, renal failure, combination therapy, elderly Excessively high dig levels may be reversed with use of digoxin immune Fab
AV = atrioventricular; CHF = congestive heart failure; SA = sinoatrial; TDD = total digitalizing dose.					
Source: [5; 13; 20; 23; 26; 44; 46; 49; 50; 51; 59; 60; 61]					Table 4

CHRONIC RATE CONTROL

If the long-term goal of clinical management is rate control, there are a number of oral preparations to choose from. Clinical decision making includes selecting the category, specific agent, effective dose, and preparation (e.g., short-acting, extended-release). As with acute rate control, no consensus exists on the best medication(s) for every patient. Specific antiarrhythmic agents should be selected on the basis of patient assessment. Again, factors to consider include the cost and complexity of the prescribed regimen, the risk of proarrhythmic effects, concurrent cardiovascular disease, and the risk of other troublesome or serious side effects. When choosing long-term therapy, the patient's lifestyle should be

considered as well. Some medications provide effective rate control when the patient is at rest but do not provide adequate rate control during activity or exercise. A heart rate is considered “controlled” if it falls between 60 to 80 bpm at rest and 90 to 115 bpm with moderate exercise [20]. Adequate rate control may be achieved by a single antiarrhythmic drug, or it may require a combination of drugs. Antiarrhythmic drugs commonly used for long-term rate control include calcium channel blockers, beta blockers, and digoxin [3; 42].

See **Table 5** for a summary of antiarrhythmic medications that may be used for long-term rate control in atrial fibrillation.

ANTIARRHYTHMIC AGENTS USED FOR LONG-TERM RATE CONTROL IN ATRIAL FIBRILLATION					
Agent	Class	Action	Dosage/Route	Side Effects	Comments
Diltiazem ^a	IV	Inhibits transport of calcium into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period Slows ventricular rate Controls ventricular rate in atrial fibrillation	Oral maintenance dose: 120–360 mg daily in divided doses Sustained-release form: 60–120 mg twice daily Extended-release form: 120–240 mg daily	Bradycardia Heart block CHF Hypotension Flushing Angina Syncope Insomnia Headache Nausea	Effective in controlling ventricular rates in patients during exercise May also be used in the management of hypertension, angina pectoris, and vasospastic angina
Verapamil	IV	Inhibits transport of calcium into myocardial and vascular smooth muscle Slows conduction through SA, AV nodes Prolongs AV node refractory period Slows ventricular rate May reduce atrial electrophysiologic remodeling	Oral maintenance dose: 120–360 mg daily in divided doses Extended release: 120–360 mg daily Immediate release: 240–480 mg daily in 3 to 4 divided doses	AV block Hypotension Bradycardia Heart failure Dizziness Fatigue CHF	Effective in controlling ventricular rates in patients during exercise May also be used in the management of hypertension, angina pectoris, and vasospastic angina Use with caution for patients with conduction disturbances Negative inotrope; may make left ventricular dysfunction worse Should not be used for patients with accessory conduction pathways
Digitalis (Digoxin)	None	Prolongs AV node refractory period Slows conduction through the SA and AV nodes Slows ventricular rate in atrial fibrillation	Half the TDD of 0–12 mcg/kg over 5 mins followed by 25% fractions of TDD at 4- to 8-hr intervals, or IV loading dose 0.25 mg IV every 2 hours up to total dose of 1.5 mg over 24 hrs at 6- to 8-hour intervals ^b Oral loading dose: 0.75–1.5 mg every 6 to 8 hours Oral maintenance dose: 0.125–0.25 mg/day	Bradycardia AV block Signs of digitalis toxicity (sinus bradycardia, multiple tachyarrhythmias, heart block) Visual disturbances Anorexia Nausea, vomiting Malaise Headache Weakness Seizures	Digoxin may also be used in the management of congestive heart failure First drug of choice for patients with CHF and atrial fibrillation Ineffective in controlling ventricular rates in patients during activity/exercise Serum digoxin levels should be periodically monitored; therapeutic level is 0.5–2 ng/mL Dig toxicity often occurs with dig levels >2 ng/mL Dig toxicity is more likely to occur with hypokalemia, renal failure, combination therapy, elderly Serious or life-threatening dig toxicity may be reversed with the use of digoxin immune Fab

Table 5 continues on next page.

ANTIARRHYTHMIC AGENTS USED FOR LONG-TERM RATE CONTROL IN ATRIAL FIBRILLATION (Continued)					
Agent	Class	Action	Dosage/Route	Side Effects	Comments
Metoprolol ^a	II	Beta adrenergic blocker Decreases AV nodal conduction Slows ventricular rate in atrial fibrillation	Oral maintenance dose: 25–100 mg twice daily Extended-release preparations are administered once daily	Bradycardia Hypotension Fatigue Weakness Insomnia CHF Bronchospasm Impotence	May be also prescribed for the management of hypertension, angina, prevention of MI, and management of acute MI Effective in controlling ventricular rate in patients during activity/exercise Contraindicated for patients with bradycardia, AV conduction abnormalities, uncompensated CHF, and asthma
Propranolol	II	Beta adrenergic blocking agent Controls ventricular rate in atrial fibrillation	Oral maintenance dose: 30–160 mg daily in divided doses	Bradycardia Heart block Hypotension CHF Nausea and vomiting Diarrhea Constipation Insomnia Depression Bronchospasm Hypoglycemia Fatigue Impotence	Propranolol may also be used in the management of angina, hypertension, prevention and management of MI
AV = atrioventricular; CHF = congestive heart failure; MI = myocardial infarction; SA = sinoatrial; TDD = total digitalizing dose. ^a Off-label use ^b Unlabeled dose					
Source: [5; 13; 20; 23; 26; 46; 49; 50; 51; 59; 60; 61]					Table 5

Diltiazem

Oral diltiazem preparations provide chronic rate control in atrial fibrillation and are a drug of choice for persons who have a physically active lifestyle; however, their use for rate control is unlabeled [26]. Diltiazem comes in immediate- and extended-release forms. Immediate-release doses must be taken three to four times per day; extended-release forms require only daily dosing. In addition to bradycardia, hypotension, and heart block, other side effects of oral diltiazem include flushing, angina, insomnia, headache, nausea, syncope, and signs of congestive

heart failure. Care should be taken when diltiazem is combined with negative inotropic drugs, other calcium channel blockers, and digoxin. Combination therapy increases the risk of bradycardia, conduction abnormalities, hypotension, and signs of congestive heart failure [3; 26; 54].

Verapamil

Oral verapamil preparations may also be prescribed for chronic rate control. Available in immediate- and extended-release forms, oral verapamil can control ventricular rate at rest and with activity.

In addition, research has shown that verapamil may have the additional benefit of reducing atrial electrophysiologic remodeling (the process thought to be responsible for frequent recurrence of atrial fibrillation and resistance to successful cardioversion). Immediate-release preparations must be taken three to four times per day at evenly spaced intervals; extended-release dosing may be administered once per day. Oral verapamil should be used with caution in persons with conduction defects and left ventricular dysfunction. Oral verapamil should not be prescribed for persons with WPW syndrome. There is increased risk of bradycardia, bradyarrhythmias, conduction abnormalities, hypotension, and development of congestive heart failure when combined with administration of other calcium channel blockers, negative inotropes, or digoxin [3; 26; 55].

Digoxin

Oral digoxin may be the first drug of choice for patients with atrial fibrillation and congestive heart failure caused by systolic dysfunction [62]. Digoxin does not provide adequate rate control during exercise or activity. The usual oral maintenance dose of digoxin is 0.125–0.25 mg daily. Serum digoxin levels should be monitored periodically. The patient should be monitored for signs of digitalis toxicity. The patient and/or family should be taught to recognize key signs of toxicity. These include nausea and vomiting, headache, unexplained weakness, malaise, and visual disturbances as well as slow heart rate. ECG changes that may occur with digitalis toxicity include sinus bradycardia, heart block, and multiple tachyarrhythmias. Digitalis toxicity is more likely to occur in elderly persons. Electrolyte imbalances such as hypokalemia, renal failure, or combined therapy with other antiarrhythmic agents may potentiate the effects of digoxin and increase the risk of digitalis toxicity. Severe digitalis toxicity may be treated with digoxin immune Fab [26].

Fab is an antibody produced in sheep. When Fab is administered intravenously, it binds to unbound digoxin in the bloodstream and facilitates its removal, thus reducing the serum digoxin level. The precise dose of Fab may be calculated on the basis of the amount of digitalis ingested or on the patient's serum digoxin level. In emergency situations when the amount of digoxin ingested is not known and a serum digoxin level is not available, a Fab dose of 800 mg in two divided doses may be administered IV. This dose should be diluted according to package instructions and administered over 15 to 30 minutes. Continuous monitoring of ECG, pulse, blood pressure, and temperature before and during infusion should be done. Following the administration of Fab, persons with atrial fibrillation (or a history of atrial fibrillation) may experience recurrence of the arrhythmia or a loss of rate control, and persons with congestive heart failure may develop signs of an exacerbation such as dyspnea, hypotension, or rales [26].

Metoprolol

Oral metoprolol is not labeled for management of atrial fibrillation; however, in patients with coronary artery disease, hypertension, and angina, it may be prescribed for rate control plus its other therapeutic effects. Its off-label use for rate control in patients with paroxysmal, persistent, or permanent atrial fibrillation is recommended by the AHA/ACC/HRS [23]. It may exert cumulative effects on heart rate, rhythm, and blood pressure when given in combination with calcium channel blockers, other beta blockers, or disopyramide resulting in bradycardia, bradyarrhythmias/heart block, and hypotension. The usual oral dose may range from 25–100 mg twice daily. Metoprolol is available in short-acting and extended-release preparations. Extended-release preparations are administered only once per day. Side effects include those common to beta blockers [3; 26].

Propranolol

Oral propranolol, another beta adrenergic blocking agent, may also be prescribed for long-term rate control in atrial fibrillation. Unlike metoprolol, propranolol is approved for use in atrial fibrillation. The usual oral maintenance dose is 30–160 mg per day in divided doses. Side effects include nausea, vomiting, diarrhea, constipation, insomnia, depression, bronchospasm, hypoglycemia, fatigue, and impotence [3; 26].

PHARMACOLOGIC CARDIOVERSION

Based on the assessment of a patient's status, it may be determined that restoration of normal sinus rhythm is a major goal. Persons who continue to demonstrate signs of decreased cardiac output from loss of atrial kick, such as continuing shortness of breath, fatigue, signs of congestive heart failure, and diminished exercise tolerance despite adequate rate control, may require restoration of sinus rhythm to alleviate symptoms and improve quality of life. Restoring normal sinus rhythm can be done chemically through the use of intravenous or oral medications, or through direct current electrical cardioversion. Although pharmacologic cardioversion remains more popular, it appears to be most effective when initiated within seven days of the onset of atrial fibrillation [3; 23]. Unlike electrical cardioversion, pharmacologic cardioversion requires no anesthesia, has fewer risks, and is less costly. This section will review the antiarrhythmic medications that may be used for pharmacologic cardioversion, including ibutilide, dofetilide, amiodarone, propafenone, procainamide, quinidine, and flecainide [3; 6; 19; 20; 23; 30; 38; 39; 42; 46; 63; 64]. See **Table 6** for a summary of select antiarrhythmic agents that may be used for pharmacologic cardioversion.

IBUTILIDE

Ibutilide is a drug approved by the FDA for the acute termination of atrial fibrillation and atrial flutter. A Class III antiarrhythmic, ibutilide acts by prolonging the duration of the action potential, the atrial refractory period, and the ventricular refractory period. It also slightly slows the sinus rate and conduction through the AV node. Ibutilide's exact mechanism of action is unknown [26]. On a cellular level, it has been reported to exert its effects by both blocking repolarizing potassium currents and initiating an inward depolarizing sodium current [49]. Ibutilide does not appear to have a direct impact on cardiac output, but monitoring for conduction disturbances and heart block is recommended [26].

Proarrhythmic Effects

Because ibutilide prolongs the ventricular refractory period (reflected by a prolonged QT interval), the risk of torsades de pointes is significant. Torsades de pointes is a rapid, polymorphic form of ventricular tachycardia. See **Figure 3** for more information about torsades de pointes. With ibutilide administration, the risk of torsades de pointes is dependent on the dose of ibutilide administered; the higher the dose, the greater the risk.

Dosage

For an adult weighing 60 kg or more, the initial dose is 1 mg diluted to a total volume of 50 mL administered over 10 minutes. If conversion to normal sinus rhythm does not occur, the dose may be repeated 10 minutes after completion of the first dose. For patients who weigh less than 60 kg, the dose of ibutilide should be reduced to 0.01 mg/kg administered over 10 minutes [26].

Drug Interactions

If administered with other antiarrhythmics and medications (e.g., tricyclic antidepressants, dronedarone) that prolong the QT interval, ibutilide can interact with these medications to create a dangerously prolonged QT interval [26].

ANTIARRHYTHMIC AGENTS USED FOR PHARMACOLOGIC CARDIOVERSION					
Agent	Class	Action	Dosage/Route	Side Effects	Comments
Ibutilide	III	Used for rapid conversion of atrial fibrillation/atrial flutter of recent (<3 months) duration Prolongs duration of action potential Prolongs atrial and ventricular refractory periods Slightly slows sinus rate Slightly slows AV conduction	IV: Dilute 1 vial (1 mg/10 mL) to total volume of 50 mL (Concentration of diluted solution: 0.02 mg/mL) 1 mg over 10 mins at rate of 5 mL/min (or 300 mL/hr) May repeat dose 10 mins after completion of 1st dose Stop infusion as soon as rhythm converts For patients <60 kg, dose reduced to 0.01 mg/kg over 10 minutes	Prolongs QT interval (greater effect with higher doses) Torsades de pointes Other ventricular arrhythmias Angina Heart block Hypotension Nausea	Discontinue other antiarrhythmic agents that prolong QT intervals before administering ibutilide Electrolyte imbalances, especially potassium and magnesium, should be corrected before ibutilide is given Continuous ECG monitoring should be performed during and 4 hours after administration Increased risk of proarrhythmia if given with Class Ia, Class III antiarrhythmics, phenothiazines, tricyclic antidepressants, some antihistamines Contraindicated for patients with history of torsades de pointes Patients with fibrillation >48 hours duration should be anticoagulated before receiving ibutilide Other antiarrhythmic agents should not be started until 4 hours after ibutilide infusion is completed
Dofetilide	III	Converts atrial fibrillation, atrial flutter to NSR Maintains NSR following conversion from atrial fibrillation Blocks delayed rectifier potassium currents, thus delaying repolarization in cardiac tissue Does not affect other repolarizing potassium currents, sodium channels, adrenergic receptors	Oral dosing must be calculated individually based on QTc and creatinine clearance Continuous ECG monitoring required In patients with heart failure, QTc and serum creatinine must be obtained before initiating therapy Maximum daily dose: 500 mcg twice daily Usual dose: 125–500 mcg twice daily	Torsades de pointes Other ventricular arrhythmias Angina Hypertension Palpitations Bradycardia MI Ventricular fibrillation Abnormal conduction Headache Dizziness Nausea Diarrhea Cerebral ischemia	May only be prescribed by prescribers who have completed the dofetilide education program on dosing and initiation of therapy When effective as cardioversion, works within 1 hour Must be initiated in hospital setting Dosage must be individualized and renal function analyzed; specific information is provided as part of required education training Contraindicated for patients with QTc interval >440 msec or severe renal insufficiency failure If QTc increases after initiation of therapy, dose must be reduced or stopped OD results in prolonged QT interval. To treat OD, may use isoproterenol infusion, cardiac pacing, IV magnesium (if torsades de pointes is present)

Table 6 continues on next page.

ANTIARRHYTHMIC AGENTS USED FOR PHARMACOLOGIC CARDIOVERSION (<i>Continued</i>)					
Agent	Class	Action	Dosage/Route	Side Effects	Comments
Amiodarone ^a	III	Inhibits AV conduction Prolongs action potential Prolongs refractory period Inhibits adrenergic stimulation Can convert atrial fibrillation to NSR (unlabeled use)	Oral dosing: 1.2–1.8 g/day in divided doses to a total of 10 g Follow with 200–400 mg/day as a single maintenance dose IV: 5–7 mg/kg over 30 to 60 minutes Follow with 1.2–1.8 g/day by continuous IV infusion. Initial loading dose may be IV followed by oral administration. After target dose of 10 g total dose achieved, switch to maintenance dose of 200–400 mg/day	Bradycardia Heart block VF, incessant VT Torsades de pointes Hypotension (with IV) Pulmonary fibrosis Corneal deposits Photosensitivity Blue skin Hyper-/hypothyroid Liver dysfunction Tremor Malaise Fatigue GI upset Dizziness Poor coordination Peripheral neuropathy	Initial drug of choice for patients with CHF May be secondary drug of choice for patients with CAD May be used to slow conduction through accessory pathways Obtain baseline data before initiating: chest x-ray, thyroid function, renal tests, pulmonary function tests Patients' QTc interval should be monitored Potassium and magnesium levels should be measured
Propafenone	Ic	Slows conduction by changing ion transport across cardiac cell membranes Converts paroxysmal atrial fibrillation to NSR	Initial oral dosing: 450 mg (weight <70 kg) ^b 600 mg (weight ≥70 kg) ^b Maintenance: 150–300 mg every 8 hours ^b	Nausea Anorexia Constipation Dizziness Headache Blurred vision CHF Bradycardia AV block	Does not prolong QT interval, so less risk of torsades de pointes Should not be used patients immediately post-MI Use in WPW under investigation
Procainamide	Ia	Increases atrial and ventricular refractory periods Converts atrial fibrillation to NSR Maintain NSR after conversion from atrial fibrillation	IV dose for conversion: Rapid loading dose: 100 mg every 5 mins until arrhythmia abolished or 1 g given. Then, wait 10 mins and administer loading infusion of 500–600 mg/30 mins. Follow with maintenance infusion at 1–4 mg/min. Stop infusion if blood pressure drops or QRS widens Oral dose: 500 mg–1 g every 4 to 6 hours (extended-release formulation)	Hypotension with IV administration Nausea and vomiting Anorexia Bradycardia Heart block Prolonged QT interval Headache Insomnia Lupus-like syndrome Rash/fever Swollen joints Agranulocytosis Pancytopenia	Serum procainamide and NAPA levels should be monitored periodically Drug of choice to treat WPW During IV administration, ECG, heart rate, and blood pressure should be continuously monitored Oral sustained-release forms should not be used for initiation of therapy

Table 6 continues on next page.

ANTIARRHYTHMIC AGENTS USED FOR PHARMACOLOGIC CARDIOVERSION (Continued)

Agent	Class	Action	Dosage/Route	Side Effects	Comments
Quinidine	Ia	Prolongs effective refractory period Increases conduction time Decreases vagal tone, thus facilitating conduction Converts atrial fibrillation to NSR Maintains NSR following conversion	Oral test dose: 200 mg several hours before full dosage Oral dosing: Sulfate: 300 mg every 8 to 12 hours Gluconate: 324 mg every 8 to 12 hours	Nausea, diarrhea Hypotension Bradycardia Tachycardia Torsades de pointes CHF Tinnitus Hearing loss	Range for therapeutic serum level is 2–6 mcg/mL Secondary drug of choice for patients with CAD Give medication with food to decrease GI side effects Rapid loading doses are associated with an increase in GI side effects Monitor QT interval, QRS width, and PR interval Indicated for use in rate controlled, stable atrial fibrillation with an uncontrolled ventricular rate, rate should be controlled with another agent before beginning quinidine IV use should be avoided due to risk of severe hypotension
Flecainide	Ic	Slows conduction through cardiac cells by blocking sodium channels Suppresses atrial fibrillation	Oral: Begin with 100 mg every 12 hours; may increase dose 50–100 mg twice daily every 4 days as needed Maximum: 400 mg/day If needed, medication may be administered every 8 hours	Dizziness Blurred vision Arrhythmias Chest pain CHF	Should be used with caution in patients with CHF, conduction defects, and impaired renal function Avoid use in patients immediately following myocardial infarction

AV = atrioventricular; CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; NAPA = N-acetylprocainamide; NSR = normal sinus rhythm; OD = overdose; VF = ventricular fibrillation; VT = ventricular tachycardia.

^a Off-label use

^b Unlabeled dose

Source: [5; 13; 20; 23; 26; 29; 30; 49; 50; 51; 52; 61; 65]

Table 6

TORSADES DE POINTES

Torsades de pointes is a very rapid type of ventricular tachycardia that is characterized by “twisting” of the QRS complexes around the ECG baseline. Occurring at a rate of 250 to 350 bpm, these complexes change from upward to a downward deflection. The amplitude of each successive complex increases gradually, then decreases gradually, leading to a spindle shape pattern. See strip below:



The major risk factor for the development of torsades de pointes is excessive prolongation of the QT interval. Antiarrhythmic medications that prolong the action potential duration (and the refractory period of ventricles) may prolong the QT interval. Contributing factors to torsades de pointes also include hypomagnesemia, hypokalemia, or pre-existing bradycardia. The drug of choice for treatment of torsades de pointes is magnesium sulfate. For treatment of torsades de pointes, dosage is 1–2 grams IV over one to two minutes followed by a continuous infusion of 1–2 grams over an hour. A total dose of 4–6 grams may be needed. Other emergency measures include use of overdrive pacing to terminate the arrhythmia, electrical cardioversion, and defibrillation.

Source: [14; 23; 26; 30; 66; 67]

Figure 3

MEASURING QT AND QTc INTERVALS

The QT interval reflects ventricular depolarization and repolarization. It is measured from the beginning of the QRS complex to the end of the T wave. The length of the QT interval is normally influenced by the heart rate, and when the rate is faster, the QT interval shortens to promote efficient depolarization, repolarization, and contraction. When the rate is slower, the QT interval is slightly longer. As a rough estimate, the QT interval is considered to be “normal” if it is less than one-half of the RR interval. When administering an antiarrhythmic medication that prolongs the QT interval, it is important to differentiate between a normally lengthened QT interval caused by a slowed heart rate and abnormally prolonged QT interval caused by side effects of the medication. This is done through a measurement known as a rate corrected QT interval or QTc. The upper limit of the QTc for women is 0.43 sec or 430 msec; for men it is 0.42 sec or 420 msec.

To calculate the QTc, follow these steps:

- Measure the QT interval. If the rhythm is irregular, measure the QT interval for 5 to 10 beats and obtain an average QT interval.
- Measure the RR interval. If the rhythm is irregular, measure the RR interval for 5 to 10 beats and obtain an average RR interval.
- Calculate the QTc by dividing the QT interval by the square root of the RR interval.

A QTc interval that increases by more than 25% from baseline (prior to medication administration) indicates that the QT interval has become dangerously prolonged.

Source: [14; 30; 58]

Table 7

Preprocedure Assessment

Prior to administering ibutilide, the patient should be assessed and the following data obtained [3]:

- When did the patient’s arrhythmia begin? Ibutilide has been found to be most effective in patients with atrial fibrillation of less than two months duration.
- What medications is the patient currently taking? Other antiarrhythmic medications that prolong the QT interval should be discontinued before ibutilide administration to reduce the risk of excessive QT prolongation and torsades de pointes.
- Is the patient adequately anticoagulated? Because of the risk that cardioversion can cause small pieces of an atrial thrombus to break loose and cause embolization, patients should be adequately anticoagulated prior to receiving ibutilide.
- Does the patient have any history of polymorphic ventricular tachycardia (torsades de pointes)? Persons with a past history of torsades de pointes should not be given ibutilide.
- Are the patient’s serum electrolytes within normal limits? The patient’s serum sodium, potassium, magnesium, and calcium levels should be assessed. Also, liver function tests, blood urea nitrogen, and creatinine levels should also be checked and be within normal limits. Hypomagnesemia and hypokalemia must be corrected before ibutilide is administered.
- What is the patient’s baseline QT interval and rate corrected QT (QTc) interval? See **Table 7** for information about calculating corrected QT intervals.

Administration

Prior to administration, ensure that the patient has a good IV access. Continuous ECG monitoring should be initiated. Consider the use of equipment that can be used for monitoring, external pacing, and defibrillation. Or, have pacing/defibrillator patches readily available for use in an emergency [26]. Have emergency equipment readily available, including a defibrillator/cardioverter, external non-invasive pacing equipment, and medications such as magnesium used in the treatment of torsades de pointes/sustained ventricular tachycardia. Some experts suggest that administering IV magnesium sulfate before administering ibutilide may lower the risk of torsades de pointes [68]. Initiate continuous blood pressure monitoring. The patient's blood pressure should be checked every five minutes during the infusion.

To prepare the ibutilide infusion for an adult 60 kg or more, 1 mg of ibutilide is diluted to a total volume of 50 mL. Ibutilide is supplied in vials containing 1 mg/10 mL or 0.1 mg/mL. It may be mixed with either D5W or 0.9 NS. When 1 mg is diluted to a total of 50 mL, the concentration of the solution will be 0.02 mg/mL [26].

Ibutilide must be administered using a volumetric pump. The desired rate is 1 mg over 10 minutes [26]. The pump may be set at a rate of 300 mL/hour or 5 mL/minute to deliver the desired dose at the desired rate. Stop infusion immediately if the patient converts to normal sinus rhythm. If the patient develops new or worsening ventricular arrhythmias, stop the infusion immediately. Check the patient's blood pressure and assess for signs of hemodynamic instability. Following the infusion, the patient's ECG should be continuously monitored for four hours or until the patient's QTc returns to his/her baseline. Although the risk of proarrhythmias is greatest within 20 minutes of the infusion, the risk persists for several hours following administration. The administration of other antiarrhythmics (e.g., amiodarone, quinidine, procainamide, disopyramide, dronedarone) that

prolong the QT interval should be avoided for four hours following ibutilide administration. Ibutilide may be used in patients who fail to convert after treatment with propafenone. It may also be used in patients whose arrhythmia recurs during treatment with propafenone or flecainide [3; 6; 14; 26; 46; 59].

DOFETILIDE

Dofetilide is a Class III antiarrhythmic approved for use in patients with atrial fibrillation and atrial flutter. Major clinical trials on dofetilide, including the European and Australian Multicenter Evaluation Research on Atrial Fibrillation Dofetilide (EMERALD) and Symptomatic Atrial Fibrillation Investigation and Randomized Evaluation of Dofetilide (SAFIRE) studies, have shown that dofetilide is effective in conversion of atrial fibrillation or atrial flutter to sinus rhythm, although it appears to be more effective in conversion of atrial flutter than atrial fibrillation [3; 64]. On the cellular level, dofetilide blocks a specific potassium current, thus prolonging the duration of the cardiac action potential and effective refractory period. Prolonging the action potential and effective refractory period increases the likelihood that the entry atrial impulses will encounter a refractory period when the cardiac cells are unable to accept another electrical impulse, and the arrhythmia will break. Because dofetilide does not slow conduction velocity, the PR and QRS intervals remain normal. It also does not cause hypotension or bradycardia. The major proarrhythmia associated with dofetilide administration is torsades de pointes due to prolongation of the QT interval. The degree of risk is related to the dosage and serum concentration of dofetilide. The higher the dose (or the higher serum concentration), the higher the risk that proarrhythmias will develop. Other proarrhythmias seen with dofetilide administration include premature ventricular contractions, broad complex ventricular tachycardia, nonsustained ventricular tachycardia, and PSVT. Following oral administration, dofetilide is almost completely absorbed; it is primarily excreted by the kidneys [26].

The administration of dofetilide is very heavily regulated by the FDA. Only approved centers and physicians who have completed required educational programming on the initiation of dofetilide may prescribe dofetilide. Physicians and centers initiating dofetilide therapy are also required to provide the patient with specific educational information [26]. This includes information on the action of the medication, its side effects, and how to obtain and take the medication. An educational kit containing a videotape, written information, and prescribing information for the patient to give to other physicians is provided to the patient. Because of the restrictions on dofetilide, only selected pharmacies may dispense the medication. The patient may be unable to obtain dofetilide from his/her usual outpatient pharmacy. At the time of discharge, the patient will be provided with a small amount of dofetilide at the prescribed dose. He/she will then receive a larger quantity of dofetilide in the mail from an approved pharmacy [69]. Dofetilide must be initiated in the hospital setting where continuous ECG monitoring and emergency resuscitation equipment is available [69]. Prior to administration, the patient's baseline QTc and creatinine clearance must be assessed. If the patient's baseline QTc exceeds 440 msec (or 500 msec if ventricular conduction abnormalities), dofetilide is contraindicated. The initial dose is determined by the patient's initial creatinine clearance [26]. A detailed algorithm is provided in the dispensing information to assist the physician and pharmacologist in determining the appropriate dosage. If the patient's renal function is severely impaired, dofetilide is again contraindicated.

Dosage and Administration

For persons with normal renal function, studies have shown that an oral dose of 500 mcg twice daily is effective in restoring normal sinus rhythm. In the presence of impaired renal function, the dose should be reduced. The dose may be as low as 125 mcg twice daily. The usual range for the maintenance dose (normal renal function) is 125–500 mcg twice daily. The administration protocol is as follows [26]:

- Admit the patient to an inpatient facility approved for dofetilide administration.
- Antiarrhythmic medications associated with prolonged QT interval (primarily Class I, Class III) should be discontinued; the guideline is at least three or more half-lives before initiation of dofetilide. Digoxin, beta blockers, and calcium channel blockers may be used to control ventricular rate during the withdrawal period of these drugs.
- Electrolyte imbalances, especially potassium and magnesium, should be corrected before therapy is initiated.
- QTc should be monitored periodically. Dosage should be reduced if QTc increases by more than 15% or exceeds 500 msec within two to three hours after initial dose. See the package labeling or website information for specific dosage reduction guidelines.
- After the second dose, if the QTc interval is greater than 500 msec (or 550 msec in the presence of ventricular conduction abnormalities), dofetilide should be discontinued.
- Continue ECG monitoring for a minimum of three days.

An overdose of dofetilide results in a dangerously prolonged QT interval. Emergency measures include isoproterenol infusion and external noninvasive cardiac pacing. If torsades de pointes develops, IV magnesium sulfate is the treatment of choice [69].

AMIODARONE

Amiodarone has received increasing attention for its ability to convert atrial fibrillation to normal sinus rhythm and to prevent atrial fibrillation in patients undergoing CABG surgery [47; 50; 70]. Categorized as a Class III antiarrhythmic, amiodarone has properties of all four classes. It inhibits conduction through the AV node, prolongs the action potential and refractory period, and inhibits adrenergic stimulation. It may be safely used for patients with congestive heart failure, coronary artery disease, and

persons with accessory pathway conduction. The proarrhythmic effects associated with amiodarone include bradycardia, heart block, ventricular fibrillation, and ventricular tachycardias including torsades de pointes. Hypotension may occur with IV administration. Amiodarone is associated with multiple severe side effects and toxic effects. These include pulmonary fibrosis, impaired vision from corneal deposits, photosensitive skin, thyroid dysfunction, and liver dysfunction [26; 71]. Prior to beginning amiodarone therapy, the physician should obtain baseline data. Appropriate data includes a chest x-ray, pulmonary function tests, thyroid function tests, liver function tests, and renal studies. Patients receiving amiodarone therapy should be monitored for development of toxic effects. Serious toxicity, including death due to bradycardia ending in cardiac arrest, has been reported [3; 26]. If symptoms develop, amiodarone should be discontinued. Use of the lowest effective maintenance dose is highly recommended due to the multitude and severity of side effects associated with amiodarone therapy. The FDA has issued a warning regarding concurrent use of amiodarone and simvastatin [72]. In patients who are taking both simvastatin and amiodarone, the dose of simvastatin should not exceed 20 mg/day [26; 68].

The usual initial dose of amiodarone is 150 mg over 10 minutes, then 1 mg/minute for six hours, then 0.5 mg/minute for 18 hours or 600–800 mg/day oral in divided doses up to 10 g/day [26]. When a cumulative dose of 10 g is reached, a maintenance dosage of 200–400 mg/day is begun. For elderly patients, dosing should be initiated at the lower end of the adult dosage range, and the maintenance dose is usually 100 mg/day. Elderly persons clear amiodarone more slowly [3; 26; 47; 50].

OTHER ANTIARRHYTHMIC MEDICATIONS

Propafenone, a Class Ic antiarrhythmic, slows conduction by changing normal ion transportation across cardiac cell membranes. Studies show it may also have Class II antiarrhythmic effects [73]. It may be used for the conversion of paroxysmal atrial fibrillation to sinus rhythm. For an adult weighing 70 kg or more, an initial dose of 600 mg orally is given, followed by a maintenance oral dose of 150–300 mg every eight hours [26]. Propafenone has less risk of torsades de pointes than other antiarrhythmic agents because it does not prolong the QT interval; however, it is still associated with the development of bradycardia, heart block, and signs of congestive heart failure. For this reason, it should not be prescribed for patients immediately following acute myocardial infarction. Other common side effects include nausea, anorexia, constipation, and headache [26]. One case of a severe drug-drug interaction with mirtazapine leading to propafenone toxicity has been reported [74].

Procainamide, a Class Ia antiarrhythmic, has been used for management of atrial arrhythmias for many years, although it may be less useful than some other agents [3]. It increases both atrial and ventricular refractory periods. It can convert atrial fibrillation to normal sinus rhythm and maintain normal sinus rhythm following conversion. Depending on a patient's status, a loading dose may be administered intravenously or orally. Extended-release forms of oral therapy should not be used for initiation of therapy. Procainamide can have proarrhythmic effects including bradycardia, a prolonged QT interval, and heart block. Worsening or refractory tachyarrhythmias can develop in the presence of procainamide toxicity. Serum levels should be carefully monitored. The therapeutic serum level of procainamide is 4–10 mcg/mL. Toxicity may develop at serum levels of more than 10 mcg/mL. For some patients, especially those with impaired renal function, the combined procainamide/N-acetylprocainamide (NAPA) level should be monitored. NAPA is an active metabolite of procainamide that has antiarrhythmic properties.

The combined procainamide/NAPA serum level should not exceed 30 mcg/mL [3; 26].

Quinidine, another Class Ia antiarrhythmic, prolongs the effective refractory period and increases conduction time. It is effective in converting atrial fibrillation to normal sinus rhythm and in maintaining sinus rhythm following conversion. Because quinidine also decreases vagal tone, thereby facilitating conduction across the AV node, it does not slow ventricular rate. It is indicated for use in patients with controlled atrial fibrillation, usually after digoxin or verapamil has been given. Patients who are in uncontrolled atrial fibrillation should receive other antiarrhythmic agents prior to starting quinidine. Although quinidine comes in an IV form, IV administration is associated with a significant risk of severe hypotension, and use of IV quinidine is discouraged [3; 26].

Flecainide is a Class Ic antiarrhythmic that acts by blocking sodium channels so that conduction through cardiac cells is slowed. Flecainide is only administered orally. Flecainide should not be prescribed for patients in the immediate post-myocardial infarction period. It should be used cautiously in patients with congestive heart failure, conduction defects, and impaired renal function [26]. It is a drug of choice for persons with paroxysmal atrial fibrillation [6; 13; 14; 15; 19; 20; 30; 39; 58; 63].

ELECTRICAL CARDIOVERSION

INDICATIONS AND TIMING

Electrical cardioversion has been found to be an effective and safe method for restoring normal sinus rhythm in a number of patients. It is the treatment of choice for persons with hemodynamically unstable atrial fibrillation [23]. Electrical cardioversion is also indicated for:

- Persons for whom there is a reasonable expectation that normal sinus rhythm can be restored and maintained

- Persons who require “atrial kick” to relieve incapacitating or unpleasant symptoms, improve exercise tolerance, and increase their ability to perform their usual daily activities
- Persons who would benefit from normal sinus rhythm but who have not been able to be successfully cardioverted pharmacologically (i.e., “failed” pharmacologic cardioversion)

It is not indicated for prevention of subsequent episodes [75]. Cardioversion of atrial fibrillation and subsequent maintenance of sinus rhythm are more likely to be successful when the duration of atrial fibrillation is less than six months [23]. Because electrical cardioversion carries the risk of thromboembolic complications, it generally should be performed when the patient is adequately anticoagulated. Cardioversion may be performed without first anticoagulating the patient only when he/she is hemodynamically unstable and requires immediate intervention, when the patient has been in atrial fibrillation less than 48 hours, or when the absence of an atrial thrombus has been confirmed by TEE [6; 20; 23; 40; 51; 75; 76].

ANTICOAGULATION GUIDELINES

As indicated, anticoagulation before cardioversion is required for most patients. Warfarin should be initiated, and the dose adjusted to reach and maintain a target goal of an international normalized ratio (INR) of 2.5 (range: 2.0 to 3.0). After the patient has been maintained for three weeks at that therapeutic goal, cardioversion may be performed. Following cardioversion, anticoagulation should be maintained for four weeks. As an alternative, patients who need cardioversion may be admitted to the hospital and placed on a heparin drip [75]. A TEE is performed to rule out the presence of atrial thrombi. If no thrombi are present, the cardioversion may be safely performed [23]. Following the procedure, the patient should receive anticoagulation therapy for four weeks [3; 6; 76; 77].



For patients with atrial fibrillation of greater than 48 hours or unknown duration undergoing elective electrical or pharmacologic cardioversion, the American College of Chest Physicians recommends therapeutic anticoagulation for at least four weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of the baseline risk of stroke.

([https://journal.chestnet.org/article/S0012-3692\(18\)32244-X/fulltext](https://journal.chestnet.org/article/S0012-3692(18)32244-X/fulltext). Last accessed October 12, 2020.)

Strength of Recommendation/Level of Evidence:
Strong recommendation, moderate-quality evidence

PREPROCEDURE

Prior to the procedure, the patient should be carefully assessed. Serum electrolytes and serum drug levels of medications such as digoxin should be checked. Electrolyte imbalances should be corrected. The administration of IV electrolytes has been found to increase the success rate of cardioversion in patients with persistent atrial fibrillation [78]. Testing for elevated C-reactive protein levels may predict the recurrence of atrial fibrillation following cardioversion [79; 80; 81; 82]. Cardioversion should not be performed if the patient has digitalis toxicity. A baseline 12-lead ECG should be obtained. Oral antiarrhythmic medications, such as oral amiodarone or sotalol, may be started prior to the cardioversion. In some patients, this will facilitate conversion to normal sinus rhythm and maintenance of sinus rhythm following the procedure. The patient should be adequately sedated with a short-acting agent (e.g., midazolam, propofol), and an opioid analgesic, such as fentanyl, is commonly used. Reversal agents (e.g., flumazenil, naloxone) should be available [76]. The risks of the procedure should be explained to the patient and family. Common risks include the problems associated with moderate sedation, skin burns, and the development of proarrhythmias [76]. The procedure should be explained briefly to patients. Consider including these points [3]:

- An IV access will be established.
- The patient will be “nothing by mouth” (NPO) for several hours prior to the procedure.
- The patient’s ECG, blood pressure, and oxygen saturation levels will be continuously monitored before, during, and following the procedure.
- The patient will be sedated or general anesthesia will be used.

Potentially life-threatening postprocedure events may occur, including the induction of ventricular tachycardia/fibrillation, asystole, and transient depression of myocardial function. Techniques to handle these situations should be readily available to prevent complications [75; 76].

PROCEDURE AND POSTPROCEDURE CARE

A variety of commercially available external cardioverters are available for external electrical cardioversion. The physician in charge of the procedure should be thoroughly familiar with the chosen device [75; 83]. ECG leads are placed on the patient. The cardioverter delivers a programmed shock in synchronization with the patient’s own QRS. Synchronization decreases the risk that the patient will go into ventricular fibrillation from the electrical shock. The initial shock may be a low voltage. If unsuccessful, the voltage will be increased. Following completion of the procedure, the patient will be monitored until he/she is recovered from the anesthesia/sedation. As noted, follow-up care includes oral antiarrhythmic therapy and oral anticoagulation with warfarin sodium [51; 60; 75]. In patients for whom external cardioversion is unsuccessful, an internal shock with electrode catheters has been shown to be successful [75; 84; 85].

PHARMACOLOGIC THERAPY FOR MAINTENANCE OF NORMAL SINUS RHYTHM

GENERAL GUIDELINES

For patients in atrial fibrillation, restoration of normal sinus rhythm may occur spontaneously or through electrical or pharmacologic cardioversion. Regardless of the mechanism of conversion, antiarrhythmic therapy is usually indicated to maintain sinus rhythm (**Table 8**). Some reversion to atrial fibrillation is likely to occur despite optimal antiarrhythmic therapy. However, some patients may benefit from therapy that restores sinus rhythm for prolonged periods [3; 23]. The effectiveness of antiarrhythmic therapy in maintaining normal sinus rhythm should be based on an evaluation of the severity and duration of episodes and not on their occurrence. The following are general principles for initiating drug therapy for maintenance of normal sinus rhythm [3; 23; 47; 78]:

- Selected medications should be given initially in low doses and increased as needed. Closely monitor the patient for therapeutic effect/desired effect and side effects.
- To prevent drug interactions, closely monitor the levels and effectiveness of other agents.
- For persons with paroxysmal atrial fibrillation, first consider the use of flecainide, propafenone, and sotalol.
- If treatment with a single medication is ineffective, combination therapy may be tried. Effective combinations include use of a beta blocker, sotalol or amiodarone, and a Class Ic medication.
- Closely monitor the patient for widening QT intervals.
- Counsel the patient to avoid the concurrent use of noncardiac medications that can prolong the QT interval.

SPECIFIC MEDICATIONS

Oral antiarrhythmic medications found to be effective in maintaining normal sinus rhythm include quinidine, disopyramide, flecainide, propafenone, sotalol, amiodarone, dofetilide, and dronedarone. However, pharmacologic therapy should be abandoned if symptomatic improvement is not achieved or if the patient experiences any adverse effects [3; 42; 86; 87]. In addition to possible adverse effects, some antiarrhythmic medications (i.e., disopyramide, quinidine, and sotalol) may increase mortality. Possible benefits on clinically relevant outcomes (e.g., stroke, embolism, heart failure) remain to be established [70].

Quinidine

Quinidine is available in different salts as quinidine sulfate or quinidine gluconate. Its use in patients with paroxysmal atrial fibrillation has not been extensively evaluated, although it appears to be as effective as Class Ic agents. It has been shown to significantly reduce the recurrence of atrial fibrillation [70]. Quinidine can be associated with severe gastrointestinal (GI) side effects, including nausea and diarrhea. Development of proarrhythmia is a concern [3]. The medication should be administered with food or milk to decrease GI effects [26]. If severe GI side effects persist, the type of preparation may be changed (i.e., from gluconate to sulfate or vice versa).

Disopyramide

Disopyramide may be administered in a short- or sustained-release form. Because it prolongs the QT interval, it is not indicated as a first drug of choice for persons who also have hypertension. The combination of left ventricular hypertrophy caused by long-standing hypertension and a prolonged QT interval greatly increases the risk of proarrhythmias such as torsades de pointes [26].

Flecainide

Flecainide is the drug of choice for the treatment of atrial fibrillation that has no identifiable cause. It is recommended for use only in the absence of structural heart disease and should not be prescribed for patients who have had a recent myocardial infarction or have abnormal left ventricular function [26].

ANTIARRHYTHMIC MEDICATIONS USED TO MAINTAIN SINUS RHYTHM					
Agent	Class	Action	Dosage/Route	Side Effects	Comments
Quinidine	Ia	Prolongs effective refractory period Increases conduction time Decreases vagal tone, thus facilitating conduction across AV node Converts atrial fibrillation to NSR Maintains NSR following conversion	Varies with preparation. Sulfate (immediate-release): 400 mg every 6 hours Sulfate (extended-release): 300–660 mg every 8 to 12 hours Gluconate (sustained-release): 324–628 mg every 8 to 12 hours	Nausea, diarrhea Hypotension Bradycardia Tachycardia Torsades de pointes CHF Tinnitus Hearing loss	Secondary drug of choice for patients with CAD Give medication with food to decrease GI side effects Monitor QT interval, QRS width, and PR interval Indicated for use in rate controlled, stable atrial fibrillation If patient is in atrial fibrillation with uncontrolled ventricular rate, rate should be controlled with another agent before beginning quinidine IV use should be avoided due to risk of severe hypotension
Disopyramide ^a	Ia	Prevents atrial fibrillation Slows conduction through accessory pathways	Usual oral dose, immediate-release: 100 – 200 mg every 6 hours Usual oral dose, controlled-release: 200 – 400 mg	Dry mouth Urinary retention Constipation Glaucoma Negative inotropic effects Increased QT interval	Monitor patient's QT interval
Flecainide	Ic	Maintains NSR Slows conduction through accessory pathways	Maintenance oral dose: 50–150 mg every 12 hours Maximum: 400 mg/day	CHF Bradycardia Heart block Blurred vision Dizziness Flushing Tinnitus Drowsiness Headache Constipation Abdominal pain Prolongs QT interval Increases risk for proarrhythmias	Drug of choice for treatment of atrial fibrillation that has no identifiable cause Recommended for use in absence of structural heart disease only Should not be used in patients with recent MI or who have abnormal LV function May take up to 5 days to achieve complete therapeutic effect
Propafenone	Ic	Slows conduction by changing ion transport across cardiac cell membranes Converts paroxysmal atrial fibrillation to NSR Maintains NSR	Maintenance oral dose: 150–300 mg three times daily	Nausea and anorexia Constipation Dizziness Headache Blurred vision CHF Bradycardia AV block	Effective for use with patients who also have hypertension Secondary drug of choice for atrial fibrillation that has no identifiable cause Does not prolong QT interval so there is less risk of torsades de pointes Should not be used in patients immediately post-MI Use in WPW under investigation

Table 8 continues on next page.

ANTIARRHYTHMIC MEDICATIONS USED TO MAINTAIN SINUS RHYTHM (Continued)					
Agent	Class	Action	Dosage/Route	Side Effects	Comments
Sotalol	II with Class III properties	Blocks beta adrenergic receptors resulting in slowed heart rate, decreased AV node conduction, and increased refractory period of AV node Prolongs cardiac action potential Maintains NSR after cardioversion	Usual oral dose: 80–160 mg twice daily May increase up to 320 mg/day in 2 to 3 divided doses	Torsades de pointes VT, VF Bradycardia Hypotension Heart block CHF Bronchospasm Fatigue Weakness GI symptoms Dizziness Dyspnea	Hypokalemia, hypomagnesemia increase risk of proarrhythmias; deficits must be corrected before therapy is initiated Effective for use in patients with concurrent CAD Use with caution in patient <2 wks post-MI Dosing should be adjusted for patients with renal impairment; see package insert for guidelines Initial drug of choice for patients with atrial fibrillation that has no identifiable cause Risk of torsades de pointes increases with doses >320 mg/day Only one sotalol preparation labeled for use in atrial fibrillation Manufacturer of labeled preparation recommends therapy be initiated in facility equipped with continuous ECG monitoring, and cardiac resuscitation Continuous ECG monitoring recommended for 3 days (when on maintenance dose)
Amiodarone ^a	III	Slows conduction through AV node Prolongs QT interval Prolongs QRS duration Maintains NSR after conversion	Oral loading dose: 800–1,600 mg/daily in divided doses for a period of 1 to 3 weeks (until control achieved or intolerable side effects occur). Follow with 600–800 mg/day in 1 to 2 doses Maintenance oral dose: 100–400 mg per day	Bradycardia Heart block Hypotension Corneal deposits Photodermatitis Paresthesias Tremor Ataxia Headache Hyper-/hypo-thyroidism Constipation Pneumonitis Pulmonary fibrosis	Initial drug of choice for patients with CHF May be secondary drug of choice for patients with CAD Obtain baseline data before initiating: chest x-ray, liver and thyroid function and renal tests, pulmonary function tests Slow-acting will take several weeks to reach therapeutic level Takes several weeks for side effects to disappear after drug stopped Patient's QTc interval should be monitored Periodic monitoring of potassium and magnesium levels should be done
Table 8 continues on next page.					

ANTIARRHYTHMIC MEDICATIONS USED TO MAINTAIN SINUS RHYTHM (Continued)					
Agent	Class	Action	Dosage/Route	Side Effects	Comments
Dofetilide	III	Converts atrial fibrillation, atrial flutter to NSR Maintains NSR following conversion from atrial fibrillation Blocks delayed rectifier potassium currents, thus delaying repolarization in cardiac tissue Does not affect other repolarizing potassium currents, sodium channels, adrenergic receptors	Oral dosing: Must be calculated individually based on QTc and creatinine clearance. Continuous ECG monitoring required Patients' heart rate, QTc, and serum creatinine must be obtained before initiating therapy Usual dose: 125–500 mcg twice daily Maximum: 500 mcg twice daily	Torsades de pointes Other ventricular arrhythmias Hypertension Palpitations Bradycardia MI Ventricular fibrillation Abnormal conduction Headache Dizziness Nausea Diarrhea Cerebral ischemia	May only be prescribed by prescribers who have completed the dofetilide education program on dosing and therapy Must be initiated in hospital setting Dosage must be individualized based on patient's QT intervals and renal function; specific information is provided as part of required educational training Contraindicated for patients with QTc interval If QTc increases after initiation of therapy, dose must be reduced or stopped
Dronedarone	III	Inhibits sodium, potassium channels, thus prolonging the action potential and refractory period Similar to amiodarone, it inhibits alpha1-receptor mediated increases in blood pressure	Usual oral dose: 400 mg twice daily	Bradycardia Dermatitis Eczema Diarrhea, nausea Abdominal pain	Contraindicated in patients with severe heart failure requiring recent hospitalization Rare but severe liver injury has been reported
AV = atrioventricular; CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; NSR = normal sinus rhythm; VF = ventricular fibrillation; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome. ^a Off-label use					
Source: [3; 26]					Table 8

Propafenone

Propafenone is an effective antiarrhythmic for persons who also have hypertension because it does not prolong the QT interval. Studies suggest it reduces the recurrence of atrial fibrillation [70]. It should not be prescribed for patients immediately following acute myocardial infarction [26].

Sotalol

Sotalol has been gaining popularity in the management of atrial fibrillation. It has both Class II (beta adrenergic blocking) and Class III properties. It slows the heart rate, decreases conduction through the AV node, increases AV node refractory period, and prolongs the cardiac action potential. It has

been found to be effective in maintaining normal sinus rhythm. Administered orally, the initial dose for the person with normal renal function is 80 mg twice daily. This dose may be gradually increased over a period of days to a maximum of 640 mg total daily dose. The usual dose is 80–160 mg twice daily. Dosage should be reduced in the presence of renal impairment [26]. For persons undergoing electrical cardioversion, sotalol may be started prior to the procedure to facilitate cardioversion and continued maintenance of sinus rhythm. The manufacturer of the proprietary form of sotalol warns that only one preparation has been labeled for use in atrial fibrillation. See the package insert for additional information [88]. Because it prolongs the QT inter-

val, sotalol has a proarrhythmic effect; arrhythmias associated include torsades de pointes, other forms of ventricular tachycardia, ventricular fibrillation, bradycardia, and heart block. Hypotension and signs of congestive heart failure may occur. Increased risk of all-cause mortality has been suggested [70]. Hypokalemia and hypomagnesemia increase the risk of proarrhythmic effects. Torsades de pointes has been associated with doses in excess of 320 mg/day [26]. The manufacturer recommends that sotalol be initiated in a hospital setting with continuous ECG monitoring. The facility must be equipped with cardiac resuscitation equipment/staff. ECG monitoring is recommended to continue for three days when the patient is on a maintenance dose [26].

Amiodarone

Amiodarone is a drug of choice to maintain normal sinus rhythm in patients with congestive heart failure. Studies suggest it reduces the recurrence of atrial fibrillation [70]. It has the added benefit of providing effective rate control, thus eliminating the need for other drugs to control rate. It is a secondary or last resort choice to maintain sinus rhythm in persons with coronary artery disease. Because of the multiple side effects and toxicities of amiodarone, persons receiving it should be monitored periodically, and the lowest effective maintenance dose should be used [3].

Dofetilide

Dofetilide may be used for maintenance of normal sinus rhythm. As described, dofetilide therapy must be initiated in an approved hospital by medical practitioners who are approved to initiate and prescribe dofetilide therapy. Evaluation for use of this drug in the elderly is imperative [3; 13; 15; 19; 26; 27; 39; 40; 46; 47; 58].

Dronedarone

Dronedarone is among several new drugs developed for the management of atrial fibrillation. It received FDA approval in 2009 for the management of atrial fibrillation and atrial flutter. Dronedarone shares many antiarrhythmic properties with amiodarone but has a more favorable safety profile and fewer adverse effects. Its use is contraindicated in patients with severe heart failure requiring recent hospitalization [23; 26; 88; 89; 90; 91; 92]. According to the 2011 focused guideline update, dronedarone may be considered in the management of patients with paroxysmal atrial fibrillation or after conversion of persistent atrial fibrillation [87]. It should not be used for rate control in permanent atrial fibrillation [23]. Dronedarone may be used for the prevention of recurrent atrial fibrillation [42; 70]. In addition, this medication may be initiated in the outpatient setting [23]. It is important to note that the FDA issued a drug safety announcement about cases of rare, but severe liver injury, in patients being treated with dronedarone. The risk of injury has been added to labeling for the drug [93].

PILL-IN-THE-POCKET APPROACH

The ACC/AHA/ESC Task Force for management of patients with atrial fibrillation has suggested that outpatient maintenance of sinus rhythm, the “pill-in-the-pocket” approach, shows promise. This approach allows for intermittent (rather than daily) administration of oral antiarrhythmic medication as an acceptable treatment option for patients with sporadic episodes of atrial fibrillation. It is not recommended for patients with daily episodes [3; 23]. Self-administration of oral antiarrhythmic drugs improves the patient’s quality of life, decreases overall hospital admissions, and reduces treatment costs. Class Ic drugs, such as propafenone and flecainide, are recommended for their efficacy, rapid action, and safety (i.e., no organ toxicity and low incidence of proarrhythmia). They are not recommended for patients with underlying structural heart disease [3; 7; 23; 87].

PREVENTION OF THROMBOEMBOLIC COMPLICATIONS

Atrial fibrillation has been identified as the most common disorder leading to systemic embolization [6; 94; 95]. Remember that in atrial fibrillation, the atria merely “quiver.” They never fully contract to expel all of the blood from the chambers into the ventricles. The blood that remains in the atria becomes stagnant, allowing clots to form. A thrombus (clot) is most likely to form in the left atrium. Soft, friable fragments of the clot may break off and flow into the ventricle, where they are ejected into the systemic or pulmonary circulation. The most common thromboembolic event linked to atrial fibrillation is the development of a CVA. The statistics are alarming. For example, atrial fibrillation is associated with a four- to fivefold increased risk of stroke and causes an estimated one in seven strokes [96]. The overall mortality rate associated with CVAs is significant. Up to 20% of persons who have a CVA may die within the first year, and one-quarter to one-half of all who survive experience permanent neurologic damage resulting in partial or total loss of independence and activities of daily living [70; 97]. The associated direct and indirect costs are high [97]. Persons with atrial fibrillation are at increased risk for CVA if they have one or more of the following risk factors: advanced age, history of previous CVA, history of transient ischemic attacks (TIAs), history of previous systemic embolism, history of left ventricular dysfunction, heart failure, diabetes mellitus, or hypertension [3; 8; 98; 99].

National recommendations are to anticoagulate persons with atrial fibrillation. Persons who should be anticoagulated include [3; 23; 33; 38]:

- Persons who fail pharmacologic or electrical cardioversion and remain in atrial fibrillation

- Persons who experience permanent/persistent/chronic atrial fibrillation
- Persons who have converted to normal sinus rhythm but have recurrence of atrial fibrillation



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

According to the AHA/ACC/HRS, antithrombotic therapy for patients with atrial fibrillation should be individualized based on shared decision making after discussion of the absolute and relative risks of stroke and bleeding and the patient's values and preferences.

(<https://www.ahajournals.org/doi/10.1161/CIR.0000000000000665>. Last accessed October 12, 2020.)

Strength of Recommendation/Level of Evidence: IC
(The procedure/therapy should be performed based on expert opinion, case studies, or standard of care.)

Despite the existence of national recommendations to anticoagulate patients with atrial fibrillation, a systematic review revealed that less than 70% of eligible patients receive oral anticoagulation treatment, including those at highest risk [100]. Another review of anticoagulation therapy in patients with high-risk atrial fibrillation before admission for stroke revealed that 29% were not receiving any anticoagulation therapy, 31% were prescribed antiplatelet therapy, and only about one-fourth of the 39% receiving warfarin achieved therapeutic INR levels [101].

The specific type of therapy recommended depends on an assessment of the patient's level of risk to develop thromboembolic complications, irrespective of the pattern of atrial fibrillation [3; 23; 38; 42]. Stroke-risk stratification schemes for patients with atrial fibrillation were developed in the late 1990s and later refined and validated in large population studies [102; 103; 104; 105; 106]. The CHADS₂ score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke [double weight]), first published in 2001, was developed to predict the risk of stroke in patients with nonrheumatic atrial

CHA ₂ DS ₂ -VASc SCORING SYSTEM FOR ATRIAL FIBRILLATION STROKE RISK			
Age	<65 years (0 points)	65–74 years (1 point)	≥75 years (2 points)
Sex	Female (1 point)		Male (0 points)
CHF History	No (0 points)		Yes (1 point)
Hypertension History	No (0 points)		Yes (1 point)
Stroke/TIA/Thromboembolism History	No (0 points)		Yes (2 points)
Vascular Disease History ^a	No (0 points)		Yes (1 point)
Diabetes History	No (0 points)		Yes (1 point)
CHF = congestive heart failure; TIA = transient ischemic attack; MI = myocardial infarction; PAD = peripheral artery disease			
^a Defined as prior MI, PAD, and/or aortic plaque.			
Source: [112]			Table 9

CHA ₂ DS ₂ -VASc SCORE AND CORRESPONDING ANNUAL STROKE RISK	
CHA ₂ DS ₂ -VASc Score	Adjusted Stroke Risk (% per year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2
Source: [116]	
Table 10	

fibrillation [103]. It was derived by combining risk factors from prior studies and then testing their validity in a cohort of 1,773 Medicare-aged patients over 2,121 patient years [102; 107]. The CHADS₂ score was found to be limited by the non-inclusion of common stroke risk factors and was subsequently expanded to include three additional independent risk factors: vascular disease, age 65 to 74 years, and female sex [108; 109; 110]. The new, more inclusive scoring system is known as the CHA₂DS₂-VASc score (**Table 9**). It has been widely used since 2010 [111; 112].



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

For patients with atrial fibrillation and an elevated CHA₂DS₂-VASc score (2 or greater in men or 3 or greater in women), the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society (AHA/ACC/HRS) recommend oral anticoagulation therapy.

(<https://www.ahajournals.org/doi/10.1161/CIR.0000000000000665>. Last accessed October 12, 2020.)

Strength of Recommendation/Level of Evidence:
IA (Strong recommendation based on high-quality evidence)

Note: Adjusted stroke rate scores (**Table 10**) are based on data from Lip and colleagues [106; 113; 114; 115]. The actual rates of stroke in contemporary cohorts may vary from these estimates.

Generally, a score of 0 indicates that no treatment is needed. A score of 1 indicates either no treatment or treatment with aspirin or an oral anticoagulant. A score of 2 or more indicates treatment with an oral anticoagulant. Anticoagulant agents routinely used for the prevention of thromboembolism in patients with nonvalvular atrial fibrillation include warfarin, direct thrombin inhibitors, factor Xa inhibitors, and antiplatelet drugs (i.e., aspirin and clopidogrel). Although anticoagulants have been effective in reducing ischemic stroke in multiple randomized controlled trials, their use is associated with an increased risk of bleeding, ranging from minor bleeding to fatal intracranial or extracranial

AHA/ACC/HRS CLASS I RECOMMENDATIONS FOR SELECTING AN ANTICOAGULANT REGIMEN

In patients with AF (except those with moderate-to-severe mitral stenosis or a mechanical heart valve), the CHA₂DS₂-VASc score is recommended for assessment of stroke risk.

For patients with AF and an elevated CHA₂DS₂-VASc score of 2 or greater in men or 3 or greater in women, OACs are recommended. Options include warfarin and the NOACs dabigatran, rivaroxaban, apixaban, and edoxaban.

NOACs are recommended over warfarin in NOAC-eligible patients with AF (except those with moderate-to-severe mitral stenosis or a mechanical heart valve). For patients with AF who have mechanical heart valves, warfarin is recommended.

Among patients treated with warfarin, the INR should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable. For patients with AF (except those with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a NOAC is recommended.

Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent, and should be individualized on the basis of shared decision-making after discussion of the absolute risks and relative risks of stroke and bleeding, as well as the patient's values and preferences. Re-evaluation of the need for and choice of anticoagulant therapy at periodic intervals is recommended to reassess stroke and bleeding risk.

Renal function and hepatic function should be evaluated before initiation of a NOAC and should be re-evaluated at least annually.

AF = atrial fibrillation, OACs = oral anticoagulants, NOAC = non-vitamin K oral anticoagulant, INR = international normalized ratio.

Source: [33]

Table 11

hemorrhage. Platelet inhibitors (alone or in combination) are less effective than warfarin, are better tolerated by some patients, and are associated with a lower risk of intracerebral hemorrhage. However, they have similar overall rates of major bleeding in some studies. Careful consideration is required to balance the benefits and risks of bleeding in each individual patient [23]. The AHA/ACC/HRS class I recommendations for risk-based anticoagulant therapy are summarized in **Table 11** [33].

Two medications used commonly in prevention of thromboembolic events are aspirin and warfarin. They may be used singly or in combination to prevent thromboembolic events, but the efficacy of combination therapy has not been established [117; 118; 119; 120]. Warfarin in comparison to aspirin leads to a 39% relative risk reduction in stroke [121]. Rather than adding aspirin, the AHA/ACC/HRS Task Force recommends increasing the intensity of the anticoagulant to a maximum target INR of 2.0–3.0 [23]. Aspirin acts by decreasing platelet aggregation. Because it offers only modest protection against stroke for patients with atrial fibrillation, its use is recommended for low-risk patients [42]. As noted, low-risk patients include those who are younger than 65 years of age and have no underlying cardiac disease. It may also be recommended for use in patients, particularly elderly persons, who cannot safely take warfarin. The usual adult dose of aspirin is 81–325 mg oral per day [42].



For patients with atrial fibrillation, the American College of Chest Physicians recommends bleeding risk assessment should be performed for all patients with atrial fibrillation at every patient contact and should initially focus on potentially modifiable bleeding risk factors.

([https://journal.chestnet.org/article/S0012-3692\(18\)32244-X/fulltext](https://journal.chestnet.org/article/S0012-3692(18)32244-X/fulltext). Last accessed October 12, 2020.)

Strength of Recommendation/Level of Evidence:
Strong recommendation, low-quality evidence

WARFARIN PATIENT EDUCATION	
Topic	Content
Purpose, action of warfarin	<p>Warfarin is used to prolong the amount of time it takes the blood to clot. This prevents clots from forming inside blood vessels and the heart; it also prevents existing clots from getting bigger. It does not dissolve an existing clot.</p> <p>The effectiveness of warfarin is measured by a blood test called the prothrombin time/international normalized ratio (PT/INR).</p> <p>The usual goal for the PT/INR for someone taking warfarin is 2.0–3.0. Your healthcare provider will determine what PT/INR numbers are best for you.</p>
How to take warfarin	<p>Take warfarin at the same time every day. Always take the dose prescribed by your physician. Do not take more warfarin or less warfarin unless directed to do so.</p> <p>If you miss a dose, take it as soon as you remember. If you do not remember until the next day, do not take two doses. Taking more medication than prescribed increases the risk of bleeding.</p> <p>If you miss more than one dose, call your physician for instructions.</p> <p>Record the date and dose in a log. Bring this to your medical appointment.</p> <p>Store the medication well out of the reach of children.</p> <p>Store the medication at room temperature, away from heat and direct light. Do not store it in damp places like the bathroom or near the kitchen sink.</p> <p>Discard the medication when out of date.</p> <p>Pregnant women should not handle crushed or broken tablets.</p>
Follow-up care	<p>Keep all appointments for blood tests as scheduled. These may initially be scheduled weekly, then monthly.</p> <p>Keep your doctor's appointments. Your physician will review your blood test and may make changes in your dose to maintain a proper balance between bleeding and clotting, weekly, then monthly.</p> <p>Before receiving any medical care, let the healthcare provider know that you are taking warfarin.</p> <p>Carry identification that states you are taking warfarin.</p> <p>If you become pregnant, let your doctor know right away.</p>
Precautions: other medications	<p>Many medications may interfere with the normal action of warfarin. These include aspirin, ibuprofen, nonsteroidal anti-inflammatory drugs, cough and cold medications, antacids, laxatives, herbal supplements, vitamins containing large amounts of vitamin K, E, or C, as well as a number of prescription drugs including antiarrhythmics.</p> <p>When starting warfarin, make sure that your physician knows all the medications, including prescription, over-the-counter, and herbal/dietary supplements, that you are currently taking.</p> <p>Do not start or stop taking any medications, including over-the-counter medications, without checking with your physician.</p> <p>Do not take other medicines that contain warfarin.</p>
Precautions: diet	<p>The effects of warfarin depend on the amount of vitamin K ingested every day. Do not make large changes in the amount of vitamin K that you consume.</p> <p>If you are ill and cannot eat for several days, notify your physician. Inability to eat your normal diet will change the amount of vitamin K in your body and change the effectiveness of the warfarin.</p> <p>If you have nausea, vomiting, diarrhea, or fever for several days, notify your physician. This too will change the amount of vitamin K in your body.</p> <p>It is best to limit foods high in vitamin K to ½ cup cooked or 3 oz raw serving. These foods include green tea, beef liver, soy oil, tofu, broccoli, Brussels sprouts, cabbage, cauliflower, chickpeas, kale, lettuce, turnip greens, seaweed, and spinach.</p> <p>Avoid drinking cranberry juice or eating cranberry products.</p> <p>Consumption of alcoholic beverages can affect the way warfarin acts in your body. Avoid drinking regularly (on a daily basis). Do not take more than one to two drinks at a time.</p>
Table 12 continues on next page.	

WARFARIN PATIENT EDUCATION (<i>Continued</i>)	
Topic	Content
Precautions: measures to reduce risk of bleeding	<p>Taking warfarin makes it more likely that you will bleed from any type of injury.</p> <p>Take special care to avoid falls or other injuries.</p> <p>Use an electric razor or hair removing cream to avoid cuts.</p> <p>Use a soft toothbrush; brush and floss gently.</p>
Signs and symptoms to report	<p>Feeling tired or looking pale (anemia)</p> <p>Cuts that do not stop bleeding after applying pressure for 10 minutes</p> <p>Bleeding from nose, gums, or ears</p> <p>Blood in urine (i.e., urine that is red or rust colored)</p> <p>Bleeding in stools, or stools that are black and tarry</p> <p>Vomiting or coughing blood</p> <p>Unusually heavy menstrual bleeding</p> <p>Bruises that appear without reason</p> <p>Continuing, severe headache</p> <p>Joint pain, stiffness, or swelling</p> <p>Severe nausea and vomiting</p> <p>Numbness or tingling of hands, feet, or face</p> <p>Paralysis</p> <p>Shortness of breath</p> <p>Weakness</p> <p>Any injuries involving falls or blows to body or head</p>
Emergency care for cuts	<p>For small cuts, apply pressure directly over the cut until the bleeding stops. This may take up to 10 minutes. If bleeding does not stop after 10 minutes, go to the emergency room.</p> <p>For larger injuries, apply constant pressure and obtain immediate medical assistance.</p>
Source: [3; 50; 124]	

Table 12

WARFARIN

Warfarin is recommended for patients at high risk to develop thromboembolic events. It acts by inhibiting the synthesis of clotting factors II, VII, IX, and X that are dependent on vitamin K. Once warfarin therapy is initiated, it can take four to five days to achieve a therapeutic level. Effectiveness of warfarin therapy is evaluated by monitoring the patient's prothrombin time (PT) with the INR. The usual target level for the INR is 2.0–3.0 (target of 2.5) [20; 42]. Some clinicians recommend using the lower end of that range for elderly patients. The risk of serious bleeding complications is greater in persons older than 75 years of age. Initially the PT/INR should be monitored at least weekly. Once the therapeutic

goal is achieved, the monitoring may be reduced to monthly [33]. Drug-drug and food-drug interactions may play a significant role in maintaining a stable INR level for persons taking warfarin. Drugs that may impact warfarin effectiveness and INR levels include many anti-infectives and amiodarone. Food interactions include vitamin K containing foods that can antagonize the action of warfarin. Herbal products and nutritional supplements may contain components that can increase or decrease the effectiveness of warfarin [3; 13; 15; 122; 123].

For patients to take warfarin safely and correctly, they should receive appropriate patient education when the medication is initiated. See **Table 12** for a summary of content to include.

In some cases, warfarin may be considered unsuitable due to patient preference or the physician's assessment of the patient's ability to safely sustain anticoagulation. In these patients, the addition of clopidogrel to aspirin to reduce the risk of major vascular events, including stroke, might be considered in patients with atrial fibrillation [42]. Aspirin as monotherapy for stroke prevention is not recommended [23; 33].

ALTERNATIVES TO WARFARIN

Several non-vitamin K oral anticoagulant (NOAC) alternatives to warfarin have emerged in the last decade, including the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. The NOACs represent an advance in therapeutic safety and reduced intracranial bleeding as compared with warfarin, including no need for regular monitoring, faster onset of action, and potentially fewer adverse interactions [33; 125]. As an alternative to warfarin, the 2019 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation recommends oral anticoagulation with one of these newer agents over warfarin for patients with nonvalvular atrial fibrillation or atrial flutter with prior stroke, transient ischemic attack, or significant stroke risk [33].

Direct Thrombin Inhibitors

Dabigatran

Dabigatran etexilate mesylate (Pradaxa) is currently the only direct thrombin inhibitor approved by the FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation [23; 26]. The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial compared dabigatran (110 mg or 150 mg twice daily) with adjusted-dose warfarin in 18,113 patients over a median follow-up of two years [126]. The risk of hemorrhagic stroke was significantly (74%) lower with both doses of dabigatran compared with warfarin. Major bleeding was significantly decreased with the 110-mg dose of dabigatran but not with the 150-mg dose. Both doses had lower rates of

intracranial bleeding and life-threatening bleeding but higher gastrointestinal bleeding in the 150-mg dose group. Results were similar for secondary stroke prevention [23].

Dabigatran is contraindicated in patients who have prosthetic heart valves and those who have hemodynamically significant valve disease, severe renal failure, or advanced liver disease [26; 127]. Dabigatran acts by inhibiting the synthesis of clotting factors V, VIII, XI, and XIII. The most common complication is bleeding; patients should be monitored for signs and symptoms of bleeding. Risk factors include concurrent use of drugs that increase the risk of bleeding (e.g., heparin). Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure [33]. Dabigatran is also associated with a significantly elevated risk of myocardial infarction or acute coronary syndrome [128]. The usual adult dose is 150 mg twice daily [26; 129].

Factor Xa Inhibitors

The factor Xa inhibitors have a unique mechanism of action compared with warfarin. Factor Xa is common to both the intrinsic and extrinsic pathways of the clotting cascade making it an excellent target for anticoagulation therapy. It plays a significant role in the formation of thrombin from prothrombin. Inhibition of Xa leads to a significant reduction in thrombin and ultimately clot formation [130]. All of the currently available factor Xa inhibitors are contraindicated for use in patients experiencing active bleeding. The most serious bleeding event is intracranial hemorrhage. Patients with atrial fibrillation should be assessed for bleeding risk using the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history, labile INR, elderly, drugs/alcohol concomitant) risk score [130]. Additionally, all of the factor Xa inhibitors carry a black-box warning advising that premature discontinuation leads to increased risk for ischemic events. There are no currently approved antidotes for reversal of these agents [26; 130].

Rivaroxaban

Rivaroxaban (Xarelto) is a factor Xa inhibitor approved for prevention of stroke and systemic embolism in patients with atrial fibrillation. Rivaroxaban 20 mg once daily was compared with warfarin among 14,264 high-risk patients with atrial fibrillation [131]. Major bleeding was similar for rivaroxaban and warfarin, but fewer cases of fatal bleeding and intracranial hemorrhage were found for rivaroxaban. The risk of stroke was similar for both drugs. Bleeding is the most common complication with rivaroxaban. Major hemorrhages (e.g., intracranial, gastrointestinal, retinal, epidural, hematoma, adrenal bleeding) have been reported. Patients at increased risk of bleeding include those with congenital or acquired bleeding disorders, recent stroke, severe uncontrolled hypertension, renal impairment, advanced age, and/or concomitant use of drugs that affect hemostasis. The patient's renal function and CBC should be evaluated prior to initiation of rivaroxaban [26]. Rivaroxaban is dosed at 20 mg once daily with the evening meal [26].

Apixaban

Apixaban (Eliquis) 2.5 mg twice daily was compared with warfarin in a double-blind randomized controlled trial of 18,201 patients with atrial fibrillation and two or more of the following conditions: age 80 years or older, weight ≤ 60 kg, or a serum creatinine level ≥ 1.5 mg/dL [132]. Patients were followed for a mean of 1.8 years. Apixaban was significantly better than warfarin, with fewer overall strokes, systemic emboli, and major bleeding events, but gastrointestinal bleeding complications were similar between apixaban and warfarin. Patients treated with apixaban had fewer deaths than those on warfarin. The benefit of apixaban was independent of type of atrial fibrillation, risk profile, CHA₂DS₂-VASc score, and whether the patient had a history of prior stroke [132].

Apixaban is indicated for patients with nonvalvular atrial fibrillation to reduce the risk of stroke and systemic embolism [26]. The most common complication is bleeding; patients should be monitored for signs and symptoms of bleeding. Risk factors include concurrent use of drugs that increase the risk of bleeding (e.g., nonsteroidal anti-inflammatory drugs). Hepatic function also should be monitored [26; 33]. The usual adult dose is 5 mg twice daily [26].

Rivaroxaban or apixaban also may be used for three weeks prior to and four weeks after cardioversion in patients with atrial fibrillation or atrial flutter of 48 hours or more duration or when the duration is unknown [23; 28; 33].

Edoxaban

Edoxaban (Savaysa) is another factor Xa inhibitor approved for the prevention of thromboembolism in patients with nonvalvular atrial fibrillation. Edoxaban was approved in 2015 on the basis of a double-blind randomized trial of 21,105 patients with nonvalvular atrial fibrillation [133]. Participants were randomized to high-dose edoxaban (60 mg daily), low-dose edoxaban (30 mg daily), or warfarin; creatinine clearance up to 30 mL/min was an exclusion criteria. Edoxaban was found to be noninferior to warfarin with regard to stroke prevention or thromboembolic complications. It also was associated with significantly lower rates of bleeding and death from cardiovascular causes [133]. In patients with upper-range creatinine clearance (95 mL/min or greater), the hazard ratios for developing embolic events were similar between the high-dose edoxaban and warfarin groups [133]. Consequently, the FDA does not recommend edoxaban for patients with end-stage renal disease or for those on dialysis [133]. The usual adult dose is 60 mg once daily [26].

ELECTROPHYSIOLOGY TESTING AND ABLATION

Electrophysiology testing is an invasive diagnostic cardiovascular procedure that can confirm and pinpoint the location of accessory conduction pathway(s) in the heart. It is performed in a specially equipped cardiac catheterization lab. Multiple catheters are introduced through the femoral vein into the right side of the heart. Each catheter contains 4 to 16 electrodes for monitoring the heart's electrical activity. The catheters are positioned in various locations in the heart; common sites include the high right atrium, the apex of the right ventricle, the AV junction/His bundle, and the coronary sinus. During the procedure, specific pacing protocols are used to determine the location and characteristics of any accessory pathways. Based on the location and characteristics of the accessory pathway(s), a treatment plan will be developed. Treatment options include medical management of the syndrome and associated arrhythmias and radiofrequency ablation of the accessory pathway(s). Radiofrequency ablation is gaining in popularity as the treatment of choice. If the pathway is to be ablated, another catheter (the ablation catheter) is advanced to the site, and more extensive/precise mapping of the accessory pathway is done. The location of the ablation catheter is adjusted until it is close to the pathway. Radiofrequency energy waves are applied to the pathway until pre-excitation disappears and the tachyarrhythmia cannot be restarted. The procedure may last from three to five hours. Postprocedure care involves bedrest, frequent vital signs, and observing the femoral insertion sites for bleeding or hematoma formation.

Source: [17; 47; 57; 135; 136]

Table 13

RADIOFREQUENCY ABLATION IN THE MANAGEMENT OF ATRIAL FIBRILLATION

INDICATIONS

Radiofrequency ablation of the AV node is an interventional therapy commonly used in the management of atrial fibrillation. It has been found to be effective for persons who have significant symptoms with atrial fibrillation and/or poorly controlled ventricular rate who also [3; 19; 42; 52; 134]:

- Have remained in atrial fibrillation despite attempts at electrical or pharmacologic cardioversion or who quickly revert to atrial fibrillation following cardioversion (referred to as “failed cardioversion”)
- Cannot take antiarrhythmic medications because of severe side effects or the development of proarrhythmias
- Have inadequate rate control despite optimal dosing of appropriate antiarrhythmic agents

EVIDENCE-BASED
PRACTICE
RECOMMENDATION

The AHA/ACC/HRS recommend catheter ablation may be reasonable in selected patients with symptomatic atrial fibrillation and heart failure with reduced left ventricular ejection fraction to potentially lower the mortality rate and reduce hospitalization.

(<https://www.ahajournals.org/doi/10.1161/CIR.0000000000000665>. Last accessed October 12, 2020.)

Strength of Recommendation/Level of Evidence:
IIbB-R (A weak recommendation based on moderate-quality evidence)

Radiofrequency ablation is performed in the electrophysiology lab. See **Table 13** for additional details about electrophysiology procedures. To ablate the AV node, radiofrequency waves are sent through catheters positioned at the AV node. Radiofrequency energy is electrical energy produced by a high frequency alternating current. As this current passes through cardiac tissue, it produces heat and creates a lesion in the AV node. The atria remain in atrial

fibrillation, but no atrial impulses are conducted through the AV node to the ventricles. With AV node ablation, the patient's only effective ventricular rhythm is a junctional or ventricular escape rhythm. Because this rhythm is insufficient to meet the body's needs for cardiac output, a permanent pacemaker is inserted [19].

PRE- AND POSTPROCEDURE CARE

Prior to radiofrequency ablation of the AV node, the patient should receive information about radiofrequency ablation and permanent pacemaker insertion. Informed consent is obtained. Preprocedure evaluation should include a thorough history, physical examination, and a review ECG (12-lead if available). Laboratory studies should minimally include a complete blood cell count and an assessment of the patient's renal function and electrolyte levels. Other tests that may be indicated include exercise testing with or without cardiac imaging and cardiac catheterization [136]. The patient should be kept NPO for at least six hours prior to the procedure. Cardiac medications with electrophysiologic effects (e.g., beta-blockers, calcium channel blockers, digoxin) and Class I and III antiarrhythmic drugs should be tapered and/or discontinued. Warfarin is usually discontinued for at least a few doses preprocedure [136]. IV access should be established.

In the electrophysiology lab, the patient will be sedated, and continuous monitoring of blood pressure, heart rate and rhythm, and oxygen saturation initiated. Following the procedure, the patient's vital signs and oxygen saturation levels will be monitored closely. The patient's ECG will be monitored to evaluate proper pacemaker functioning. The sites used for insertion of the ablating catheters (usually the right and left femoral veins) will be monitored for signs of bleeding or hematoma formation.

Depending on the size of catheters used, the patient may be on bed rest for four to six hours. During this time, the patient will need to keep his/her legs straight to decrease the risk of the bleeding from the catheter insertion sites. The pacemaker insertion pocket (often in the subclavian area) is monitored for signs of bleeding or excessive swelling. The head of the patient's bed is often elevated 30 degrees for 24 hours to maintain stable placement of the pacemaker leads.

DISCHARGE INSTRUCTIONS

Patients who have received pacemakers frequently have many questions and concerns. Careful discharge teaching and provision of written information can help to alleviate anxiety. General measures to cover in discharge teaching include [46; 136]:

- Check the incision daily for signs of infection or redness, tenderness, or drainage. Notify your physician if these develop.
- Do not apply lotion or powder to the incision.
- Do not lift more than 10 pounds (or as specified by your physician) for the first four weeks following implantation. Avoid excessive pushing or pulling.
- Limit activity involving the affected arm for the length of time directed by your physician.
- Always carry your pacemaker identification card with you.

Patients and their family members often have many questions about operating home, office, or industrial equipment. Pacemaker manufacturers provide detailed information in written booklets that should be given to the patient at the time the pacemaker is implanted.

ELECTROPHYSIOLOGIC MAPPING AND ABLATION

Because the ectopic beats of atrial fibrillation can occur in various portions of the atrium, electrophysiology studies have been performed on many patients to determine the site or sites of the abnormal foci. The most common area of abnormal activity has been found to be in the vicinity of the pulmonary veins in the left atrium. This discovery led to the use of radiofrequency ablation of the pulmonary vein region as a cure for atrial fibrillation. It has even been suggested that the procedure could be used as a first-line approach to curing atrial fibrillation, because there is no need for long-term antiarrhythmic drug use. However, there is not yet a consensus on this approach as curative [136; 137; 138; 139].

Pulmonary vein isolation is achieved in the electrophysiology lab, and a dose of radiofrequency energy is delivered to ablate the desired region. New energy sources such as laser, ultrasound, and cryothermia have also been used [140; 141]. Multidimensional computed tomography (CT) and magnetic resonance angiography help visualize the anatomic landmarks necessary for ablation procedures and may also help prevent procedure-related complications [137; 140; 142]. Increasing evidence suggests that comprehensive evaluation of the left atrium using cardiac magnetic resonance imaging or CT has significant prognostic value for long-term outcomes [142; 143]. Complications include fistulas, pseudoaneurysms, TIA, and cardiac tamponade. Pulmonary vein stenosis and stroke are rare, but serious, complications [75; 137]. As with other ablation techniques, anticoagulation is initiated at the time of the procedure and continued for at least three months.

This procedure is suggested only for patients who have not responded to pharmacologic therapy with multiple antiarrhythmic medications, patients with paroxysmal atrial fibrillation, and patients with ECG evidence of an underlying electrophysiologic

disorder (e.g., WPW syndrome) [65; 144]. In 2013, the recommendations for catheter ablation were expanded to include patients with symptomatic persistent atrial fibrillation and symptomatic paroxysmal atrial fibrillation in patients with significant left atrial dilation or with significant left ventricular dysfunction [42].

MANAGEMENT OF ATRIAL FIBRILLATION FOLLOWING CORONARY ARTERY BYPASS GRAFT SURGERY

SCOPE OF THE PROBLEM AND RISK FACTORS

A common complication of CABG surgery is atrial fibrillation. Although reported rates vary, it is estimated that 15% to 50% of persons undergoing CABG surgery will develop atrial fibrillation postoperatively [3; 145]. If a patient undergoes CABG surgery combined with valve repair, the likelihood of developing atrial fibrillation increases markedly. This represents a serious problem, as it increases the length of a patient's stay and cost of care, increases the risk of CVA and of hemodynamic compromise in the postoperative patient, and causes discomfort for the patient from palpitations, dyspnea, and other signs and symptoms. Postoperative atrial fibrillation has also been found to be an independent predictor of long-term mortality [146]. Atrial fibrillation generally occurs within five days following surgery and is most likely to occur within two to three days. However, it can develop as late as three weeks postoperatively [3]. Risk factors associated with development of atrial fibrillation include [39; 40; 60; 75; 147; 148]:

- Increasing age; the risk increases in patients older than 60 years of age
- COPD

- Abrupt discontinuation of beta blocking agents prior to surgery. Research has shown that after CABG surgery, catecholamine levels may be elevated and normal beta adrenergic receptor function can be altered. These changes have been linked to the development of atrial fibrillation. Pre-operative use of beta blockers may provide some protection from these changes.
- Length of aortic cross-clamp time during the procedure. Longer cross-clamp times have been linked with an increased incidence of atrial fibrillation following surgery. Less common risk factors include chronic renal failure, an enlarged left atrium, cardiomegaly, and a history of rheumatic heart disease.
- Postoperative pericarditis

RECOMMENDED MEDICAL THERAPIES

For prevention of postoperative atrial fibrillation following CABG, many sources recommend that beta-blocker therapy be initiated (or resumed) as soon as reasonably possible following surgery [147; 149]. Prophylactic use of other antiarrhythmic agents has not been recommended. Use of digoxin has been found to have little effect and is not recommended [23]. Preoperative administration of statins may reduce postoperative atrial fibrillation and shorten the patient's stay on the ICU and in the hospital [150; 151]. Studies have found that the postoperative prophylactic use of amiodarone reduces the risk of atrial fibrillation and decreases the total cost of care [149; 152; 153]. However, the use of amiodarone and other antiarrhythmic medications, such as calcium channel blockers and procainamide has been linked to the unacceptable side effects of bradycardia and hypotension [70]. Early intervention for patients who develop increasingly frequent premature atrial contractions (PACs) has been recommended by some clinicians. However, there is no consensus regarding the best treatment. Immediate intervention is indicated for persons who develop atrial fibrillation in the postoperative period. Based on an assessment

of the patient's symptoms and hemodynamic status, medical treatment may involve intravenous medications for rate control, pharmacologic cardioversion, or electrical cardioversion along with identification and correction of factors that may contribute to the development of arrhythmias such as hypokalemia and hypomagnesemia. If atrial fibrillation persists despite appropriate therapy, anticoagulation therapy should be started as soon as the surgeon decides it is feasible. Four to six weeks following surgery, the patient's status should be re-evaluated [154; 155]. In some persons, postoperative atrial fibrillation is a relatively transient arrhythmia that may spontaneously resolve. However, for others, the arrhythmia may persist and require medical management as previously described for persons with coronary artery disease [3].

ATRIAL FIBRILLATION IN WOLFF-PARKINSON- WHITE SYNDROME

Atrial fibrillation is an arrhythmia that may develop in persons with WPW syndrome. Management of atrial fibrillation in WPW is very different than management of atrial fibrillation caused by other cardiac and noncardiac causes. To understand the seriousness of this arrhythmia and rationale for treatment, let's look briefly at the WPW syndrome itself.

PATHOPHYSIOLOGY OF WPW

During early fetal development, a number of bundles of fibers exist that connect the atria and ventricles. As fetal development progresses, these connections disappear until the AV node is left as the only functional electrical connection between atria and ventricles. In persons with WPW, one or more of these fibrous connecting bundles has persisted into adulthood. The connecting bundle, called an accessory pathway, provides an alternative route for the conduction of an electrical impulse through the heart. Depending on a number of factors, an electrical impulse may travel only through the normal conducting pathway, through both the normal and

the accessory pathways, or only through the accessory pathway. When the impulse travels through the accessory pathway, it bypasses the normal delay in the AV node and reaches the ventricles early. It initiates ventricular depolarization before the impulse traveling down the normal conduction pathway can reach the ventricles. The ventricles depolarize abnormally. The abnormal conduction through the accessory pathway alters the normal ECG waveform. The changes include [156]:

- A shortened PR interval (less than 0.12 sec). The PR interval is shortened because the impulse from the atria reaches the ventricles through the accessory pathway more rapidly than normal.
- The presence of a delta wave. A delta wave is a slurring of the initial deflection (either positive or negative) of the QRS complex. It reflects the early, abnormal depolarization of the ventricles that occurs when the impulse travels through the accessory pathway.
- An abnormally widened QRS complex (greater than 0.12 sec). The widened, abnormal QRS occurs when most of the ventricular depolarization is stimulated by an impulse traveling down the accessory pathway. In normal conduction, both ventricles depolarize almost simultaneously. With accessory pathway conduction, one ventricle is stimulated to depolarize before the other.
- Abnormal ST waves. An ST wave represents repolarization. When depolarization is abnormal, the pattern of repolarization will also be abnormal.

These ECG characteristics are often very subtle and may be confused with ECG changes associated with other conditions, such as acute myocardial infarction, bundle branch block, and left ventricular hypertrophy. The early depolarization of ventricles through accessory pathway conduction is called pre-excitation. The degree of pre-excitation (i.e., the extent to which the ventricles depolarize

from accessory pathway conduction) can vary. Factors that increase conduction across the AV node decrease conduction through the accessory pathway. These factors include exertion, intense emotion that increases adrenergic stimulation, and certain medications, such as procainamide, beta agonists (e.g., epinephrine, albuterol, metaproterenol, terbutaline), and atropine. Factors that inhibit or slow conduction across the AV node increase the extent of pre-excitation. These factors may include a normal increase in vagal tone associated with sleep, and medications such as digoxin, adenosine, beta blockers, and calcium channel blockers. Medications known to slow conduction through the AV node should be not used for persons with WPW [157; 158].

The presence of multiple conduction pathways (normal and one or more abnormal) often leads to development of tachyarrhythmias, including atrial fibrillation. Patients with WPW who develop atrial flutter or atrial fibrillation are at increased risk of dangerous ventricular arrhythmias due to the extremely fast conduction across the bypass tract [156]. Atrial fibrillation develops in approximately one-third of persons with WPW. Atrial fibrillation seen in WPW is characterized by [17; 19; 156; 157; 158]:

- Irregularly irregular rhythm
- QRS that may appear different and reflect varying degrees of pre-excitation. Some impulses will be conducted through the normal pathway, others through the accessory pathway.
- A higher than usual ventricular rate. In “normal” atrial fibrillation, the AV node blocks conduction of most of the fib waves and keeps the ventricular rate from exceeding 150 to 250 bpm. Because impulses in atrial fibrillation associated with WPW can bypass the AV node, the ventricular rate may approach 350 bpm. At this rate, the risk that the atrial fibrillation will degenerate into ventricular fibrillation is high.

DIAGNOSIS

WPW should be suspected in any person who shows the following signs and symptoms:

- Shortened PR interval and delta wave associated with accessory pathway conduction present on ECG
- Subjective complaint of palpitations
- History of syncope, presyncope, or sudden cardiac arrest episodes

Definitive diagnosis can be done through electrophysiology testing [156].

MANAGEMENT OF ATRIAL FIBRILLATION WITH RAPID VENTRICULAR RESPONSE IN WPW

When a patient with WPW presents with atrial fibrillation with rapid ventricular response, the patient's hemodynamic status should be immediately assessed. If there are signs of hemodynamic instability, such as hypotension, signs of congestive heart failure, or ischemic chest pain, the patient should be immediately cardioverted [156]. If the patient is not hemodynamically unstable, rate control is the high priority. Appropriate medication selection is critical. Use of medications such as verapamil and digoxin that slow or block conduction through the AV node will aggravate atrial fibrillation in WPW and run the risk of accelerating the ventricular rate to the point that ventricular fibrillation can occur [26; 156]. The treatment of choice for hemodynamically stable patients with atrial fibrillation and WPW is IV procainamide or ibutilide [23]. Verapamil, diltiazem, adenosine, digoxin (oral or intravenous), and intravenous amiodarone can precipitate ventricular fibrillation and should not be used [23].

SIMULATED CASE STUDY: THE PATIENT WITH ACUTE- ONSET ATRIAL FIBRILLATION

Patient D is a man, 68 years of age, who presents to the emergency department late one evening complaining of increasing shortness of breath, dizziness, and the sensation of his "heart racing." On admission, his heart rate is 160 bpm, blood pressure 100/50 mm Hg, respirations 26 breaths per minute, and oxygen saturation 88% on room air. Patient D says that his symptoms started abruptly earlier that day and have steadily become worse. He reports a history of long-standing hypertension, coronary artery disease, and a recent percutaneous transluminal angioplasty with placement of two stents.

Comments and rationale: Symptoms such as those Patient D presents are common indications of acute onset atrial fibrillation with rapid ventricular response. His past medical history is positive for risk factors for the development of atrial fibrillation. These include a positive cardiac history, with hypertension and coronary artery disease, as well as increasing age.

A 12-lead ECG is obtained. It shows a narrow QRS complex tachycardia with an irregularly irregular rhythm. A diagnosis of atrial fibrillation with rapid ventricular response is made. Oxygen via nasal cannula at 2 liters is started. Patient D is attached to continuous telemetry, oxygen saturation, and noninvasive blood pressure monitoring. Telemetry monitoring shows a variable heart rate ranging from 120 to 160 bpm. At lower rates, fibrillatory waves are present. Crackles are present in the bases of both lungs. Peripheral pulses are diminished and irregular. Patient D's skin is cool but dry. A peripheral IV access is established. After determining that Patient D has no known allergies to medications, 20 mg of diltiazem is prescribed to be given by IV push.

Comments and rationale: ECG characteristics associated with atrial fibrillation with rapid ventricular rate include a QRS complex within normal limits (sometimes called “narrow complex”) and an irregularly irregular ventricular rhythm. Sinus P waves are absent. At rapid rates, the irregular rhythm and absence of P waves may be difficult to determine. Fibrillatory waves are present but are often not seen at rapid rates. Because of the variable filling time associated with atrial fibrillation, pulse pressure may be intermittent and some beats may not perfuse well to the periphery. Loss of normal atrial contraction coupled with tachycardic heart rates may precipitate signs of heart failure, such as dyspnea, rales, and hypotension. Patient D is symptomatic with his atrial fibrillation but not dangerously unstable (with rapidly falling blood pressure, rapidly increasing signs of heart failure, or increasing chest pain). Therefore, the initial goal of treatment is to slow his heart rate. Diltiazem, a calcium channel blocker, slows conduction through the AV node and prolongs the AV node refractory period, thus slowing the ventricular rate in atrial fibrillation. It has a rapid onset of action. Because IV diltiazem administration is associated with development of bradycardia, heart block, increased signs of congestive heart failure, and hypotension, the patient should be continuously monitored during and after its administration. If the diagnosis of atrial fibrillation with rapid ventricular response cannot be made, adenosine may be used to establish a diagnosis. Oxygen by nasal cannula is used to increase oxygen saturation and decrease the subjective sensation of dyspnea.

In response to the IV diltiazem, Patient D’s heart rate initially slowed to a rate of 110 to 120 bpm but rapidly returned to a high rate. After 15 minutes, another bolus was ordered, followed by a continuous infusion of diltiazem at 5 mg/hour. The orders indicated that the drip could be titrated up to a maximum of 15 mg/hour to achieve the desired rate (as long as Patient D’s blood pressure remained within ordered parameters). Additional laboratory and diagnostic tests are ordered to rule out or identify any precipitating causes for the arrhythmia. The tests included a complete blood count, serum electrolytes, thyroid function studies, renal and liver function studies, and cardiac enzymes. A portable chest x-ray is performed. Patient D is questioned about

his use of over-the-counter medications, alcoholic beverages, illicit drugs, and dietary supplements or herbal medicines. He is then transferred to an inpatient telemetry unit for further monitoring and clinical management.

Comments and rationale: A diltiazem bolus may be repeated after 15 minutes if the desired rate control is not achieved from the initial bolus. The patient should be monitored for the development of side effects, such as hypotension and bradyarrhythmias. Following a bolus, a continuous infusion may then be started to achieve rate control. Blood pressure, ECG, and oxygen saturation monitoring should be done continuously during continuous intravenous infusion. Signs, such as falling blood pressure, decreasing oxygen saturation, and failure to control rate, should be noted and handled immediately. If intolerable side effects develop, the diltiazem will be discontinued and another medication prescribed. If side effects do not develop but rate control is not achieved, additional medications may be prescribed. Other medications used for rate control include procainamide, esmolol, metoprolol, and propranolol. Patients receiving multiple antiarrhythmics should be monitored closely as combination therapy may result in a cumulative effect on heart rate and rhythm, blood pressure, and the patient’s risk of developing congestive heart failure. To effectively manage atrial fibrillation, any underlying or precipitating causes should be identified and corrected. Precipitating causes may include anemia, consumption of alcohol, use of cocaine or other similar substance, hyperthyroidism, and electrolyte imbalances (especially potassium and magnesium). Atrial arrhythmias may also develop during acute stages of myocardial infarction.

Patient D is transferred to an appropriate inpatient unit. Continuous ECG, blood pressure, and oxygen saturation monitoring are maintained. After one to two hours on the diltiazem drip, the patient’s heart rate drops and stabilizes at 80 to 90 bpm. Fibrillatory waves and an irregularly irregular ventricular response are clearly present on ECG. His laboratory data comes back showing normal serum electrolytes, renal function studies, thyroid function tests, and liver function tests. His hematocrit and hemoglobin are within normal limits. His cardiac enzymes and troponin are negative for myocardial infarction.

His chest x-ray shows some congestion in his lower lobes consistent with mild congestive heart failure. Intravenous furosemide is ordered at a low dose to relieve the pulmonary congestion. Patient D's vital signs improve. His blood pressure increases to 118/70 mm Hg, his respiratory rate slows to 18 breaths per minute, and he reports a decreased sensation of dyspnea and palpitations. After he stabilizes, the process of weaning the IV drip and starting the patient on oral diltiazem is initiated. Low-dose oral diltiazem is effective in maintaining rate control for Patient D when his activity is limited; however, when his activity level is increased, he begins to experience increasing episodes of an uncontrolled rate. The dose is increased, and rate control during activity improves. Evaluation of Patient D's medical therapy shows his heart rate controlled at 70 to 80 bpm, his blood pressure is stable, and his symptoms relieved. Because of the high risk of thromboembolic events and serious consequences of CVA, Patient D is started on anticoagulation therapy. It is determined that he is at high risk for a CVA, and a heparin drip is started. Oral anticoagulation with warfarin also begins at this time. Routine monitoring of his partial thromboplastin time and PT/INR is ordered.

Comments and rationale: Once rate control is achieved and maintained, the patient's vital signs are stable, and other signs (e.g., signs of congestive heart failure, angina) have resolved, the patient may be changed to an oral dose for maintenance therapy. Short periods of a rapid rate may still occur, especially with exertion. If these episodes are intermittent and nonsustained, they may be effectively managed by adjusting the medication dose or adding additional antiarrhythmic medications. Rate control is considered successful if it alleviates troublesome symptoms, relieves dyspnea, increases activity tolerance, and improves the patient's ability to perform activities of daily living. Anticoagulation is indicated for persons who remain in atrial fibrillation. Because the atria never fully contract in atrial fibrillation, stasis of blood can occur, which may lead to the development of clots. To prevent thromboembolic events such as CVA, anticoagulation should be started. For high-risk patients, warfarin is the drug of choice. In an inpatient setting, intravenous heparin may be used to provide adequate anticoagulation until warfarin reaches a therapeutic serum level.

With careful questioning, it is determined that Patient D's subjective symptoms of atrial fibrillation actually began a week or more prior to his admission. Patient D admits to feeling some palpitations and shortness of breath intermittently but did not seek medical care until the symptoms became severe. Current assessment of Patient D's status shows normal breath sounds with absence of rales, the chest x-ray shows resolution of pulmonary congestion, vital signs are stable, and he is able to participate in activities of daily living and ambulate without trouble. It is decided to send Patient D home on oral medication to maintain rate control, on warfarin for anticoagulation, and monitoring his status over the next several weeks to evaluate the effectiveness of this therapy.

Comments and rationale: Options for long-term management of the patient with atrial fibrillation include restoration of normal sinus rhythm through pharmacologic or electrical cardioversion or rate control through use of oral antiarrhythmic medications. For patients known (or suspected) to be in atrial fibrillation for more than 48 hours, national standards recommend adequate anticoagulation for three weeks prior to either pharmacologic or electrical cardioversion. Or, a transesophageal echo may be performed to rule out a left atrial thrombus. If no thrombus exists, the patient may be safely cardioverted. For patients whose symptoms are controlled by rate control, oral therapy/antiarrhythmics coupled with oral anticoagulation often is sufficient treatment. If the patient develops recurrent episodes of rapid atrial fibrillation, or experiences troublesome symptoms at home despite optimal antiarrhythmic therapy, he/she may benefit from restoration of normal sinus rhythm by more aggressive methods.

Patient D receives verbal and written instructions on how to take his warfarin and his antiarrhythmic medications. Appointments with the outpatient laboratory for PT/INR monitoring are set up, and a follow-up appointment with his physician is scheduled. Patient D is instructed on signs and symptoms to report to the doctor, including signs of bleeding and recurrence of his signs of rapid atrial fibrillation. Indications that medical therapy is effective in managing his atrial fibrillation include: ability to perform normal activities without symptoms of

fatigue, dyspnea, dizziness, or palpitations; vital signs within desired parameters; absence of annoying or problematic side effects from medications; and absence of signs of thromboembolic events.

SIMULATED CASE STUDY: CLINICAL MANAGEMENT OF THE PATIENT WITH PERSISTENT ATRIAL FIBRILLATION

Patient W is a woman, 58 years of age, who is admitted to the unit with bradycardia and near syncope. She says that this morning she had been grocery shopping, became very dizzy, and nearly passed out. On admission assessment, her blood pressure is 116/74 mm Hg, and her heart rate is 48 bpm and irregular. Her respirations are even and easy at a rate of 20 breaths per minute. Her oxygen saturation on room air is 99%. Peripheral pulses are slightly diminished. Lung fields are clear to auscultation. Patient W is placed on continuous telemetry monitoring, and a 12-lead ECG is obtained. The ECG shows that her underlying rhythm is atrial fibrillation with a slow ventricular response. Patient W says that she has had atrial fibrillation for several months. Initially, her heart rate had been controlled on oral antiarrhythmic medications. However, over the last month, she has been experiencing increasing episodes of palpitations and a rapid heart rate. Her medication had been increased, but she developed hypotension and a slow heart rate on the increased dose. A few days prior to her admission, her oral antiarrhythmic medication was changed. On the new medication, she has not had any prolonged episodes of a rapid heart rate but experienced some “dizzy spells.”

Comments and rationale: Lack of adequate rate control coupled with development of serious side effects such as bradycardia, hypotension, and syncope with multiple oral agents are indications that oral antiarrhythmic therapy is not effective in managing the patient's atrial fibrillation. Other options include pharmacologic cardioversion, electrical cardioversion, radiofrequency ablation with or without pacemaker insertion, or continuation of oral medications with insertion of a demand pacemaker to treat symptomatic bradycardia.

Laboratory tests are ordered, including a complete blood count, serum electrolytes, renal and hepatic function tests, chest x-ray, urinalysis, and PT/INR. A peripheral IV access is established. Continuous telemetry monitoring is maintained, and Patient W's vital signs are monitored every four hours. Her heart rate remains between 48 and 52 bpm. Patient W's oral antiarrhythmic medication is discontinued. Analysis of Patient W's ECG shows that her QTc is 580 msec. The therapeutic options of electrical cardioversion, radiofrequency ablation, and continued oral antiarrhythmic therapy with insertion of a demand pacemaker are discussed with the patient. The patient expresses reluctance to undergo pacemaker insertion at this time. With the patient's agreement, she is scheduled for electrical cardioversion. Patient W expresses the understanding that pacemaker insertion or ablation with pacemaker insertion might still be required if cardioversion is unsuccessful or if she becomes symptomatic on therapy to maintain sinus rhythm following successful cardioversion.

Comments and rationale: Laboratory tests such as a complete blood count and serum electrolytes are ordered to rule out any abnormal findings (e.g., anemia, hypokalemia, hypomagnesemia) that may make management of atrial fibrillation more difficult. Due to Patient W's continued bradycardia, her oral antiarrhythmic medication is discontinued. Her QTc interval is significantly prolonged. Because Patient W has developed bradycardia and a prolonged QTc interval, she is not a candidate for pharmacologic cardioversion.

Patient W's complete blood count, renal and hepatic function studies, and urinalysis come back within normal limits. Her serum electrolytes show hypokalemia but a normal serum magnesium level. IV potassium replacement is given, and a repeat potassium level returns within normal limits. Patient W's INR comes back at 2.7. Her usual warfarin dose is continued. A review of her outpatient laboratory results shows that her INR has been maintained between 2.6 and 3.1 for more than six weeks.

Comments and rationale: Hypokalemia may contribute to the continuation of atrial fibrillation. It should be corrected prior to electrical cardioversion or other intervention. Because of the risk of thromboembolic complications caused by left atrial thrombi for persons with atrial fibrillation of more than 48 hours duration, anticoagulation with warfarin is indicated. National standards require anticoagulation for at least three weeks prior to cardioversion. The therapeutic target for warfarin is an INR of 2.0–3.0.

Patient W is kept NPO for six hours prior to the cardioversion. She is taken to the preoperative area prior to the procedure and sedated with IV medications. Continuous ECG, blood pressure, and oxygen saturation monitoring is initiated. The cardioverter/defibrillator is set for a low-energy, synchronized shock. The initial shock is ineffective in restoring sinus rhythm. A second, slightly higher energy shock is effective. ECG monitoring shows Patient W is now in normal sinus rhythm at a rate of 62 bpm. Her vital signs are monitored closely until she wakes up from the sedation. Patient W is returned to her room. Continuous telemetry monitoring is continued.

Comments and rationale: Electrical cardioversion is a painful procedure; sedation or general anesthesia is required. Because of the risks associated with sedation/anesthesia, and the risk that the patient may go into ventricular fibrillation from an electrical shock, cardioversion should be performed in a setting where emergency equipment for intubation and management of cardiac arrest is readily available.

Patient W remains in normal sinus rhythm at an acceptable rate in the immediate period postcardioversion. Her blood pressure is stable, and her dizzy spells do not recur. She is discharged on a low-dose oral antiarrhythmic and warfarin. Patient W is instructed to notify a physician if she experiences palpitations, dizziness, or near-fainting spells.

Comments and rationale: Oral antiarrhythmic therapy is generally required to maintain normal sinus rhythm following successful cardioversion. Although Patient W had been unable to take higher dose oral antiarrhythmics, she was able to tolerate low-dose therapy. It is likely that Patient W will experience short episodes of atrial fibrillation. However, therapy is considered successful if these episodes are brief, do not cause debilitating symptoms, and resolve without additional treatment. National standards recommend that anticoagulation therapy be continued for at least four weeks following cardioversion.

CONCLUSION

Atrial fibrillation is an increasingly common health problem in the United States. As the American population continues to age, the number of older adults who require clinical management of atrial fibrillation will also increase. Appropriate clinical management involves careful assessment of the patient's symptoms and status, correction of any underlying or contributing causes, and identification of realistic medical goals. Therapies available for the management of atrial fibrillation include a wide variety of antiarrhythmic medications, pharmacologic cardioversion, electrical cardioversion, and radiofrequency ablation with or without pacemaker insertion. Because the risk of CVA is high for persons with atrial fibrillation, anticoagulation therapy should be considered and initiated when appropriate. Ongoing monitoring of the patient's response to antiarrhythmic and anticoagulation therapy is crucial to the effective management of atrial fibrillation and the prevention of serious complications.

RESOURCES

American Heart Association

7272 Greenville Avenue

Dallas, TX 75231

1-800-242-8721

<https://www.heart.org>

Heart Rhythm Society

1325 G Street NW, Suite 400

Washington, DC 20005

202-464-3400

<https://www.hrsonline.org>

National Heart, Lung, and Blood Institute

Building 31

31 Center Drive

Bethesda, MD 20892

1-877-645-2448

<https://www.nhlbi.nih.gov>

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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