Understanding atrial fibrillation and new therapeutic advances to improve its management
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Articles based on the proceedings of educational activities recorded in February 2010. This activity is supported by an independent educational grant from sanofi aventis U.S.

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See page S35 or http://ce.ashp.org to locate the continuing-education learning objectives, self-assessment questions, and instructions covering the articles in this supplement.
Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, and it has become a major public health problem in the United States. The prevalence of this age-related disorder is increasing because of the graying of the American population and improved survival in patients with common conditions that increase the risk for AF (e.g., coronary heart disease, hypertension, heart failure, valvular heart disease). Contributing to the problem are increases in the prevalence of obesity, which is an independent risk factor for AF, and in the use of coronary artery bypass grafting and other cardiothoracic surgical procedures, which also increase the risk for AF.

The economic impact of AF is substantial because of the high rate of consumption of health care resources, most notably hospitalizations, associated with the disorder. The total annual cost of AF in the United States exceeds $12 billion and is expected to grow in the future.

Health-system pharmacists need to be knowledgeable about the most appropriate drug therapies for AF, including rate-control, rhythm-control, and antithrombotic strategies, as well as evolving nonpharmacologic interventions for the disorder. Tolerability problems are associated with many of the antiarrhythmic agents. Warfarin is highly effective for preventing stroke, a serious complication of AF; however, the drug is not used when indicated, especially in elderly patients, because of its many limitations.

New and emerging antiarrhythmic agents and anticoagulants hold promise for overcoming some of the shortcomings of established agents and for improving outcomes in patients with AF. The place in therapy of these agents remains to be determined as additional data from comparative clinical trials become available.

In the first article, the components and interpretation of the 12-lead electrocardiogram (ECG) are discussed, and the ECG waveforms and clinical presentation associated with major arrhythmias are compared and contrasted. The second article describes the prevalence, pathophysiology, and consequences of AF. The use of risk-scoring systems for predicting the risk for AF and ischemic stroke is illustrated in a patient case.

In the third article, the therapeutic goals for patients with AF are discussed. Antithrombotic, rate-control, and rhythm-control drugs used in these patients as well as the rationale for choosing between rate-control and rhythm-control strategies for the treatment of AF are reviewed. The safety, efficacy, and patient-specific considerations in choosing among antiarrhythmic drugs in patients are also discussed.
with AF are explained and illustrated in patient cases.

The fourth article compares and contrasts the pharmacology, efficacy, and safety of new, emerging, and established antiarrhythmic and anticoagulant drugs used in the treatment of AF. In addition, nonpharmacologic interventions for patients whose AF cannot be managed with pharmacotherapy because of a lack of efficacy or intolerable adverse effects are described.

References
Overview of electrocardiographic findings and clinical presentation of common cardiac arrhythmias

CYNTHIA A. SANOSKI

Recognizing various cardiac arrhythmias can be challenging for pharmacists because their education and training focus on the selection and monitoring of drug therapies for these conditions rather than on their diagnosis. Pharmacists should have a basic understanding of electrocardiogram (ECG) interpretation for several reasons. First, pharmacists need to understand the differences between various types of arrhythmias, especially atrial and ventricular rhythm disturbances, in order to select appropriate antiarrhythmic drug therapy. Certain antiarrhythmic agents can be used only for atrial arrhythmias, and other agents are used only for ventricular arrhythmias. Second, the ECG is useful for monitoring the safety and efficacy of antiarrhythmic drug therapy. When drug therapies are used to control the ventricular rate (e.g., β-blockers, digoxin, nondihydropyridine calcium-channel blockers) in atrial fibrillation (AF), the ECG can be used to monitor safety of the treatment. When antiarrhythmic drugs are used to restore or maintain sinus rhythm in a patient with an arrhythmia, the ECG can be used to monitor for the achievement of these goals. Finally, pharmacists should be able to evaluate the QT interval on the ECG because a prolonged QT interval may place a patient at risk for developing torsades de pointes, a lethal form of ventricular tachycardia. A variety of cardiac and noncardiac drugs can cause QT interval prolongation. Monitoring the ECG can facilitate early detection and treatment of such abnormalities to reduce the potential for harm.

This article provides an overview of key characteristics to look for on a 12-lead ECG and typical clinical presentations of some of the most common arrhythmias, including atrial fibrillation (AF), atrial flutter, ventricular tachycardia (VT), and ventricular fibrillation.

Purpose. To review the components and interpretation of the 12-lead electrocardiogram (ECG) and compare and contrast the ECG waveforms and clinical presentation associated with major cardiac arrhythmias.

Summary. A 12-lead ECG reflects the electrical activity of the heart from many different perspectives, and individual leads may reveal conduction disturbances and disorders in a particular area of the heart. Components of the ECG complex include the P wave, QRS complex, and T wave. The timing and amplitude of ECG waveforms provide valuable information about heart rate and rhythm. This information can be used in conjunction with clinical signs and symptoms to differentiate between major arrhythmias, including atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.

Conclusion. The monitoring of drug therapies used to treat arrhythmias is facilitated by an understanding of ECG interpretation and the typical clinical characteristics of major cardiac arrhythmias.

Index terms: Arrhythmia; Cardiac drugs; Diagnosis; Electrocardiography

Am J Health-Syst Pharm. 2010; 67(Suppl 5): S5-10

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CYNTHIA A. SANOSKI, PHARM.D., FCCP, BCPS, is Chair and Associate Professor, Department of Pharmacy Practice, Jefferson School of Pharmacy, Thomas Jefferson University, Philadelphia, Pennsylvania.

Address correspondence to Dr. Sanoski at the Department of Pharmacy Practice, Jefferson School of Pharmacy, Thomas Jefferson University, 130 9th St., Suite 1540, Philadelphia, PA 19107-5233 (cynthia.sanoski@jefferson.edu).

Based on the proceedings of an educational activity recorded in February 2010 and supported by an independent educational grant from sanofi aventis U.S. Dr. Sanoski has disclosed no relevant financial relationship with a commercial interest, as defined by the Accreditation Council for Pharmacy Education (ACPE). Dr. Sanoski received an honorarium from the American Society of Health-System Pharmacists for her participation in the program and her work on this article. This article was developed with the assistance of a medical writer working with ASHP Advantage. The medical writer, Susan R. Dombrowski, M.S., reports that she has no relevant financial relationship with a commercial interest, as defined by ACPE. The author approved the final article and all its contents.

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The 12-lead ECG

A 12-lead ECG is produced using six limb leads and six chest (i.e., precordial) leads. Each lead provides a view of the heart's electrical activity from a slightly different angle. Abnormalities in a lead may suggest an electrical or mechanical disturbance in a particular area of the heart.

Electrodes are placed on both arms (at the wrist) and both legs (at the ankle), with the right ankle lead serving as the ground (i.e., neutral) electrode. There are three unipolar limb leads and three bipolar limb leads. The unipolar leads record the difference in electrical potential between one limb (positive electrode) and a reference point (negative) that is calculated by using the summation of the two negative leads. The unipolar limb leads are augmented vector right (aVR), augmented vector left (aVL), and augmented vector foot (aVF). With the aVR lead, the electrical potential of the right arm is compared with a reference point that is obtained by adding together the potential of leads aVL and aVF. With the aVL lead, the electrical potential of the right arm is compared with a reference point that is obtained by adding together the potential of leads aVR and aVF. Finally, with the aVF lead, the electrical potential of the right arm is compared with a reference point that is obtained by adding together the potential of leads aVL and aVR.

Bipolar limb leads I, II, and III record the difference in electrical potential between two limbs (Figure 1). One of the limbs serves as the positive electrode, and the other limb is the negative electrode: left arm (+) and right arm (–) for lead I, left leg (+) and right arm (–) for lead II, and left leg (+) and left arm (–) for lead III.

There are six precordial leads (V1, V2, V3, V4, V5, and V6). The arrangement of the electrodes on the chest wall for these leads is depicted in Figure 2. These leads are unipolar and record the electrical potential changes in the heart in a cross-sectional plane. Each of these leads looks at the heart from a different angle. An isolated waveform abnormality in one precordial lead may suggest a conduction disturbance or disorder in a particular area of the heart.

ECG waveforms

Figure 3 shows the components of the ECG complex. The first upward deflection of the ECG complex is the P wave. The P wave represents atrial depolarization and contraction and usually lasts less than 0.12 second (120 msec).

The P wave usually is followed by the QRS complex, which represents ventricular depolarization and contraction. The QRS complex is composed of the Q wave, R wave, and S wave. The Q wave is the first downward deflection in the ECG complex and is often not seen. The presence of Q waves in certain leads may be a normal finding, but the presence of Q waves in other leads may be pathological and may suggest that the patient has suffered a myocardial infarction in the past. The R wave is the first upward deflection in the QRS complex, and the S wave is the subsequent downward deflection. The QRS complex usually lasts less than 0.12 second (120 msec). Widening (i.e., lengthening) of the QRS complex can represent toxicity from certain antiarrhythmic agents.

The QRS complex is followed by the T wave, which is an upward deflection representing ventricular repolarization. T waves that have a pointed appearance or sharp peaks may reflect the presence of hyperkalemia.

The PR interval is the time from the beginning of the P wave to the beginning of the QRS complex. It represents the time between the on-
set of atrial depolarization and the beginning of ventricular depolarization. In other words, it corresponds to the time it takes for the electrical impulse to travel from the sinoatrial (SA) node through the atrioventricular (AV) node and into the ventricles. The PR interval usually is 0.12-0.2 second (120-200 msec) in duration. A prolonged PR interval suggests delayed conduction through the AV node and is referred to as AV block. This conduction disturbance may be associated with drugs with negative chronotropic properties, such as β-blockers, non-dihydropyridine calcium-channel blockers (e.g., verapamil, diltiazem), digoxin, and certain antiarrhythmic agents with β-blocking or calcium channel-blocking properties. The PR interval is a key monitoring parameter for patients receiving any of these drugs.

The ST segment is the portion of the ECG complex between the end of the QRS complex and the beginning of the T wave. It represents the plateau phase in the cardiac action potential and usually is isoelectric with the PR segment. Elevation or depression of the ST segment usually signifies a cardiac abnormality (e.g., myocardial ischemia or infarction).

The QT interval is measured from the beginning of the QRS complex to the end of the T wave. This interval represents the period of ventricular refractoriness. A normal QT interval is less than 0.44 second (440 msec). Drugs that prolong the QT interval have the potential for causing torsades de pointes, which is considered a medical emergency. Therefore, when patients are receiving these particular drugs, their QT interval should be monitored on a regular basis.

Reading ECG rhythm strips

The duration of various intervals (horizontal direction) on the ECG and the amplitude of the waveforms (vertical direction) can be measured by counting the blocks on the grid pattern on the paper on which the ECG is printed. The
grid has heavier lines marking off every five small boxes to facilitate counting. At the standard ECG paper speed of 25 mm/sec, each small box in the horizontal direction represents 0.04 second (40 msec), and each large square of five boxes represents 0.2 second (200 msec). Each small box in the vertical direction represents 1 mm (0.1 mV) in amplitude, and each large square of five boxes represents 5 mm (0.5 mV).

The “rule of 300” and the “6-second method” are quick and easy techniques for determining the approximate heart rate from a printed ECG rhythm strip. The “rule of 300” method involves finding an R wave that coincides with a bold line on the ECG paper and counting off 300-150-100-75-60-50 for each bold line that falls after this line until the next R wave appears (Figure 4). This method provides a ballpark estimate of the heart rate. If the next R wave falls between two bold lines, the heart rate can be estimated as falling between the heart rates corresponding to those two lines. For example, if the next R wave falls between two bold lines that correspond to 100 beats per minute and 75 beats per minute, the heart rate can be estimated as 75-100 beats per minute.

The “6-second” method for determining the approximate heart rate involves counting the number of R waves in a 6-second ECG rhythm strip (i.e., 30 large horizontal boxes) and multiplying this number by 10. Rhythm strips often have markings at 3-second intervals, which facilitate counting. For example, if a 6-second rhythm strip has eight R waves, the heart rate is 80 beats per minute.

By contrast, atrial flutter is characterized by a slower atrial rate (270-330 beats per minute) and a regular ventricular rhythm, with a consistent R–R interval from one ECG complex to another. The P waves are replaced by “flutter waves” that often appear in a “sawtooth” pattern. The ratio of atrial contractions to ventricular contractions can be 1:1, 2:1, or 3:1 in atrial flutter. Typically, patients with atrial flutter have 2:1 conduction, which means that if the atria are beating at 300 beats per minute, the ventricles would then beat at 150 beats per minute. Atrial flutter with 1:1 conduction is usually considered a medical emergency.

Palpitations are a common symptom of both AF and atrial flutter. Patients may describe a sensation of butterflies in their chest. They also may complain of dizziness, fatigue, shortness of breath, and diminished exercise tolerance. Patients with underlying left ventricular dysfunction may experience an exacerbation of heart failure symptoms. Patients with underlying ischemic heart disease may experience angina because the associated increase in ventricular rate can lead to an increase in myocardial oxygen demand.

### Ventricular arrhythmias

Ventricular tachycardia is defined as three or more consecutive premature ventricular contractions occurring at a rate exceeding 100 beats per minute. Ventricular tachycardia can appear as either monomorphic or polymorphic complexes. In monomorphic complexes...
VT, the QRS complexes are similar in morphologic characteristics from beat to beat. In polymorphic VT, the QRS complexes vary in shape and/or size between beats. The arrhythmia can also be classified as nonsustained or sustained. Nonsustained VT self-terminates after a brief duration (usually less than 30 seconds). Sustained VT requires therapeutic intervention to restore a stable rhythm or persists for a relatively long time (usually greater than 30 seconds). Ventricular tachycardia may develop acutely as a result of metabolic abnormalities, ischemia, or drug toxicity, or it may be chronic and recur in a paroxysmal fashion.

Torsades de pointes is a type of polymorphic VT. It is a potentially lethal arrhythmia that is considered a medical emergency. The term “torsades de pointes” literally means a twisting of the points as the ECG complexes appear to twist around the baseline. This form of polymorphic VT is associated with delayed ventricular repolarization and a prolonged QT interval. Torsades de pointes may be inherited or acquired. Various cardiac and noncardiac drugs, including antibiotics, antiarrhythmic agents, and antipsychotic agents, can cause QT interval prolongation and torsades de pointes.

The severity of symptoms in patients with VT usually depends on the duration of the arrhythmic episode. Patients with brief episodes often are asymptomatic or complain of palpitations. Chest pain may develop during prolonged VT episodes because of the increased myocardial oxygen demand from rapid ventricular contraction. Loss of consciousness and absence of a pulse may also occur, requiring cardiac resuscitation; in this circumstance the patient would be considered to have pulseless VT, which is a form of cardiac arrest.

Ventricular fibrillation is an arrhythmia characterized by utter electrical disorganization within the myocardium and no organized waveforms on the ECG. It is considered to be a form of cardiac arrest or sudden cardiac death. Patients with ventricular fibrillation become unconscious and have no pulse or blood pressure. The survival rate in patients with ventricular fibrillation is low, especially if the arrhythmia develops outside the hospital setting. Therefore, prompt detection of this arrhythmia is critical so that cardiopulmonary resuscitation and administration of appropriate drug therapy can be implemented as soon as possible.
Patient case

**Ventricular arrhythmia**

PD, a 70-year-old woman with a past medical history of coronary artery disease and heart failure, was recently admitted to the coronary care unit for treatment of an episode of acutely decompensated heart failure. She has been receiving milrinone for the past 48 hours. While having her blood pressure checked in the morning, PD complains of dizziness and suddenly loses consciousness. No pulse or blood pressure can be detected. Telemetry reveals the rhythm strip for ECG lead II in Figure 6.

The loss of consciousness, absence of a detectable pulse and blood pressure, and electrical disorganization on the rhythm strip reflect ventricular fibrillation and cardiac arrest. A “code blue” is called and resuscitation efforts are initiated immediately.

**Conclusion**

Pharmacists need a basic understanding of ECG waveforms and the signs and symptoms of cardiac arrhythmias so that they can identify these conditions and ensure the selection of appropriate treatment. This understanding will also enable pharmacists to appropriately monitor the efficacy and safety of drug therapies used to treat arrhythmias.

**References**

Purpose. To describe the prevalence, pathophysiology, and consequences of atrial fibrillation (AF) and the risk factors for the rhythm disturbance.

Summary. The prevalence of AF, a common age-related disorder that causes substantial morbidity and mortality, is increasing. Structural heart disease (e.g., coronary heart disease, hypertension, heart failure, valvular heart disease) is a common comorbidity of and risk factor for AF, although various other factors have been shown to play a role in the pathogenesis of this disorder. The risk for AF and ischemic stroke, a major complication of AF, can be estimated using risk-scoring systems. The rate of hospitalization for AF and the costs of treating AF are increasing in the United States.

Conclusion. Understanding the pathogenesis of and risk factors for AF and using risk-scoring systems to estimate the risk for AF and stroke can facilitate treatment of this rhythm disorder and potentially minimize its morbidity, mortality, and costs.

Index terms: Age; Atrial fibrillation; Economics; Epidemiology; Geriatrics; Mortality

Prevalence, pathogenesis, and impact of atrial fibrillation

CYNTHIA A. SANOSKI

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is considered to be a major health problem in the United States.1 According to recent American Heart Association statistics, this arrhythmia is expected to affect 2.66 million Americans in 2010.1 Several studies have been conducted to estimate the future prevalence of AF. All of their results indicate that the number of patients with AF in the United States is expected to increase approximately 2- to 2.5-fold by the year 2050.2-4 Factors that may contribute to the increased prevalence of AF include the aging population; improved survival rates in patients with heart failure (HF), coronary heart disease (CHD), and hypertension (all are significant risk factors for AF); and the increasing prevalence of obesity.

As with many other cardiovascular diseases, AF is primarily a disorder of the elderly; its prevalence increases with advancing age.2,5 The median age of patients with AF is 75 years, and most affected patients (approximately 70%) are between 65 and 85 years of age.2 In a cross-sectional study of adults with a diagnosis of AF at a large health maintenance organization, the prevalence of this arrhythmia was 0.1% in patients less than 55 years of age and 9.0% in patients 80 years of age or older.2

Men are disproportionately affected by AF compared with women at all ages.2 This arrhythmia is more common in whites than in blacks.2

The lifetime risk for developing AF was estimated from data on 8725 male and female participants in the Framingham Heart Study who were at least 40 years old and did not have AF at the time of enrollment.7 The lifetime risk for AF was 26% in women and 23% in men (i.e., approximately 1 in 4 for the overall study population) and did not change with advancing age. In a subset of patients without a history of congestive HF or myocardial infarction (MI), the lifetime risk for AF was approximately 16% (i.e., 1 in 6). These lifetime risk estimates...
for AF can be placed in perspective by comparing them with those for other common noncardiovascular diseases. For example, the lifetime risk for breast cancer at the age of 40 in women is 1 in 8; the lifetime risk for HF in men and women 40 years of age or older is 1 in 5; and the lifetime risk for hip fracture at age 50 is 1 in 6 for white women and 1 in 20 for white men. Therefore, the 1 in 4 lifetime risk for AF at age 40 or older is comparatively high. These findings underscore the need to develop effective prevention strategies for AF.

**Estimating the risk of AF**

Because of the evidence that AF has become a significant public health problem, research has been focusing on identifying risk factors and potential pharmacologic strategies for preventing this arrhythmia. Historically, however, it has been a challenge to determine which patients would be considered at high risk for developing AF and thus should be included in such trials. To address this issue, a risk-scoring system that estimates the 10-year risk for developing AF was recently developed. The system is based on data from 4764 Framingham Heart Study participants 45–95 years of age who did not have AF at the time of enrollment. Seven risk factors associated with the development of AF in this study were identified, and a weighted point scoring system was devised for calculating the 10-year risk for AF (Table 1).

**Pathophysiology**

Reentry is the primary mechanism by which AF develops and persists. This arrhythmia appears to result from multiple reentry circuits (i.e., wavelets) that develop in the atria. By contrast, atrial flutter is caused by a single, dominant reentry circuit that occurs in the atria. Being associated with multiple reentry circuits makes AF more difficult to treat than atrial flutter.

### Table 1.
**Risk-Scoring System for Estimating 10-Year Risk for Atrial Fibrillation**

<table>
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<th>Variable</th>
<th>Score</th>
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<td><strong>Age (yr)</strong></td>
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<td>≥30</td>
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<td><strong>Use of antihypertensive therapy</strong></td>
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<td><strong>Total Score</strong></td>
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<tr>
<td>10-Year Risk (%)</td>
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*Obtained by adding the scores for each of the seven variables in this table.
Atrial fibrillation usually occurs in conjunction with various forms of structural heart disease (e.g., CHD, hypertension, HF, valvular heart disease) that cause atrial distention and subsequent electrical instability. The presence of left ventricular hypertrophy in patients with hypertension especially increases the risk for AF.

In addition, mitral valve disease is a significant risk factor for the development of AF.

Although structural heart disease continues to be the most common cause of AF, increasing evidence suggests that other factors may also play a significant role in the pathogenesis of this arrhythmia. Activation of the renin–angiotensin–aldosterone system is thought to precipitate and sustain AF by causing both structural and electrical remodeling in the atria. Inflammation also has been implicated as a potential cause of AF because significant elevations of various inflammatory markers, including C-reactive protein, have been observed in patients with AF compared with individuals in sinus rhythm.

Obesity and obstructive sleep apnea are also considered independent risk factors for AF. Increases in left atrial size are associated with increased body mass index (BMI), and atrial dilation could predispose to AF. Obstructive sleep apnea is common in obese persons. Potential mechanisms by which obstructive sleep apnea could contribute to the development of AF include prolonged hypoxemia, sympathetic and parasympathetic nervous system imbalances, systemic inflammation, and diastolic dysfunction. The degree of nocturnal oxygen desaturation, a consequence of obstructive sleep apnea, has been shown to be an independent predictor of risk for AF.

Other causes of AF include pulmonary embolism and chronic obstructive pulmonary disease, both of which can lead to atrial dilation. Excessive sympathetic stimulation due to hyperthyroidism, acute alcohol intoxication (also known as holiday heart syndrome), or surgery (especially cardiothoracic surgery) can also lead to AF. Electrolyte disturbances such as hypokalemia and hypomagnesemia are risk factors for all arrhythmias, including AF.

Atrial fibrillation in the absence of structural heart disease in persons less than 60 years of age is known as lone or idiopathic AF. This condition is relatively uncommon, accounting for approximately 1 in 10 patients with AF.

Clinical presentation of AF

A rapid and irregular ventricular rate often accompanies AF and is the cause of many AF symptoms. Patients typically present with palpitations, dizziness, fatigue, reduced exercise tolerance, and shortness of breath. Tachycardia-induced cardiomyopathy and potentially irreversible HF may develop if the rapid ventricular rate that accompanies AF remains untreated for a long time. If the heart rate is markedly elevated, syncope may also occur, although it is relatively uncommon. Patients with underlying CHD who develop AF may also experience angina because the associated increase in ventricular rate can lead to an increase in myocardial oxygen demand.

Patients with systolic HF who develop AF often experience worsening HF symptoms because of a reduction in cardiac output. Several factors contribute to this reduction in cardiac output. First, because the atria are contracting so rapidly, these patients lose their “atrial kick.” In patients with systolic HF who do not have AF, atrial contraction immediately before ventricular systole increases ventricular filling to maintain cardiac output. These patients rely on the contribution that this “atrial kick” makes to their overall cardiac output. When AF develops in patients with systolic HF, this compensatory “atrial kick” often is lost, and cardiac output is reduced, which usually leads to worsening HF symptoms. Second, the rapid ventricular rate in AF can shorten ventricular diastolic filling time, which subsequently leads to a reduction in cardiac output.

Thromboembolic consequences of AF

Thromboembolic complications, particularly ischemic stroke, are a major concern in patients with AF. At least 15% of all ischemic strokes occur in patients with AF. A 4- to 5-fold increase in the risk for ischemic stroke is associated with AF, and the risk for ischemic stroke in patients with AF increases with age. The risk for ischemic stroke in patients with AF is approximately 5% per year without antithrombotic therapy.

The risk for stroke in patients with AF can be estimated by using the CHADS2 risk-scoring system, which assigns weighted point values to several risk factors. The resulting score can be used to stratify a patient’s risk for stroke. The ability of the CHADS2 score to predict the risk for stroke in patients with AF was validated in a study of 1733 Medicare beneficiaries 65–95 years of age with nonrheumatic AF who did not receive warfarin at the time of hospital discharge. The CHADS2 score was more accurate for predicting stroke than the two older risk classification schemes (the Atrial Fibrillation Investigators and the Stroke Prevention and Atrial Fibrillation classification schemes). Each 1-point increase in the CHADS2 score was associated with a 1.5-fold increase in the stroke rate in this study.

The most recent guidelines developed in 2008 by the American College of Chest Physicians recommend the CHADS2 risk-scoring system for stroke risk stratification in patients with AF. According to these guidelines, patients are considered to be at high risk for stroke if they have a CHADS2 score of 2 or greater. Patients would be in this high-risk group if they have a history of a...
transient ischemic attack, ischemic stroke, or systemic embolism (such as a pulmonary embolism or deep vein thrombosis), which has a point value of 2. They would also be considered to be at high risk if they have at least two of the following risk factors (each of which contributes one point to the score): age greater than 75 years, hypertension, diabetes, or moderately or severely impaired left ventricular systolic function and/or HF. Patients would be considered to be at intermediate risk for stroke if they have a CHADS$_2$ score of 1. They would be in this risk group if they have only one of the following risk factors: age greater than 75 years, hypertension, diabetes, or moderately or severely impaired left ventricular systolic function and/or HF. Patients would be considered to be at low risk for stroke if they have a CHADS$_2$ score of 0, meaning they are 75 years of age or less with none of the risk factors in the high- or intermediate-risk categories. The CHADS$_2$ score can be used to determine the most appropriate antithrombotic therapy for patients with AF.

### Impact of AF on mortality

In addition to causing significant morbidity, AF has been associated with an increase in mortality. For patients with AF, the risk of dying is double that for individuals without AF.$^{16}$ In the first 4 months after a diagnosis of AF, patients’ risk of dying is more than 9-fold higher than for patients without AF.

The high rate of death associated with AF may result from several mechanisms. Atrial fibrillation may facilitate the development of HF or the HF led to the development of AF.$^{18}$ Atrial fibrillation may facilitate the development of HF via several mechanisms that have already been discussed (i.e., reduction in cardiac output due to loss of atrial kick and/or shortened ventricular diastolic filling time). There are also a number of mechanisms by which HF can lead to the development of AF. In patients with HF, increased cardiac filling pressures can lead to dysfunction of the atria, which can predispose patients to AF. Heart failure is associated with dysregulation of intracellular calcium and activation of various neurohormonal systems, both of which can facilitate the development of AF. Heart failure also is associated with increased interstitial fibrosis, which can result in abnormal atrial conduction, electrical instability, and subsequent arrhythmia formation.$^{15}$

The development of AF has adverse prognostic implications in patients with HF.$^{19,20}$ In a retrospective analysis of more than 6500 patients with asymptomatic or symptomatic HF, the

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**Patient case**

**Risk of AF**

MW is a 78-year-old woman with a history of hypertension, CHD, and HF with a left ventricular ejection fraction of 30%. Her HF was diagnosed 6 years ago. Her current medications are as follows:

- Lisinopril 40 mg orally once daily
- Metoprolol CR/XL 100 mg orally once daily
- Furosemide 40 mg orally once daily
- Felodipine 10 mg orally once daily
- Simvastatin 80 mg orally once daily
- Aspirin 81 mg orally once daily

MW’s vital signs include a blood pressure of 125/65 mm Hg, heart rate of 68 beats per minute, and BMI of 32 kg/m$^2$. A recent electrocardiogram revealed sinus rhythm, a PR interval of 140 msec, and a QT interval of 410 msec.

MW’s 10-year risk for AF can be estimated by using the risk-scoring system in Table 1, with 6 points for her age, 1 point for her elevated BMI, 0 points for having a systolic blood pressure less than 160 mm Hg, 1 point for receiving antihypertensive therapy, 0 points for her PR interval less than 160 msec, and 2 points for her HF diagnosis at the age of 72 (she has no heart murmur, so this part of the risk-scoring system does not apply). MW has a total score of 10 points, which means she has a greater than 30% risk of developing AF in the next 10 years.

**Risk of thromboembolic stroke**

MW has now developed AF with a rapid ventricular rate. Her vital signs include a blood pressure of 110/70 mm Hg and a heart rate of 135 beats per minute. What is her risk of thromboembolic stroke?

Her risk for stroke can be estimated by using the CHADS$_2$ risk-scoring system. The CHADS$_2$ score for MW is 3 points, based on her age, HF, and hypertension; each factor contributes 1 point to the score. Therefore, MW is considered to be at high risk for stroke. This information can be used to determine the most appropriate antithrombotic therapy for MW.
presence of AF increased the rates of all-cause mortality, progressive pump failure-related death, and a composite endpoint of death or hospitalization for HF compared with patients who were in sinus rhythm. The time course of development of AF has also been shown to have an adverse impact on prognosis in patients with HF. In a study of 944 elderly patients hospitalized with HF, new-onset AF was associated with a 41% increase in risk for death compared with patients without AF; chronic AF was not associated with an increased risk for death in this study.

Atrial fibrillation is also a common complication of acute MI, with a reported incidence as high as 21%. Risk factors for AF in patients with an acute MI include advanced age, the presence of HF symptoms, a high heart rate at the time of hospital admission, and the presence of left ventricular dysfunction. As with HF, the presence of AF has been associated with adverse prognostic implications for patients with MI. The occurrence of AF during a acute MI has consistently been associated with a significantly higher risk of in-hospital and long-term mortality, which persists regardless of the mode of treatment.

Hospitalizations and costs

Hospitalizations for AF have increased 2- to 3-fold since 1985. In a study of 4498 patients with a new diagnosis of AF who were followed for a mean duration of 5.5 years, slightly more than half of the patients were hospitalized for cardiovascular causes at least once during the study period, and the cumulative rates of hospitalization after one year, three years, and five years were 31%, 48%, and 59%, respectively.

In 2001, AF was responsible for 350,000 hospitalizations, 276,000 emergency department visits, 234,000 hospital outpatient department visits, and 5 million office visits in the United States. The total cost of treating AF was estimated at $6.65 billion, with 44% of these costs being attributed to hospitalizations.

A more recent estimate of the overall cost of AF in the United States was based on a retrospective analysis of health insurance claims data for 2005 and 2006 from more than 35,000 managed care patients at least 20 years of age with a diagnosis of AF. To be included in this analysis, patients must have been hospitalized with a primary or secondary discharge diagnosis of AF or have at least two outpatient AF-related claims without a hospitalization during this period. A total of 35,255 patients were included in the analysis. In the 5008 patients hospitalized with a primary discharge diagnosis of AF, the mean 12-month inpatient costs (including the costs of readmissions as well as the initial hospitalization) were $11,307, and the mean 12-month outpatient costs were $2827, for a total annual cost of $14,134. In the 10,776 patients hospitalized with a secondary discharge diagnosis of AF, the mean annual inpatient, outpatient, and total costs were $5181, $1376, and $6557, respectively. In the 19,471 patients whose AF was managed on an outpatient basis, the inpatient costs were $176 and the outpatient costs were $2002, for a total annual cost of $2178. These costs were then affixed to the 2005 prevalence projections for AF from a previous study to provide estimates of the annual costs of AF in the United States. Overall, the total annual AF-related costs for 2005 were projected to be $12.7 billion, including $8 billion for hospitalization costs (63%) and $4.7 billion for outpatient costs (37%).

Given that the prevalence of AF is expected to dramatically increase by the year 2050, the cost of treating this disorder is predicted to reach staggering levels. This arrhythmia is expected to become an increasing burden on the health care system, which further underscores the need to identify treatment strategies that have the potential to reduce associated hospitalizations and readmissions associated with the disorder.

Conclusion

The morbidity and mortality from need for hospitalization for, and economic impact of AF are substantial and are projected to increase in the future. An understanding of the pathogenesis of and risk factors for the arrhythmia and the use of risk-scoring systems to estimate the risk for AF and stroke can provide insight for making decisions regarding interventions to minimize the impact of AF and its sequelae.

References


Pharmacotherapeutic decision-making for patients with atrial fibrillation

JAMES S. KALUS

The three primary therapeutic goals in patients with atrial fibrillation (AF) are to prevent thromboembolic stroke, control heart rate, and control rhythm. When rate control is the goal, AF is allowed to persist but symptoms are managed by reducing the heart rate. When rhythm control is the goal, electrical or pharmacologic cardioversion is used to establish and maintain sinus rhythm. This article reviews the established pharmacologic options for the prevention of thromboembolic stroke and control of heart rate and rhythm in patients with AF. The rationale for choosing between rate-control and rhythm-control strategies in patients with AF, as well as safety, efficacy, and patient-specific considerations in choosing among established antiarrhythmic medications for these patients, is discussed. Patient cases are used to illustrate the application of this information.

Antithrombotic therapy

Meta-analyses of studies comparing the efficacy of aspirin with placebo, no therapy, or warfarin for preventing stroke in patients with nonvalvular AF suggest that aspirin provides modest benefit in reducing the risk for ischemic stroke compared with placebo and control therapy and that warfarin is more effective than aspirin for this purpose. However, neither aspirin nor warfarin has been shown to reduce mortality in patients with AF.

Purpose. To discuss the therapeutic goals in patients with atrial fibrillation (AF); antithrombotic, rate-control, and rhythm-control medications used in these patients; rationale for choosing between rate-control and rhythm-control strategies; and safety, efficacy, and patient-specific considerations in choosing among established antiarrhythmic medications for these patients.

Summary. The three primary goals for patients with AF are prevention of thromboembolic stroke, heart rate control, and rhythm control. Warfarin is more effective than aspirin for stroke prevention in patients with AF, and it is recommended for patients at high risk for stroke. However, warfarin is underused, especially in elderly patients. Diltiazem, verapamil, β-blockers, digoxin, and amiodarone may be used for rate control; the choice among these agents is based on the patient’s blood pressure and the presence of certain underlying diseases. Rhythm-control strategies for patients with AF offer no advantage over rate-control strategies in terms of mortality or quality of life, and they are associated with a higher rate of hospitalization. Exercise tolerance is greater with rhythm control, however. The choice among antiarrhythmic agents for maintenance of sinus rhythm after cardioversion is based on safety, efficacy, and the presence of underlying structural heart disease (e.g., heart failure, coronary artery disease, hypertension with or without left ventricular hypertrophy) and renal impairment.

Conclusion. Careful consideration of patient-specific characteristics and the differences in safety and efficacy among antithrombotic, rate-control, and rhythm-control medications is needed to optimize treatment of and outcomes in patients with AF.

Index terms: Amiodarone; Anticoagulants; Aspirin; Atrial fibrillation; Blood pressure; Cardiac drugs; Decision making; Digoxin; Diltiazem; Drugs; Geriatrics; Heart rate; Mortality; Platelet aggregation inhibitors; Quality of life; Stroke; Sympatholytic agents; Thromboembolism; Toxicity; Verapamil; Warfarin

Am J Health-Syst Pharm. 2010; 67(Suppl 5): S17-25

JAMES S. KALUS, PHARM.D., BCPS (AQ Cardiology), is Senior Manager, Patient Care Services, Henry Ford Hospital, Detroit, Michigan.

Address reprint requests to Dr. Kalus at the Henry Ford Hospital, Department of Pharmacy Services, 2799 West Grand Blvd., Detroit, MI 48202 (jkalus1@hfhs.org).

Based on the proceedings of an educational activity recorded in February 2010 and supported by an independent educational grant from sanofi aventis U.S. Dr. Kalus has disclosed no relevant financial relationship with a commercial interest, as defined by the Accreditation Council for Pharmacy Education (ACPE). Dr. Kalus received an honorarium from the American Society of Health-System Pharmacists for his participation in the program and for his work on this article. This article was developed with the assistance of a medical writer working with ASHP Advantage. The medical writer, Susan R. Dombrowski, M.S., reports that she has no relevant financial relationship with a commercial interest, as defined by ACPE. The author approved the final article and all its content.

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The optimal international normalized ratio (INR) during warfarin therapy in patients with AF is 2.0-3.0, according to INR data from studies of the rates of stroke and intracranial hemorrhage in patients with non-valvular AF who received warfarin. The risk for stroke increases as the INR decreases markedly below 2.0, and the risk for intracranial hemorrhage increases dramatically as the INR approaches or exceeds 4.0.

The choice between warfarin and aspirin for stroke prevention in patients with AF is based on the risk for stroke. A history of stroke or transient ischemic attacks is a major risk factor for stroke. Other risk factors for stroke include moderately or severely impaired left ventricular systolic function (ejection fraction <35%) with or without heart failure (HF), hypertension, age 75 years or older, and diabetes mellitus. The risk for stroke in patients with AF may be estimated by using the CHADS2 score, which is determined by assigning 1 point each to the presence of congestive HF, hypertension, age ≥75 years, and diabetes mellitus and 2 points to a history of stroke or transient ischemic attack. These points are added to determine the patient’s CHADS2 score. Patients with scores of 2 or more points, 1 point, and 0 points are considered to be at high, intermediate, and low risk for stroke, respectively.

According to the most recent guidelines developed by the American College of Chest Physicians, warfarin is recommended for patients with AF and a high risk for stroke (i.e., patients with a CHADS2 score of 2 or higher). Warfarin or aspirin is recommended for patients with a CHADS2 score of 1 (i.e., an intermediate risk for stroke), and aspirin should be used for patients with a CHADS2 score of 0 (i.e., a low risk for stroke).

Many clinicians are reluctant to use warfarin in patients with AF. In a large study of patients hospitalized for heart failure who also had AF, only 65% of patients received warfarin at the time of hospital discharge. Among patients not prescribed warfarin in this study, only 9% of patients had a documented contraindication to warfarin use (e.g., a high risk for bleeding or falling). Predictors of warfarin nonuse included the use of antiplatelet agents, advanced age, anemia, female sex, and renal disease. There was an inverse correlation between the CHADS2 score and warfarin use (i.e., warfarin use decreased as the risk for stroke increased). These findings suggest that warfarin is underused in patients with AF.

Advanced age is a common concern and barrier to the use of warfarin in patients with AF. In the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study, warfarin and aspirin were compared in 973 elderly patients with AF. The mean age of participants was 82 years. Most patients (72%) had a CHADS2 score of 1 or 2 (i.e., an intermediate or high risk for stroke), although a considerable percentage (28%) had a CHADS2 score of 3-6 (i.e., a very high risk for stroke). After a mean follow-up period of 2.7 years, the risk for stroke or intracranial hemorrhage was 52% lower with warfarin than with aspirin (p = 0.003). There was no significant difference between warfarin and aspirin in the occurrence of major hemorrhage. These findings demonstrate that, despite potential concern about the safety of warfarin in elderly patients, the benefits of warfarin therapy likely outweigh the risks in an octogenarian patient population.

The efficacy of combination antiplatelet therapy with aspirin and clopidogrel has also been evaluated in patients with AF. A study known as ACTIVE-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) was stopped early because of clear evidence of greater efficacy and safety of warfarin compared with a combination of aspirin and clopidogrel in patients with AF and at least one risk factor (i.e., at intermediate or high risk) for stroke. In a related study known as ACTIVE-A, aspirin was compared with aspirin plus clopidogrel therapy in patients with AF who were at increased risk for stroke and unable to take warfarin. The rate of stroke was significantly lower in the group receiving aspirin plus clopidogrel (2.4% per year) than in the group receiving aspirin alone (3.3% per year) (p < 0.001). However, a significantly higher rate of major bleeding was associated with the use of clopidogrel plus aspirin than with aspirin alone (2.0% per year versus 1.3% per year, respectively, p < 0.001). Therefore, this combination antiplatelet therapy should be reserved for patients who do not have a high risk of bleeding and who are either unwilling or unable to participate in the laboratory monitoring needed for warfarin therapy.

### Patient case

**Risk of stroke in AF**

JN is an 82-year-old woman who presents to the emergency department after a syncopal episode. She has a history of paroxysmal AF, but she has never been offered long-term antithrombotic therapy. On examination, she is found to have experienced a recurrence of AF. JN’s past medical history includes osteoarthritis, stroke, and HF, with a left ventricular ejection fraction of 25%. Pertinent laboratory values and vital signs include a blood pressure of 110/70 mm Hg, heart rate of 70 beats per minute, and serum creatinine (SCr) of 0.6 mg/dL. JN’s CHADS2 score is 4 points based on her history of stroke (2 points), HF (1 point), and age greater than 75 years (1 point); therefore, she is considered to be at high risk for stroke. Warfarin with a target INR of 2.0-3.0 is recommended by the American College of Chest Physicians guidelines for patients like JN who are at high risk for stroke. However, because of her syncopal episode, some clinicians might view JN as being at risk for falling and might be inclined to avoid warfarin and choose aspirin.
It should be noted that the FDA recently added a Black Box warning to the clopidogrel package insert. This warning suggests the presence of several genetic variants of CYP2C10 can influence a patient’s ability to metabolize clopidogrel to its active form.10 The full implications of this warning are not yet known, particularly in patients with atrial fibrillation. It is important for pharmacists to be aware of this new warning.

Rate control

Patients with new-onset AF often feel better once their heart rate is controlled because many symptoms are directly or indirectly related to the rapid ventricular rate in AF. Palpitations and chest pain are a direct result of the rapid ventricular rate in AF. Syncope, life-threatening adverse effects of rate-control drugs, ventricular tachycardia or fibrillation, or implantation of a cardioverter-defibrillator or pacemaker. Lenient heart rate control was found to be noninferior to strict control with a hazard ratio of 0.84 (90% CI = 0.58 to 1.21). There are some limitations to this study, and widespread adoption of this more lenient heart rate target would be premature; however, targeting a heart rate of less than 110 beats per minute could be warranted in some patients.14 If a heart rate below 80 beats per minute cannot be achieved in an asymptomatic patient or if avoidance of multiple negative dromotropic agents is desired, perhaps a heart rate target of less than 110 beats per minute could be considered.

The same agents used for rate control in acute-onset AF are used for chronic rate control. If the patient has no contraindications to their use (e.g., heart block, severe bradycardia, reactive airway disease), β-blockers are considered first-line therapy. These drugs are particularly useful in patients with certain conditions, including coronary artery disease (CAD) and HF, although β-blockers are generally avoided in severely decompensated HF.

The non-dihydropyridine calcium-channel blockers diltiazem and verapamil also are considered first-line agents for chronic rate control unless contraindications (e.g., heart block, severe bradycardia) are present. However, these agents should be used with caution in patients with HF, especially decompensated HF. Digoxin is useful in patients with HF or low blood pressure because of its lack of an effect on systemic blood pressure.12 It also is useful as add-on therapy when a β-blocker or non-dihydropyridine calcium-channel blocker alone is inadequate. The use of amiodarone for rate control is reserved for situations in which other agents have not been effective in controlling the heart rate or are contraindicated.12

### Patient case

Rate control in new-onset AF

BT is a 68-year-old woman who presents with palpitations and mild shortness of breath. She is diagnosed with new-onset AF. Her past medical history includes hypertension and chronic kidney disease. Pertinent laboratory values and vital signs include a blood pressure of 140/80 mm Hg, heart rate of 140 beats per minute, ejection fraction of 45%, and SCr of 3.8 mg/dL.

Immediate cardioversion would be effective for treating BT’s new-onset AF, but it probably is not necessary because her symptoms are mild and are caused by a rapid ventricular rate. Rate control is a better approach to resolve BT’s symptoms, and i.v. diltiazem is an appropriate choice because her blood pressure is not low and she does not have HF.

Digoxin has a slow onset of effect, and it is not the most effective option for rate control in patients like BT with new-onset AF who do not have HF or low blood pressure.12 Moreover, BT’s elevated SCr and history of chronic kidney disease would make the use of digoxin problematic because elimination of the drug is prolonged by renal failure.15

Amiodarone might be an option for rate control if other standard therapies could not be used for BT. However, other safer and more effective options are available.
null
of the class Ia agent procainamide was withdrawn from the market because of low use.

Amiodarone

Amiodarone is the most commonly used antiarrhythmic agent. It has a unique pharmacologic profile in that it possesses electrophysiologic properties of all four Vaughan-Williams classes. While it is primarily considered a class III antiarrhythmic (potassium-channel blocker), it also has sodium-channel (class I), β-receptor (class II), and calcium-channel (class IV) blocking properties.12

Amiodarone is highly effective for maintaining sinus rhythm after cardioversion in patients with AF, and it is associated with a relatively low risk of proarrhythmia.12,24 In randomized studies of patients with persistent AF who were followed for more than one year, amiodarone was significantly more effective than sotalol and propafenone in preventing AF recurrence.25,26 In a study of 665 patients with persistent AF, the recurrence rate of AF after one year was 48% with amiodarone and 68% with sotalol (p = 0.002).25 In another study of 403 patients with persistent AF, the recurrence rate of AF after a mean follow-up time of 16 months was 35% with amiodarone and 63% with sotalol or propafenone (p < 0.001).26

In a randomized, double-blind, placebo-controlled study of 674 patients with HF and premature ventricular contractions, there was no significant difference in the two-year survival rate between amiodarone (69.4%) and placebo (70.8%).27 While most (85%) of the patients in this study did not have AF, these findings still have important implications concerning the safety of administering amiodarone to patients with AF who have HF.

Amiodarone has complex pharmacokinetics with a long half-life and a large volume of distribution, both of which result in the need for complicated loading doses.28 Amiodarone interacts with many other drugs (e.g., warfarin, digoxin) by inhibiting cytochrome P450 enzymes or P-glycoprotein membrane transporters.

Amiodarone is the most toxic antiarrhythmic agent, primarily because of extracardiac adverse effects that include neuropathy, corneal deposits, optic neuritis, thyroid dysfunction (i.e., hyperthyroidism and hypothyroidism), pulmonary fibrosis, nausea, vomiting, hepatotoxicity, rash, and photosensitivity.28 The drug also can cause bradycardia and heart block. In a meta-analysis of studies of amiodarone in patients with persistent AF, the rate of discontinuation of therapy because of intolerable adverse effects was 3-fold higher with amiodarone than with placebo or rate-control therapy.29 Amiodarone was not associated with an increased risk for long-term mortality or hospitalization in this study.

Dofetilide

Dofetilide is a pure class III antiarrhythmic agent that blocks only potassium channels and has modest efficacy for maintaining sinus rhythm after cardioversion in patients with AF.12,30 In a randomized, double-blind, dose-ranging study of 325 patients with persistent AF or atrial flutter, sinus rhythm was maintained after one year in significantly more patients treated with dofetilide 500 mcg orally twice daily than those receiving a placebo (58% versus 25%, respectively, p = 0.001).30 The results of two randomized, double-blind, placebo-controlled mortality studies of dofetilide in patients with asymptomatic left ventricular dysfunction due to a recent myocardial infarction (MI) or symptomatic congestive heart failure (HF) and severe systolic dysfunction provide insight about the safety of the drug in patients with heart failure.31,32 The rate of mortality was similar between the dofetilide and placebo groups after a period of more than three years in these studies. When data from these two studies for a subset of 506 patients with AF or atrial flutter were pooled, the percentage of patients remaining in sinus rhythm after one year was 79% with dofetilide and 42% with placebo (p < 0.001).33 These findings suggest that dofetilide is safe to use in patients with AF who have symptomatic or asymptomatic HF.

Dofetilide dosage reduction is required for patients with renal impairment; the drug is contraindicated in patients with a creatinine clearance (CrCl) less than 20 mL/min.34 The use of dofetilide is contraindicated in patients receiving verapamil, hydrochlorothiazide, ketoconazole, cimetidine, or trimethoprim because these drugs may increase dofetilide concentration, which could place patients at risk for torsades de pointes.34 The concomitant use of dofetilide and drugs that prolong the QT interval is also contraindicated because of the increased risk of torsades de pointes.34 A high rate of torsades de pointes was observed in dofetilide clinical trials (0.3-4.7%), although the risk may depend on the dosage used and patient characteristics.34

Sotalol

Sotalol is a class III antiarrhythmic agent that also has β-blocking properties.35 This antiarrhythmic is only modestly effective for maintaining sinus rhythm in patients with AF, and it is less effective than amiodarone.12,25 Sotalol should be avoided in patients with HF.12 Sotalol is eliminated by the kidneys; therefore, dosage adjustment is required for patients with renal impairment.35 Sotalol is contraindicated in patients with AF who have a CrCl less than 40 mL/min.36 Torsades de pointes is the primary toxicity from sotalol (0.3-3.2%). The risk for this arrhythmia depends on the sotalol dosage and patient characteristics.36 Adverse effects related to the β-blocking properties of sotalol, such as hypotension, bradycardia, and bronchospasm, also can occur.12
Dronedarone
Dronedarone, the newest class III antiarrhythmic agent, is structurally related to amiodarone, with a similar electrophysiologic profile, potential for drug interactions, and low risk for proarrhythmia.37,38 Dronedarone differs from amiodarone in its shorter half-life, lower lipophilicity, less extensive distribution, and lower potential for extracardiac effects (pulmonary fibrosis, liver and thyroid dysfunction). The lack of an iodine moiety on dronedarone confers a number of benefits over amiodarone, including a lower impact on thyroid function and reduced lipophilicity that makes it less likely to cause various organ toxicities.

Dronedarone has modest efficacy for maintaining sinus rhythm after cardioversion in patients with AF. It is less effective than amiodarone for this purpose, although the likelihood of toxicity is lower with dronedarone than with amiodarone.37,38 Most early studies excluded patients with heart failure.39,40 A study in which patients with moderate or severe HF were included was terminated prematurely because of higher mortality in dronedarone-treated patients than in placebo-treated patients, largely because of worsening of HF.41 Therefore, dronedarone is contraindicated in patients with class IV HF or symptomatic HF with a recent decompensation.42

Other agents
The class la antiarrhythmic agents disopyramide and quinidine usually are avoided in patients with AF because of intolerable anticholinergic adverse effects and GI adverse effects, respectively.12,43 The class lc agents flecainide and propafenone are comparatively well tolerated, but their use is limited because they are not safe to use in patients with structural heart disease (e.g., valvular heart disease, HF, CAD, hypertension with or without left ventricular hypertrophy).12,43 As with class III agents, all of these class la and lc agents are associated with a risk for proarrhythmia.12

In a comparative study of patients with AF, propafenone was more effective than sotalol for the long-term maintenance of sinus rhythm and had fewer adverse effects.46 Another study showed that amiodarone was more effective than propafenone for this purpose, but propafenone caused fewer adverse effects than amiodarone.47 Safety concerns outweighed efficacy considerations (i.e., the net benefit of propafenone was greater than that of amiodarone) in this study.47 A final study, mentioned previously, also demonstrated superior efficacy and similar tolerability of amiodarone compared with propafenone.25 Thus, although propafenone should not be used in patients with structural heart disease, the drug may be useful for certain patient populations that do not have structural heart disease.

In a meta-analysis of studies of the efficacy of various antiarrhythmic agents for maintaining sinus rhythm and preventing AF recurrence, amiodarone and dofetilide appeared to be the most effective agents.48 Disopyramide was the least effective agent for this purpose.

Initiation of antiarrhythmic therapy
Most of the antiarrhythmic agents used to treat AF should be initiated in the inpatient setting because of the risk for proarrhythmia (e.g., torsades de pointes).12 Amiodarone is an exception because it is associated with a low risk for proarrhythmia.

Hospital admission for three days with laboratory monitoring and replacement as needed of potassium and magnesium, measurement of a baseline corrected QT (QTc) interval before the first dose, and monitoring of the QTc interval a few hours after each dose during initial therapy is warranted.34,36 Dosage adjustments should be made as appropriate for certain drugs (e.g., dofetilide, sotalol) in patients with renal dysfunction. The potential for drug interactions, particularly with dofetilide, should be taken into consideration during initial therapy.

Selection of antiarrhythmic drug therapy for AF
The choice among available an-

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Table 1.
Antiarrhythmic Drug Therapy Decision-making in Patients with Atrial Fibrillation (AF)12,33,35,41,a

| Patients with presence of structural heart disease and patients with hypertension who do not have significant left ventricular hypertrophy (wall thickness < 1.4 cm) |
| First-line agents: flecainide, propafenone, or sotalol b |
| Second-line agents: amiodarone or dofetilide c |
| Patients with hypertension and significant left ventricular hypertrophy (wall thickness ≥ 1.4 cm) |
| First-line agent: amiodarone |
| Patients with coronary artery disease (CAD) |
| First-line agents: sotalol b or dofetilide c |
| Second-line agent: amiodarone |
| Patients with heart failure |
| First-line agents: amiodarone or dofetilide c |

aAccording to evidence-based guidelines published in 2006 by the American College of Cardiology, American Heart Association, and European Society of Cardiology. Dronedarone was not available at the time these guidelines were released. It may be an alternative therapeutic option in patients without cardiovascular disease, patients with hypertension with or without substantial left ventricular hypertrophy, and patients with CAD, but it should not be used in patients with heart failure.
bSotalol is contraindicated in patients with a creatinine clearance (CrCl) < 40 mL/min.
cDofetilide is contraindicated in patients with CrCl < 20 mL/min.
Antiarrhythmic agents for initial and maintenance therapy in patients with AF depend on the drug’s safety and efficacy, as well as the presence of underlying structural heart disease and renal impairment (Table 1). Evidence-based guidelines on making therapeutic decisions for patients with AF were published in 2006 by the American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC), which was before dronedarone became available. In patients without cardiovascular disease and in patients with hypertension who do not have significant left ventricular hypertrophy (left ventricle >1.4 cm), flecainide, propafenone, and sotalol are considered first-line agents; amiodarone and dofetilide are reserved for use as second-line agents. On the basis of the evidence currently available, dronedarone also might be considered a second-line agent in these patient populations.

In the presence of significant left ventricular hypertrophy (i.e., left ventricle wall thickness ≥1.4 cm), amiodarone is the only agent recommended for patients with AF because it is less likely to cause proarrhythmia in this population than are other antiarrhythmic drugs. Dronedarone might be an alternative antiarrhythmic for this patient population; patients with hypertension and structural heart disease participated in dronedarone clinical trials, although the number of participants who had significant left ventricular hypertrophy is unclear.

In patients with CAD, sotalol and dofetilide are considered first-line therapy for preventing AF recurrence. Amiodarone is considered a second-line therapy in these patients. Dronedarone also might be considered a second-line agent for this patient population. Neither flecainide nor propafenone is recommended for these patients because these drugs may increase mortality in patients with CAD.

The therapeutic options for patients with HF are limited to amiodarone and dofetilide, although the latter is not an option for patients with severe renal impairment. Dronedarone is not an option for patients with HF.

### Patient cases

**Antiarrhythmic therapy in a patient with persistent AF**

DB is a 50-year-old man with persistent AF who recently underwent electrical cardioversion. His past medical history includes hypertension treated with hydrochlorothiazide. He does not have left ventricular hypertrophy. Pertinent laboratory values and vital signs include a blood pressure of 140/90 mm Hg, heart rate of 100 beats per minute, and SCr of 0.8 mg/dL.

Flecainide, propafenone, and sotalol are considered first-line agents for preventing AF recurrence in hypertensive patients like DB who do not have left ventricular hypertrophy. DB does not appear to have renal impairment, which would be a concern with the use of sotalol. Amiodarone, a second-line therapy, is not the best choice for DB because he is young and does not have significant left ventricular hypertrophy. Dofetilide is not a good choice because of the potential for interaction with hydrochlorothiazide. Dronedarone is a possible alternative for DB because he does not have heart failure.

**Rhythm control in a patient with persistent AF, HF, and renal dysfunction**

DD is a 70-year-old man with persistent AF who recently underwent cardioversion to sinus rhythm. His past medical history includes HF, with a left ventricular ejection fraction of 30% and a recent hospitalization for exacerbation of HF, and end-stage renal disease (ESRD). Pertinent laboratory values and vital signs include a blood pressure of 140/90 mm Hg, heart rate of 80 beats per minute, creatinine clearance of 10 mL/min, and QT interval of 440 msec.

For DD, amiodarone is the only good therapeutic option for preventing AF recurrence because his ESRD precludes the use of dofetilide (amiodarone and dofetilide are the only two options for patients with AF who have HF). Amiodarone, a second-line therapy, is not the best choice for DB because he is young and does not have significant left ventricular hypertrophy. Dofetilide is not a good choice because of the potential for interaction with hydrochlorothiazide. Dronedarone is a possible alternative for DB because he does not have heart failure.

**Rhythm control in a patient with persistent AF and HF**

LG is a 71-year-old man with persistent AF treated with flecainide who is admitted for a non-ST-segment elevation MI. He is treated with percutaneous coronary intervention and is found to have a left ventricular ejection fraction of 25%. LG currently is in sinus rhythm. His past medical history is significant only for hypertension, and his medications prior to admission included lisinopril, metoprolol, and amlodipine. Pertinent laboratory values and vital signs include a blood pressure of 110/70 mm Hg, heart rate of 60 beats per minute, SCr of 0.9 mg/dL, and QT interval of 420 msec.

Flecainide therapy was appropriate for LG before his MI, but it is no longer safe because of his recent MI and his new-onset left ventricular systolic dysfunction. Propafenone should be avoided for the same reason. Sotalol also probably should be avoided because of LG’s HF and lower heart rate. Switching to amiodarone or dofetilide is appropriate for LG. In contrast to patient DD, who had ESRD, for LG dofetilide is an option because his SCr suggests that his renal function is normal.
**SYMPOSIUM** Pharmacotherapeutic decision-making

**Conclusion**

Warfarin often is underused in patients with AF, especially elderly patients. Although rhythm-control strategies offer few advantages over rate-control strategies, rhythm control is needed for some patients. Safety, efficacy, and patient-specific factors, particularly the presence of underlying structural heart disease and renal impairment, should be taken into consideration in selecting antiarrhythmic therapy to prevent AF recurrence.

**References**


Various drug therapies are used to control heart rate or rhythm or prevent stroke in patients with atrial fibrillation (AF). The shortcomings of established antiarrhythmic agents and anticoagulants have led to efforts to develop new agents with improved safety and efficacy profiles. In this article, new and emerging antiarrhythmic and anticoagulant medications for the treatment of AF are reviewed, as are nonpharmacologic interventions. A patient case is used to illustrate the potential application of new and emerging options for AF management.

Emerging antiarrhythmic agents

The usefulness of most established antiarrhythmic agents for treating patients with AF is limited because of poor efficacy, safety concerns, or both. A risk for proarrhythmias, intolerable adverse effects, and drug interactions and the need for dosage adjustment in patients with renal impairment are associated with some antiarrhythmic agents. A new oral antiarrhythmic agent, dronedarone, was approved by the Food and Drug Administration (FDA) in July 2009. Vernakalant, another antiarrhythmic agent initially developed for intravenous (i.v.) administration, was recommended for approval by the FDA Cardiovascular and Renal Drugs Advisory Panel in December 2007, but additional safety data were requested by FDA in August 2008. An oral form of the drug currently is in Phase II clinical trials.

Purpose. To compare and contrast the pharmacology, efficacy, and safety of new, emerging, and established antiarrhythmic and anticoagulant medications and describe nonpharmacologic interventions for the treatment of atrial fibrillation (AF).

Summary. Shortcomings of established antiarrhythmic agents include a risk for proarrhythmias and intolerable adverse effects. Dronedarone is a recently introduced amiodarone congener for maintenance of sinus rhythm after cardioversion in patients with AF that is better tolerated than amiodarone. Vernakalant is an emerging antiarrhythmic agent for conversion of AF to normal sinus rhythm with atrial-selective activity that appears to minimize the risk for proarrhythmia. An unpredictable dose-response relationship and the need for laboratory monitoring are among the many shortcomings of warfarin. Rivaroxaban, an emerging oral direct factor Xa inhibitor, and dabigatran, an emerging oral direct thrombin inhibitor, have predictable dose-response relationships and do not require laboratory monitoring. Additional data from comparative clinical trials will clarify the role of these emerging agents in the treatment of AF. Various nonpharmacologic interventions may be used for rhythm control, rate control, or cardioversion in patients whose AF cannot be managed with pharmacotherapy because of a lack of efficacy or intolerable adverse effects.

Conclusion. New and emerging antiarrhythmic and anticoagulant agents offer advantages over established agents and may improve outcomes in patients with AF.
Antiarrhythmic agents are classified on the basis of their electrophysiologic and pharmacologic effects. The class Ic agents (e.g., flecainide and propafenone) block the inward flow of sodium ions through sodium channels in cardiac myocytes, which reduces the conduction of electrical impulses and disrupts the reentry circuits that contribute to AF.4 Class II agents are β-blockers. Class III agents (e.g., amiodarone, dofetilide, ibutilide, sotalol) inhibit potassium ion influx through rapid and ultra-rapid potassium channels, which increases tissue refractoriness and interferes with the reentry circuits associated with AF.5 Class IV agents (e.g., diltiazem, verapamil) block calcium channels. Class II and class IV agents are used for rate control, but not rhythm control, in patients with AF.

Amiodarone blocks sodium and calcium channels as well as potassium channels, and it has anti-adrenergic (i.e., β-blocking) properties.4 Sodium channels and rapid potassium channels are found in both the atria and the ventricles; therefore, antiarrhythmic agents that inhibit ion influx through these channels affect the ventricles as well as the atria.4 Ultra-rapid potassium channels are found only in the atria; therefore, agents that act selectively on ion influx through these channels in theory may be less likely to cause proarrhythmia.

### Dronedarone

Dronedarone is an amiodarone congener with a similar electrophysiologic profile but some important differences (Table 1). Dronedarone has a much shorter half-life than amiodarone, and steady-state plasma concentrations are achieved after four to eight days.1,6 By contrast, the time to therapeutic response is one to three weeks for most patients receiving amiodarone, even with the use of loading doses.8

Dronedarone is extensively metabolized, primarily by cytochrome P-450 (CYP) 3A4. It is a moderate inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. This could lead to increased exposure to calcium-channel blockers and β-blockers, respectively, if the drugs are used concurrently with dronedarone.2 Concomitant use of dronedarone with strong CYP3A4 inhibitors (e.g., ketoconazole) is contraindicated.1,2 Dronedarone also has the potential to inhibit P-glycoprotein membrane transporters, increasing exposure to concomitantly administered digoxin.2 Consideration should be given to either discontinuing digoxin or reducing the digoxin dose by 50% before initiating dronedarone.1

Amiodarone also is metabolized by CYP enzymes, primarily 3A4 and 2C8.6 It can interact with drugs that are substrates for or inhibitors or inducers of 3A4 (e.g., calcium-channel blockers) and 2C8 (e.g., trimethoprim, gemfibrozil, torsemide). Amiodarone also inhibits P-glycoprotein membrane transporters. Both amiodarone and dronedarone are highly protein bound, which may result in displacement from protein binding sites of other drugs that are highly protein bound (e.g., phenytoin).1,6 Dronedarone has a more favorable adverse effect profile than amiodarone.2 The adverse effects from dronedarone primarily involve the gastrointestinal tract.1 The drug can increase serum creatinine (SCR) concentrations by inhibiting creatinine tubular secretion, not by affecting glomerular filtration rate. Dronedarone’s effect on SCR usually occurs rapidly, with SCR concentrations reaching a plateau after seven days, and it is reversible after discontinuation of the drug.

By contrast, amiodarone is widely distributed and causes numerous extracardiac adverse effects, although the kidneys typically are not affected.6 Thyroid dysfunction in the form of hypothyroidism or hyperthyroidism, pulmonary fibrosis, and liver function abnormality are associated with amiodarone but not with dronedarone, most likely because dronedarone lacks the iodine moiety found on amiodarone. Both amiodarone and dronedarone

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**Table 1. Characteristics of Amiodarone and Dronedarone**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amiodarone</th>
<th>Dronedarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>40–55 days</td>
<td>13–19 hours</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>~ 96</td>
<td>&gt; 98</td>
</tr>
<tr>
<td>Metabolism*</td>
<td>CYP3A4 and 2C8</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Neuropathy, corneal deposits, optic neuritis, hyperthyroidism, hypothyroidism, pulmonary fibrosis, nausea, vomiting, hepatotoxicity, rash, photosensitivity, bradycardia, QT interval prolongation, and proarrhythmia</td>
<td>Gastrointestinal effects (diarrhea, nausea, abdominal pain, vomiting), increases in serum creatinine due to inhibition of creatinine tubular secretion, bradycardia, QT interval prolongation, and proarrhythmia</td>
</tr>
</tbody>
</table>

*The enzymes listed are involved in metabolism of the drug. CYP = cytochrome P450.
can cause bradycardia, QT interval prolongation, and proarrhythmia, although the risk of these effects is low compared with most other antiarrhythmic agents.1,6

Clinical experience. The efficacy and safety of dronedarone for maintaining sinus rhythm after electrical cardioversion were demonstrated in two randomized, double-blind, placebo-controlled studies of patients with at least one episode of AF within the preceding three months.7 The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) study was conducted in Europe, and the American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) study was conducted in the United States, Canada, Australia, South Africa, and Argentina. The mean age of participants was approximately 63 years. The mean left ventricular ejection fraction (LVEF) was approximately 59% (i.e., patients did not have left ventricular systolic dysfunction). Patients with New York Heart Association (NYHA) functional class III or IV (i.e., moderate to severe) heart failure (HF) were excluded, but approximately 17% of enrolled patients had milder HF. A total of 828 patients received dronedarone 400 mg orally twice daily for 12 months, and 409 patients received placebo. The primary endpoint was the time to the first recurrence of AF.

The median times to AF recurrence were significantly greater with dronedarone than placebo in both the European trial (96 days versus 41 days, \( p = 0.01 \)) and the non-European trial (158 days versus 59 days, \( p = 0.002 \)).7 When data from the two studies were pooled, the rate of AF recurrence after 12 months was significantly lower in the dronedarone group than in the placebo group (64.1% with dronedarone versus 75.2% with placebo, \( p < 0.001 \)). The rate of SCR elevation was 2.4% in the dronedarone group and 0.2% in the placebo group (\( p = 0.004 \)).

Two randomized, double-blind, placebo-controlled studies known as ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) and ATHENA (Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) were conducted to evaluate the impact of dronedarone on mortality and hospitalization rates.8,9 In the ANDROMEDA study, 627 patients at least 18 years of age who were hospitalized with new or worsening HF and had experienced NYHA functional class III or IV symptoms or paroxysmal nocturnal dyspnea within the month before admission received dronedarone 400 mg or placebo twice daily.8 Approximately 38% of participants had a history of AF. The median age of participants was approximately 71 years. The primary endpoint was the composite of all-cause mortality or hospitalization for HF. Treatment for at least 12 months was planned, but the study was terminated after seven months because of significantly higher mortality in the dronedarone group (8.1%) compared with the placebo group (3.8%) after a median follow-up time of two months (\( p = 0.03 \)). Most of the excess mortality was attributed to worsening HF. The number of patients requiring hospitalization for acute cardiovascular causes was significantly higher with dronedarone (71 patients, or 22.9%) than with placebo (50 patients, or 15.8%) (\( p = 0.02 \)). Elevated SCR values were observed in 2.6% of the dronedarone-treated patients and none of the placebo-treated patients (\( p = 0.01 \)).

The ATHENA study involved 4628 high-risk patients with AF who received dronedarone 400 mg or placebo twice daily with a mean duration of follow-up of 21 months.8 Patients were eligible to participate if they were at least 70 years old or had hypertension; diabetes mellitus; a history of stroke, transient ischemic attack, or systemic embolism; left atrial diameter of \( \geq 50 \) mm; or LVEF of \( \leq 40\% \). The mean age of participants was approximately 72 years. Most patients had a normal LVEF. Approximately 20% of patients had a history of NYHA functional class II or III HF. Patients with NYHA functional class IV HF or recent decompensated HF were excluded from the study. The primary endpoint was the composite of all-cause death or cardiovascular hospitalization.

Dronedarone significantly reduced the occurrence of the primary endpoint from 39.4% in the placebo group to 31.9% in the dronedarone group (\( p < 0.0001 \)). Death from cardiovascular causes also was significantly less common in the dronedarone group than in the placebo group (2.7% versus 3.9%, respectively, \( p = 0.03 \)), largely because of a significantly lower rate of death from arrhythmia (1.1% with dronedarone versus 2.1% with placebo, \( p = 0.01 \)). Serum creatinine elevations were observed in 4.7% of dronedarone-treated patients and 1.3% of placebo-treated patients (\( p < 0.001 \)). These findings suggest that dronedarone is safe and effective in carefully selected patients with AF (i.e., patients without functional class IV HF or symptomatic HF with recent decompensation).

The safety and efficacy of dronedarone and amiodarone for maintaining sinus rhythm were compared in 504 patients with AF in a randomized, double-blind study known as the Efficacy and Safety of Dronedarone versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation (DIONYSOS) trial.2 Patients were eligible to participate if they had a need for cardioversion and antiarrhythmic therapy and were receiving anticoagulants. The mean age of participants was approximately 70 years.
64 years. Approximately 20% of participants had a history of HF; patients with NYHA functional class III or IV HF were excluded, however. Patients received dronedarone 400 mg twice daily or amiodarone 600 mg once daily for 28 days followed by 200 mg once daily. Treatment was continued for at least six months. The primary endpoint was defined as recurrence of AF or premature study drug discontinuation because of intolerance or a lack of efficacy.

The results of the DIONYSOS trial are not yet published, but they were made available to FDA in March 2009 when the agency reviewed dronedarone for approval. The incidence of the primary endpoint after 12 months was significantly higher in the dronedarone group (75.1%) than in the amiodarone group (58.8%, p < 0.0001). The rate of AF recurrence was higher in the dronedarone group (63.5%) than in the amiodarone group (42.0%), but the rate of premature study drug discontinuation because of intolerance was lower in the dronedarone group (10.0%) than in the amiodarone group (13.3%). The frequency of thyroid disorders was significantly lower with dronedarone than amiodarone (1.2% versus 7.8%, respectively, p = 0.0006). Neurologic events (e.g., sleep disorders, tremor) also were significantly less common in the dronedarone group (1.2%) than in the amiodarone group (9.4%) (p < 0.0001). No pulmonary events (e.g., interstitial lung disease, hypersensitivity pneumonitis, interstitial or alveolar pneumonitis) were reported during the study.

Role in therapy. Currently available evidence from clinical trials suggests that dronedarone is useful for maintaining sinus rhythm in patients with AF who are at high risk for recurrence according to the inclusion criteria in the ATHENA trial (i.e., age ≥70 years old; hypertension; diabetes mellitus; a history of stroke, transient ischemic attack, or systemic embolism; left atrial diameter ≥50 mm; LVEF ≤40%). Although dronedarone may not be as effective as amiodarone for preventing AF recurrence, it may be preferred for patients who cannot tolerate amiodarone, according to the DIONYSOS study findings. Dronedarone should not be used in patients with functional class IV HF or symptomatic HF (i.e., NYHA functional class II or III) with recent decompensation, given the results of the ANDROMEDA study.

Dronedarone has the potential to cause bradycardia, QT interval prolongation, and proarrhythmias. However, as with amiodarone, the risk of torsades de points is relatively low with dronedarone. Patients receiving dronedarone should be monitored for signs of new or worsening HF (e.g., weight gain, increasing shortness of breath, edema) because the drug may need to be temporarily or permanently discontinued.

If an elevation in SCr concentration occurs and a plateau is reached within about one week after the initiation of dronedarone, this value should be used as a baseline for the patient. If a plateau is not reached promptly, other possible causes for SCR elevation should be investigated.

Vernakalant

Vernakalant is an inhibitor of ultra-rapid potassium channels, which confers atrial-selective activity and minimal effects on the ventricles. Because it has minimal ventricular effects, vernakalant does not prolong the QT interval. The drug also is a rate- and voltage-dependent inhibitor of sodium channels. Its effects on sodium channels, therefore, may be enhanced during AF compared with sinus rhythm, promoting conversion of AF to normal sinus rhythm.

Vernakalant is rapidly and extensively metabolized, primarily by CYP2D6. It is a short-acting agent with a half-life of approximately 2 hours.

Clinical experience. The safety and efficacy of vernakalant for the conversion of AF to sinus rhythm have been explored in four clinical studies known as Atrial Arrhythmia Conversion Trial (ACT) I, II, III, and IV. Many data from these studies are not yet published, but they have been presented to the FDA. Patients with a duration of AF exceeding three hours and lasting up to 45 days were enrolled in ACT I and ACT III, which were Phase III, randomized, double-blind, placebo-controlled studies. The study design used in ACT III was similar to that in ACT I, but additional safety data were collected in ACT III. Vernakalant 3 mg/kg or placebo was given by i.v. infusion over 10 minutes to 336 patients in ACT I and 239 patients in ACT III. A second i.v. infusion of vernakalant 2 mg/kg or placebo was administered 15 minutes later if AF had not terminated. The mean age of participants in these studies was approximately 62 years. The primary endpoint was the rate of conversion to sinus rhythm within 90 minutes after the first infusion.

In ACT I, the percentage of patients achieving the primary endpoint was significantly higher with vernakalant (62.1%) than placebo (4.9%) (p < 0.001). In the subset of patients with a duration of AF from three hours to seven days, the drug significantly improved the success rate compared with placebo (51.7% versus 4.0%, respectively, p < 0.001). By contrast, the success rates were considerably lower and no longer significantly different between vernakalant (7.9%) and placebo (0%) in patients with a longer duration of AF (8–45 days) (p = 0.09). Thus, vernakalant was more effective for converting AF to sinus rhythm in patients who had a relatively short duration of AF than in those who had a longer duration of AF. Similar findings were reported in ACT III.

The most common serious adverse event in ACT I was recurrent
AF requiring hospitalization, which occurred in 5.9% of patients in the vernakalant group and 12.2% of patients in the placebo group. There were no reports of torsades de pointes or ventricular fibrillation within the first 24 hours after vernakalant administration in ACT I or ACT III. Common adverse events reported in this time frame by vernakalant-treated patients include dysgeusia (29.9%), sneezing (16.3%), paresthesia (10.9%), nausea (9.0%), and hypotension (6.3%).

The efficacy and safety of vernakalant for conversion of AF to sinus rhythm were evaluated in ACT II. This randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of vernakalant in 150 patients undergoing coronary artery bypass graft, valvular surgery, or both. The same vernakalant dosage and primary efficacy endpoint used in ACT I and ACT III were used in this trial. The conversion success rate was significantly greater with vernakalant than placebo (47% versus 14%, respectively, p < 0.001). Two serious adverse events (hypotension and complete ativoventricular [AV] block) were reported within 24 hours after vernakalant administration. No cases of torsades de pointes, sustained ventricular tachycardia, or ventricular fibrillation were reported.

Safety was the focus of ACT IV, an open-label study of patients with AF lasting for more than three hours and up to 45 days, but some efficacy data also were collected. The same vernakalant dosage used in ACT I, II, and III was used in ACT IV. In patients with a duration of AF up to seven days, the rate of conversion to sinus rhythm was 50.9% with vernakalant, which was consistent with the findings of ACT I and III.

Role in therapy. If vernakalant receives FDA approval, it will play a role in converting recent-onset AF to sinus rhythm. The drug has a low risk of torsades de pointes and other forms of proarrhythmia, but blood pressure monitoring will be needed because of the risk for hypotension.

Anticoagulants

Warfarin, the only oral anticoagulant currently available in the United States for the prevention of stroke in patients with AF, interferes with hepatic synthesis of vitamin K-dependent clotting factors II, VII, IX, and X by binding to the enzyme vitamin K epoxide reductase. Warfarin has many shortcomings, including a narrow therapeutic index, unpredictable dose-response relationship, risk for hemorrhage, need for laboratory monitoring, interactions with certain foods and other drugs, and increased sensitivity to warfarin due to genetic polymorphisms in the enzymes that metabolize the drug (CYP2C9) or mediate its clinical effects (vitamin K epoxide reductase [VKOR]).

Rivaroxaban and dabigatran, the two anticoagulants furthest along in development, may potentially offer advantages over warfarin in patients with AF.

Rivaroxaban. Rivaroxaban is an oral direct factor Xa inhibitor. The FDA has not yet made a decision about approving the drug. Additional safety data, especially data pertaining to the effects of the drug on liver function, were requested by the FDA in March 2009. The drug was approved in Europe and Canada in 2008 for the prevention of venous thromboembolism (VTE) in adults undergoing elective hip or knee replacement surgery. Rivaroxaban is rapidly absorbed after oral administration, with peak plasma concentrations achieved 2.5-4 hours after a dose. The drug has a half-life of 5-9 hours, although elimination may be prolonged in elderly patients. Rivaroxaban is eliminated primarily by the kidneys (66% of a dose), although there is no evidence to date of drug accumulation or bleeding in patients with renal impairment. Biliary and fecal elimination of rivaroxaban also occurs, which may minimize the impact of renal impairment on elimination of the drug. Rivaroxaban is metabolized primarily by the CYP3A4 isoenzyme; therefore, the concomitant use of potent inhibitors of this isoenzyme could increase rivaroxaban plasma concentrations.

Rivaroxaban has a predictable dose-response relationship; therefore, fixed doses may be used without laboratory monitoring of coagulation values, which is a major advantage over warfarin. Clinical trials of once-daily administration of rivaroxaban for the prevention of thrombosis in patients with AF are in progress (e.g., the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation study known as ROCKET-AF).

Dabigatran. Dabigatran is an oral direct thrombin (i.e., factor IIa) inhibitor that became available in Europe and Canada in 2008 for the prevention of VTE after hip and knee replacement surgery. A new drug application for dabigatran has been submitted to FDA in 2010.

Dabigatran is administered as dabigatran etexilate, which is rapidly absorbed after oral administration and converted to its active form, dabigatran, by esterase-catalyzed hydrolysis in plasma and the liver. Peak plasma concentrations are achieved 0.5-2 hours after a dose. Up to 80% of a dose is excreted renally; therefore, dosage reduction probably will be required for patients with renal impairment to prevent drug accumulation. The half-life of dabigatran is 12-17 hours. Strong inhibitors of P-glycoprotein membrane transporters (e.g., verapamil, quinidine, clarithromycin) could increase dabigatran plasma concentrations.

As with rivaroxaban, dabigatran has a predictable dose-response relationship. Therefore, fixed doses may be used without laboratory monitoring of coagulation.
Dabigatran was compared with warfarin in a randomized, open-label, noninferiority study known as the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial. This study enrolled 18,113 patients with a history of AF within the preceding six months. Patients were required to be at risk for stroke because of a previous stroke or transient ischemic attack, LVEF < 40%, NYHA functional class II–IV HF within six months before screening, age ≥75 years, or age 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease. Participants were randomly assigned to receive dabigatran 110 mg or 150 mg twice daily in a blinded fashion or warfarin adjusted to maintain an international normalized ratio (INR) of 2.0-3.0. The primary endpoint was 1.69% per year in the warfarin group, 1.53% per year in patients receiving dabigatran 110 mg twice daily, and 1.11% per year in patients receiving dabigatran 150 mg twice daily. The smaller of the two dabigatran dosages was judged noninferior in efficacy to warfarin, and the larger of the two dabigatran dosages was judged superior to warfarin ($p < 0.001$ for both comparisons). The rate of major bleeding was not significantly different between the two dabigatran dosages and the larger of the two dabigatran dosages was judged superior to warfarin ($p < 0.001$ for both comparisons). The rate of major bleeding was not significantly different between the dabigatran 150 mg group (3.11% per year) and warfarin. The rate of hemorrhagic stroke was significantly lower in patients receiving dabigatran 150 mg twice daily, and 1.11% per year in patients receiving dabigatran 150 mg twice daily. The smaller of the two dabigatran dosages was judged noninferior in efficacy to warfarin, and the larger of the two dabigatran dosages was judged superior to warfarin ($p < 0.001$ for both comparisons). The rate of major bleeding was not significantly different between the two dabigatran dosages and the larger of the two dabigatran dosages was judged superior to warfarin ($p < 0.001$ for both comparisons). The rate of major bleeding was not significantly different between the dabigatran 150 mg group (3.11% per year) and warfarin. The rate of hemorrhagic stroke was significantly lower in both dabigatran groups (0.12% per year with 110 mg and 0.10% per year with 150 mg) than in the warfarin group (0.38% per year) ($p < 0.001$ for both comparisons). Thus, the higher dabigatran dosage (150 mg twice daily) was more effective than warfarin for stroke prevention in patients with AF and did not increase the risk for bleeding.

Until additional comparative data for dabigatran and warfarin become available, the initial place in therapy of dabigatran once FDA approval is obtained might be stroke prevention in patients with AF who are at intermediate or high risk for stroke and are unable to comply with warfarin monitoring requirements or who respond to warfarin inconsistently because of interactions with foods or other drugs. If the results of ROCKET-AF prove to be favorable, rivaroxaban could potentially assume a similar role.

### Patient case

**Potential role of new and emerging antiarrhythmic therapies**

BC, a 68-year-old man, presents to the emergency department complaining of palpitations and dizziness since last evening, which prevent him from "having a good night's sleep." He has a history of AF and hypertension. BC's medications on admission are sotalol 80 mg twice daily, warfarin 5 mg once daily, and lisinopril 20 mg once daily. In the past, he tried amiodarone, which caused pulmonary fibrosis, and propafenone, but he experienced recurrent AF despite using an appropriate propafenone dosage. BC has an LVEF of 50% and no evidence of left ventricular hypertrophy. Pertinent vital signs include a blood pressure of 150/95 mm Hg, heart rate of 145 beats per minute, and respiratory rate of 35 breaths per minute. Pertinent laboratory values include SCr of 0.8 mg/dL and INR of 2.3. An electrocardiogram reveals AF and a corrected QT interval of 480 msec.

A key decision in patients like BC who present to the emergency department with symptomatic AF is whether to use rate-control therapy and allow AF to persist or use cardioversion and subsequent rhythm-control therapy to maintain sinus rhythm. In most cases, rate-control therapy is preferred because it provides prompt stabilization of the patient's symptoms while a decision is made about the best strategy for cardioversion to restore sinus rhythm. This approach could be used for BC, since reducing his ventricular rate may make him feel more comfortable. A different rhythm-control strategy, however, should also be considered for this patient.

The fact that BC has tried different agents for rhythm control in the past suggests that his AF symptoms were probably not adequately controlled by rate-control agents alone when he first developed AF. Since BC is already anticoagulated, cardioversion can be performed without delay. If BC were not properly anticoagulated, cardioversion could not be performed until he had been therapeutically anticoagulated for a month or echocardiographic findings demonstrated no thrombi present in the atrium or ventricle. Otherwise, the risk of thromboembolism during cardioversion would be very high.

BC's cardiologist inquires about the use of dronedarone because of BC's inadequate response to sotalol and history of difficulty with other established antiarrhythmic agents. BC appears to be a good candidate for dronedarone because of his history of AF and hypertension, which were among the inclusion criteria in the ATHENA study. The drug could help maintain BC's sinus rhythm after cardioversion and reduce his risk for cardiovascular hospitalization and death. There is no reason to expect pulmonary fibrosis during BC's dronedarone therapy simply because he experienced this problem during amiodarone therapy. The adverse effect profiles for the two drugs differ, and dronedarone has not been associated with pulmonary fibrosis.

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Nonpharmacologic management

Nonpharmacologic intervention is indicated for patients whose AF cannot be managed with pharmacotherapy because of a lack of efficacy or intolerable adverse effects. Pharmacotherapy usually is tried before nonpharmacologic interventions are used because the latter strategies are invasive. Nonpharmacologic approaches to managing AF have evolved considerably over the past few years. Several options currently are available.

Ventricular rate control can be achieved by using AV node ablation or modification, which terminates or reduces transmission of electrical impulses from the atria to the ventricles. Controlling the ventricular rate reduces AF symptoms. However, with these procedures, fibrillation of the atria is allowed to continue, resulting in the need for long-term anticoagulant therapy to prevent thromboembolic events. In addition, because communication between the atria and ventricles is disrupted, a permanent pacemaker must be implanted to regulate the ventricular rate. Long-term survival in patients with AF who undergo AV node ablation and permanent pacemaker implantation is comparable to that in patients with AF managed with drug therapy.

Rhythm control can be achieved through one of two procedures that result in focal ablation of the arrhythmia (i.e., destruction of specific areas of the atria that are responsible for AF). The older of the two procedures is an open-heart surgical procedure known as MAZE, which requires a thoracotomy and numerous incisions in the atria in a maze-like pattern. This procedure is no longer commonly performed.

The other rhythm-control procedure for patients with AF is pulmonary vein isolation ablation. This focal ablation technique is gaining in popularity because it is less invasive than the MAZE technique. Pulmonary vein isolation ablation involves inserting a catheter outfitted with a device that delivers heat energy via radiofrequency waves into the femoral vein at the groin. The catheter is then threaded through the inferior vena cava into the right atrium and across the atrial septum into the left atrium (Figure 1). Tissue at selected locations in the left atrium at the base of the pulmonary veins where abnormal rhythms often originate is burned (i.e., ablated) to prevent AF and maintain sinus rhythm. The success rate of pulmonary vein isolation ablation is higher in patients with paroxysmal AF than in patients with persistent AF. In a study of 70 consecutive patients with paroxysmal or persistent AF who underwent pulmonary vein isolation ablation, 70% of patients with paroxysmal AF and 22% of patients with persistent AF were free from recurrent AF five months later ($p < 0.001$). These findings are consistent with what is known about the greater difficulty in treating chronic AF compared with new-onset AF.

Patient case

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The cardiologist inquires whether a lower LVEF (e.g., 30% instead of 50%) would influence the decision to try dronedarone in BC and other patients. Dronedarone is contraindicated in patients with functional class IV HF or symptomatic HF with recent decompensation on the basis of the ANDROMEDA study findings. BC did not present with and does not have a recent history of HF symptoms, which is a more important consideration in using dronedarone than his LVEF. Patients with stable chronic HF may be candidates for dronedarone therapy even if their LVEF is low (e.g., <40%), provided they do not have a recent history of acute HF symptoms (e.g., weight gain, increasing shortness of breath, edema). Patients like BC should be educated about the need to monitor for these symptoms during dronedarone therapy because the drug may need to be temporarily or permanently discontinued.

The cardiologist mentions that she has heard about vernakalant and wonders if this agent might be suitable for BC in the future, once it is approved by FDA. Experience with the drug in patients like BC with short-duration AF in ACT I, III, and IV suggests that it might be useful for conversion of AF to sinus rhythm in BC in the future if he experiences AF recurrence.

Potential role of new and emerging anticoagulants

The cardiologist also inquires about the potential usefulness of dabigatran instead of warfarin for BC. BC has had difficulty in the past with warfarin because of drug interactions and dietary indiscretions, and he finds the need for monthly blood draws to monitor his INR bothersome. Dabigatran would be an alternative to warfarin for BC, given the findings of the RE-LY study. Dabigatran 110 mg twice daily might be used because it was at least as effective as warfarin for preventing stroke and showed a lower risk for major bleeding. Alternatively, dabigatran 150 mg twice daily might be used because its efficacy was superior to that of warfarin without an increased risk for major bleeding. The choice between these two dosages probably will hinge on the dosage recommended in the product labeling once FDA approval is received. The use of dabigatran involves twice-daily dosing, which is less convenient than the once-daily dosing used for warfarin. The need for twice-daily dosing instead of once-daily dosing might deter adherence to dabigatran in some patients. However, other patients, such as BC, might prefer to accept the inconvenience of twice-daily dosing of dabigatran to avoid the need for laboratory monitoring during warfarin therapy. Once-daily rivaroxaban may offer an adherence advantage if clinical trials prove it safe and effective for the prevention of stroke in patients with AF. Patient preferences should be taken into consideration in therapeutic decision-making regarding anticoagulant therapy in patients like BC who have AF.
Improvements in pulmonary vein isolation ablation have been achieved in the past several years through the use of computerized mapping of the locations where abnormal rhythms arise and guidance of the catheter to these locations, as well as through the use of balloon-based catheter ablation systems that allow “single shot” circumferential ablation instead of point-by-point catheter ablation at the base of the pulmonary vein. These technologies allow the electrophysiologist greater accuracy in burning the tissues associated with AF and success in maintaining sinus rhythm.

Balloon-based catheter systems can deliver various energy sources for ablation (cryothermal energy, ultrasound, laser, and radiofrequency). Among these different energy sources, cryothermal energy appears to have minimal risk in terms of causing pulmonary vein stenosis, atrio-osophageal fistula, and thrombus formation.27 In the Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP-AF) study, 245 patients with paroxysmal AF were randomized to receive cryoballoon ablation or antiarrhythmic therapy.28,29 Preliminary results indicate that 69.9% of patients who underwent cryoballoon ablation remained free from AF at the end of one year compared with 7.3% of those on medical therapy (p < 0.001). Serious complications to cryoablative therapy, namely pulmonary vein stenosis and phrenic nerve palsy, developed in 3% and 11% of patients undergoing cryoballoon ablation or receiving medical therapy, respectively.

Although pulmonary vein isolation ablation is less invasive than the MAZE procedure, it is currently only used as an alternative to pharmacotherapy for rhythm control in patients with recurrent AF who remain symptomatic with heart rate control and for whom antiarrhythmic medication is either not tolerated or ineffective. The risks of pulmonary vein isolation ablation may include pulmonary vein stenosis, infection, and cardiac tamponade.25,30

Implantation of an internal atrial defibrillator is another nonpharmacologic intervention for AF management. The device serves the same role as an external defibrillator, but an internal device automatically detects the recurrence of AF and delivers a shock for conversion to normal sinus rhythm. The use of internal atrial defibrillator devices is limited because of poor tolerability. In most cases, patients remain conscious when AF recurs, and the delivery of shocks is uncomfortable despite the low voltage used. Frequent shocks are required for patients with frequent AF recurrences, with a substantial adverse impact on quality of life.

Conclusion

New and emerging antiarrhythmic agents that are better tolerated than established agents have been developed. Oral anticoagulants that do not require laboratory monitoring may be introduced soon. These therapies have the potential to improve patient outcomes in patients with AF.

References

Understanding atrial fibrillation and new therapeutic advances to improve its management

Learning objectives

After studying these articles, the reader should be able to

1. Explain the rationale for use of a 12-lead ECG, components of the ECG complex, and interpretation of ECG rhythm strips, and identify major cardiac arrhythmias based on ECG readings and clinical presentation.

2. Describe the prevalence, pathophysiology, and consequences of atrial fibrillation (AF); list the risk factors for the rhythm disorder; and estimate the risk for AF and ischemic stroke based on patient-specific risk factors.

3. Identify the primary goals of pharmacotherapy in patients with AF; describe the antithrombotic, rate-control, and rhythm-control medications used in these patients; explain the rationale for choosing between a rate-control and rhythm-control strategy; and recommend antiarhythmic drug therapy for a patient with AF based on safety, efficacy, and patient-specific considerations.

4. Compare and contrast the pharmacology, efficacy, and safety of new, emerging, and established antiarhythmic and anticoagulant medications and describe nonpharmacologic interventions for the treatment of AF.

Self-assessment questions

For each question there is only one best answer.

1. The 12 leads in a 12-lead electrocardiogram (ECG) are used to
   a. Accommodate changes in patient body position.
   b. Generate multiple readings that are averaged.
   c. Provide redundancies in case the electrodes fall off.
   d. Detect abnormalities in different parts of the heart.

2. Which of the following intervals on the ECG reflects a period of ventricular refractoriness?
   a. The R–R interval.
   b. The PQ interval.
   c. The PR interval.
   d. The QT interval.

3. Finding an R wave that coincides with a bold line on an ECG rhythm strip and counting off 300-150-100-75-60-50 for each bold line that falls after this line until the next R wave appears is known as
   a. The 6-second method for determining the approximate heart rate.
   b. The 300-second method for determining the approximate heart rate.
   c. The rule of 6 for determining the approximate heart rate.
   d. The rule of 300 for determining the approximate heart rate.

4. Which of the following major cardiac arrhythmias is characterized by the absence of discernable P waves and irregularly irregular R–R intervals on the ECG?
   a. Atrial fibrillation (AF).
   b. Atrial flutter.
   c. Ventricular tachycardia (VT).
   d. Ventricular fibrillation.

5. Torsades de pointes is an example of which of the following major cardiac arrhythmias?
   a. AF.
   b. Atrial flutter.
   c. VT.
   d. Ventricular fibrillation.

6. Which of the following statements about trends in the prevalence of AF in the United States is correct?
   a. It is decreasing because of improvements in treatment.
   b. It is decreasing because of the aging of the baby boom generation.
   c. It is increasing because of the aging of the baby boom generation.
   d. It is increasing because of improvements in detection.

7. Which of the following statements about the comparative approximate lifetime risks for AF, breast cancer, and congestive heart failure (CHF) in American women 40 years of age is correct?
   a. The risk for AF is higher than the risk for breast cancer or CHF.
   b. The risk for breast cancer is higher than the risk for AF or CHF.
   c. The risk for CHF is higher than the risk for breast cancer or AF.
   d. The risk for AF, CHF, and breast cancer is roughly the same.
8. Which of the following is a proposed mechanism for the increased risk for AF in patients with structural heart disease?
   a. Atrial distension and electrical instability.
   b. Coronary occlusion and hypoxia.
   c. Excessive sympathetic stimulation.
   d. Systemic inflammation.

9. Which of the following is associated with a predisposition to AF that is thought to be caused by increased left atrial size and atrial dilation?
   a. Acute alcohol intoxication.
   b. Obesity.
   c. Obstructive sleep apnea.
   d. Hyperthyroidism.

10. Which of the following is a common consequence of the loss of the atrial kick in patients with heart failure who develop AF?
    a. Decreased cardiac output and worsening of heart failure symptoms.
    b. Decreased cardiac output and sudden death.
    c. Increased cardiac output and worsening of heart failure symptoms.
    d. Increased cardiac output and improvement in heart failure symptoms.

11. Which of the following is the estimated 10-year risk for AF in a 53-year-old man with a body mass index of 35 kg/m² who takes hydrochlorothiazide to maintain a systolic/diastolic blood pressure of 135/88 mm Hg and has a PR interval of 150 msec without heart failure or a heart murmur?
    a. 3%.
    b. 4%.
    c. 6%.
    d. 8%.

12. The risk for stroke in a 63-year-old woman with AF and a recent history of congestive heart failure but no history of diabetes, hypertension, stroke, or transient ischemic attacks is
    a. High.
    b. Intermediate.
    c. Low.
    d. Negligible.

13. Which of the following is the largest component of the cost of AF in the United States?
    a. Emergency department visits.
    b. Hospitalization.
    c. Physician office visits.
    d. Medications.

14. Which of the following is recommended in guidelines of the American College of Chest Physicians for patients with AF who are at a high risk for stroke?
    a. Aspirin but not warfarin.
    b. Warfarin but not aspirin.
    c. Aspirin or warfarin.
    d. Neither aspirin nor warfarin.

15. Which of the following is the optimal goal international normalized ratio during warfarin therapy in patients with AF?
    a. 1.0–2.0.
    b. 1.8–2.5.
    c. 2.0–3.0.
    d. 2.5–3.5.

16. Which of the following statements about the role of combination antiplatelet therapy with aspirin plus clopidogrel for stroke prevention in patients with AF who are at intermediate or high risk is correct?
    a. It is preferred over warfarin because it is safer and more effective than warfarin.
    b. It is less safe and effective than warfarin, but it might be used by patients who are unwilling or unable to take warfarin.
    c. It is less effective but safer than warfarin, and it might be used by patients who are unwilling or unable to take warfarin.
    d. It is more effective but less safe than warfarin, and it might be used by patients who are not at risk for bleeding or falling.

17. Which of the following is the goal of rate-control therapy in patients with AF?
    a. Elimination of AF symptoms by causing cardioversion to sinus rhythm.
    b. Prevention of symptom recurrence by maintaining sinus rhythm after cardioversion.
    c. Elimination of AF and associated symptoms by reducing the heart rate to the appropriate target.
    d. Control of symptoms by reducing the heart rate to the appropriate target while allowing AF to persist.

18. Which of the following rate-control agents is considered first-line therapy for patients with AF and heart failure?
    a. Amiodarone.
    b. Beta-blockers.
    c. Digoxin.
    d. Diltiazem or verapamil.

19. Which of the following is the greatest limitation in the use of amiodarone in patients with AF?
    a. The high risk for proarrhythmias.
    b. The low efficacy in preventing AF recurrence.
    c. The increased risk for hospitalization.
    d. The high likelihood of toxicity.

20. Which of the following is the primary toxicity from sotalol?
    a. Anticholinergic adverse effects.
    b. Extracardiac effects.
    c. Gastrointestinal adverse effects.
    d. Torsades de pointes and other proarrhythmias.
21. Which of the following antiarrhythmic agents are contraindicated in patients with severe renal impairment?
   a. Amiodarone and propafenone.
   b. Disopyramide and quinidine.
   c. Dofetilide and sotalol.
   d. Dronedarone and flecainide.

22. Which of the following antiarrhythmic agents is associated with a relatively low risk for proarrhythmias and usually does not require initiation in the inpatient setting?
   a. Amiodarone.
   b. Dofetilide.
   c. Propafenone.
   d. Sotalol.

23. Which of the following antiarrhythmic agents currently are considered first-line therapy for patients with AF and heart failure?
   a. Amiodarone and dofetilide.
   b. Amiodarone and dronedarone.
   c. Dofetilide and dronedarone.
   d. Dofetilide and sotalol.

24. Amiodarone and dronedarone differ in their
   a. Electrophysiologic profile.
   b. Interaction with CYP3A4 inhibitors.
   c. Propensity to cause proarrhythmia.
   d. Propensity to cause thyroid dysfunction.

25. Which of the following laboratory abnormalities was associated with dronedarone in clinical trials?
   a. Hyperkalemia.
   b. Hypermagnesemia.
   c. Serum creatinine elevations.
   d. Thrombocytopenia.

26. Which of the following is the likely place in therapy of vernakalant?
   a. Maintenance of sinus rhythm in chronic AF.
   b. Maintenance of sinus rhythm in recent-onset AF.
   c. Conversion to sinus rhythm of recent-onset AF.
   d. Conversion to sinus rhythm of chronic AF.

27. Which of the following shortcomings of warfarin is eliminated by rivaroxaban and dabigatran?
   a. The lack of a parenteral dosage form.
   b. The need for laboratory monitoring.
   c. The potential for drug interactions.
   d. The risk for bleeding.

28. Which of the following types of patients with AF will most likely be candidates for treatment with rivaroxaban or dabigatran?
   a. Patients who fail to respond to pharmacologic interventions for rate control.
   b. Patients who fail to respond to nonpharmacologic interventions for rate control.
   c. Patients who fail to respond to nonpharmacologic interventions for rhythm control.
   d. Patients at intermediate or high risk for stroke who are unable to comply with warfarin monitoring requirements.

29. Which of the following statements best characterizes the role of nonpharmacologic interventions for AF?
   a. Used only in emergent situations to prevent sudden death.
   b. Used primarily for rhythm control in patients who are properly anticoagulated.
   c. Used primarily for rate control in patients who are properly anticoagulated.
   d. Used primarily for patients whose AF cannot be managed with pharmacotherapy because of a lack of efficacy or intolerable adverse effects.
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ACPE #: 204-000-10-428-H01P
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