Chapter 40: Arrhythmias

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UPDATE SUMMARY

Update Summary

September, 2023

The following table was updated:

- Table 40-7
  - Dose adjustments for sotalol were corrected for patients with atrial fibrillation/flutter with chronic kidney disease.
  - Recommendations also added for hepatic dysfunction.

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 6, Arrhythmias.

KEY CONCEPTS

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1. The use of antiarrhythmic drugs (AADs) in the United States has declined because clinical trials have shown increased mortality with their use due to proarrhythmic adverse medication reactions and limited efficacy. AADs have been increasingly replaced by nonpharmacologic approaches such as ablation and the implantable cardioverter defibrillator (ICD). However, AADs remain a key tool in the management of many rhythm disorders.

2. AADs frequently cause adverse medication reactions and are complex in their pharmacokinetic characteristics. Close monitoring is required of all of these medications to assess for adverse reactions as well as potential medication interactions.

3. The most commonly prescribed AAD is amiodarone, which is effective in terminating and preventing a wide variety of symptomatic supraventricular and ventricular arrhythmias. However, amiodarone is plagued by frequent adverse medication reactions and requires close monitoring. The most concerning toxicity is pulmonary fibrosis. The side effect profiles of the intravenous (IV) (acute, short-term) and oral (chronic, long-term) forms of amiodarone differ substantially.

4. In patients with atrial fibrillation (AF), therapy is traditionally aimed at controlling the ventricular rate, preventing thromboembolic (TE) complications, and restoring and maintaining sinus rhythm (SR). Traditionally, many have pointed to the AFFIRM trial that maintenance of SR was often not necessary. However, several recent studies challenge this idea, particularly for patients with heart failure with reduced ejection fraction (HFrEF). AADs are also useful in reducing early AF recurrence in the periprocedural period and may improve long-term post-ablation outcomes.

5. Paroxysmal supraventricular tachycardia (PSVT) is usually a result of either reentry (involving either the atrioventricular [AV] node or incorporating an accessory pathway) or ectopic atrial activity (atrial tachycardia). Common supraventricular tachycardias are often terminated acutely with AV nodal-blocking medications, such as adenosine. For most patients, catheter ablation effectively cures this arrhythmia.

6. Patients with Wolff-Parkinson-White (WPW) syndrome may have several different tachycardias that are acutely treated by different strategies: orthodromic reentry (adenosine), antidromic reentry (adenosine or procainamide), and AF (procainamide or ibutilide). AV nodal-blocking medications are contraindicated in patients with WPW syndrome and AF. The mainstay of long-term therapy for WPW remains catheter ablation.

7. AADs (except for β-blockers) should not be used routinely in patients with prior myocardial infarction (MI) or left ventricular (LV) dysfunction for the treatment of premature ventricular complexes (PVCs). More specifically, the routine suppression of asymptomatic PVCs with AADs is not recommended.

8. Patients with hemodynamically significant ventricular tachycardia (VT) or ventricular fibrillation (VF) not associated with an acute MI who are successfully resuscitated (with electrical cardioversion, epinephrine, amiodarone, and/or lidocaine) are at high risk for sudden cardiac death (SCD). In most cases, implantation of an ICD is recommended for “secondary prevention.” AADs can be useful to prevent recurrent ICD shocks, particularly when catheter ablation is not an option or has been unsuccessful.

9. Implantation of an ICD should be considered for the primary prevention of SCD in certain high-risk patient populations. High-risk patients include those with a history of MI and LV dysfunction (regardless of whether they have inducible sustained ventricular arrhythmias) as well as those with New York Heart Association (NYHA) class II or III HFrEF.

10. Life-threatening medication-induced ventricular proarrhythmia generally takes two forms: sinusoidal or incessant monomorphic VT (caused by class Ic AADs) and torsades de pointes (TdP) (caused by class Ia or III AADs and many other noncardiac medications).

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video entitled "Normal Sinus Rhythm on an EKG" in Khan Academy (duration: 8:52) by Bianca Yoo. This video provides a brief overview of the cardiac conduction system and how it translates to an electrocardiogram. The video is useful to enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

The heart has two basic properties, namely, an electrical property and a mechanical property. The synchronous interaction between these two properties is complex, precise, and relatively enduring. The study of the electrical properties of the heart has grown at a steady rate, interrupted by periodic salvos of scientific breakthroughs. Einthoven's pioneering work allowed graphic electrical tracings of cardiac rhythm and probably represents the first of these breakthroughs. This discovery of the surface electrocardiogram (ECG) has remained the cornerstone of diagnostic tools for cardiac rhythm disturbances. Since then, intracardiac recordings and programmed cardiac stimulation have advanced our understanding of arrhythmias, and microelectrode, voltage clamping, and patch clamping techniques have allowed considerable insight into the electrophysiologic actions and mechanisms of antiarrhythmic drugs (AADs). The new era of molecular biology and mapping of the human genome promises even greater insights into mechanisms (and potential therapies) of arrhythmias. Noteworthy in this regard is the discovery of genetic abnormalities in the ion channels that control electrical repolarization (heritable long QT syndrome) or depolarization (Brugada syndrome).

1 There was some expectation that advances in AAD discovery would lead to a highly effective and nontoxic agent that would be effective for a majority of patients. Instead, significant problems with medication toxicity and proarrhythmia (provoking a new arrhythmia or exacerbating a preexisting arrhythmia) have resulted in a decline in AAD usage in the United States since 1989. The other phenomenon that has significantly contributed to the decline in AAD use is the development of extremely effective nonpharmacologic therapies. Technical advances have made it possible to permanently interrupt reentry circuits with radiofrequency ablation, which renders long-term AAD use unnecessary in certain arrhythmias. Furthermore, the impressive survival data associated with the use of implantable cardioverter defibrillators (ICDs) for the primary and secondary prevention of SCD have led most clinicians to choose "device" therapy as the first-line treatment for patients who are at high risk for life-threatening ventricular arrhythmias. These nonpharmacologic therapies have become increasingly popular for the management of arrhythmias, avoiding the potential proarrhythmic effects and organ toxicities associated with AADs.

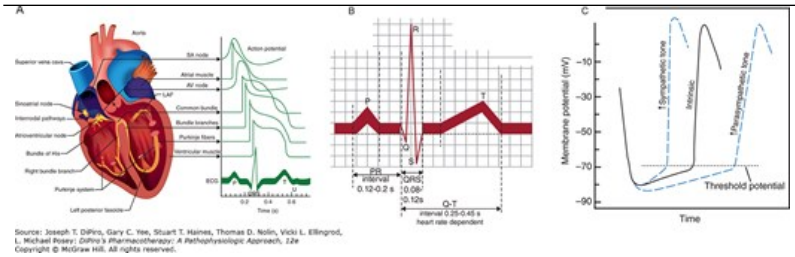
PATHOPHYSIOLOGY

Normal Conduction

Electrical activity is initiated by the sinoatrial (SA) node and moves through cardiac tissue through a specialized conduction system that rapidly propagates the electrical wavefront through the ventricular muscle (Fig. 40-1, panel A). The SA node initiates cardiac rhythm under normal circumstances because this tissue possesses the highest degree of automaticity or rate of spontaneous impulse generation at a rate of 60 to 100 beats/min. The degree of automaticity of the SA node is largely influenced by the autonomic nervous system in that both cholinergic and sympathetic innervations control the sinus rate (Fig. 40-1, panel C). Most tissues within the conduction system also possess varying degrees of inherent automatic properties. However, the rates of spontaneous impulse generation of these tissues are generally less than that of the SA node. Thus, these latent automatic pacemakers are continuously overdriven by impulses arising from the SA node (primary pacemaker) and do not become clinically apparent.

FIGURE 40-1

Cardiac action potentials and electrocardiogram tracing. LAF, left anterior fascicle; SA, sinoatrial; AV, atrioventricular. (*A*) Characterizes the action potentials from different areas of the heart and how those action potentials are illustrated on an ECG. (*B*) Describes the different intervals of an ECG. Normal interval ranges for PR, QRS, and QT are provided. (*C*) Describes the influence the autonomic system has on cardiac pacemaker potentials.



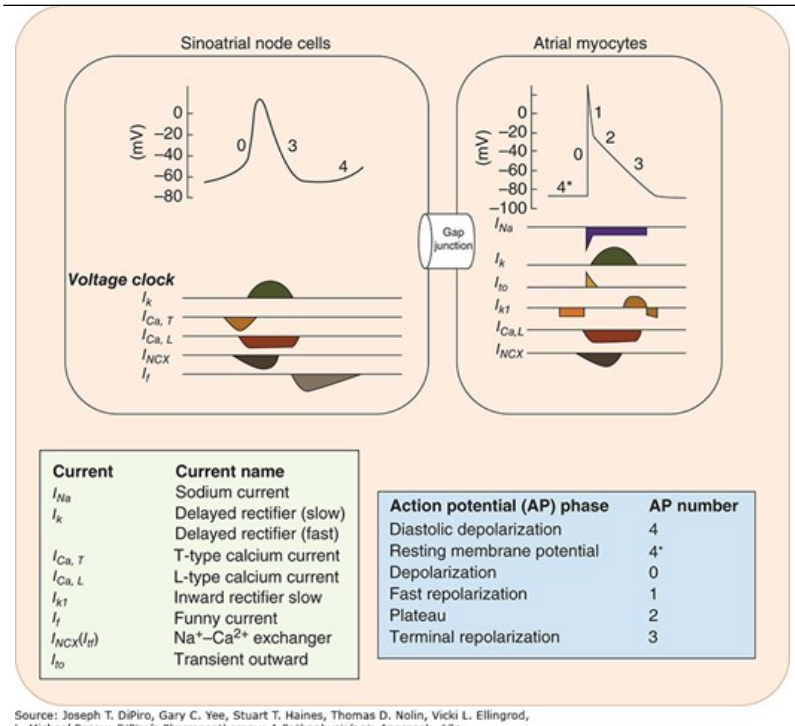
From the SA node, electrical activity moves in a wave front through a specialized atrial conducting system and eventually gains entrance to the ventricle via the AV node and a large bundle of conducting tissue referred to as the bundle of His. The AVN and bundle of His are largely influenced by autonomic input and possess a relatively high degree of inherent automaticity at about 40 beats/min. From the bundle of His, the cardiac conduction system bifurcates into several (usually three) bundle branches: one right bundle and two left bundles. These bundle branches further arborize into a conduction network referred to as the Purkinje system. The conduction system innervates the mechanical myocardium and serves to initiate excitation–contraction coupling and the contractile process in a precise and organized fashion. Following electrical stimulation, cells within the heart enter a brief period during which they cannot again be excited, referred to as the refractory period. As the electrical wave front moves down the conduction system, the impulse eventually encounters tissue refractory to stimulation (recently excited) and subsequently dies out. The SA node subsequently recovers, fires spontaneously, and begins the process again.

Prior to cellular excitation, an electrical gradient, referred to as the resting membrane potential (RMP), results from differences in ion concentrations inside and outside of the cell. At RMP, the cell is polarized primarily by the action of active membrane ion pumps, the most notable of these being the sodium–potassium pump. For example, this specific pump (in addition to other systems) attempts to maintain the intracellular sodium concentration at 5 to 15 mEq/L (mmol/L), the extracellular sodium concentration at 135 to 142 mEq/L (mmol/L), the intracellular potassium concentration at 135 to 140 mEq/L (mmol/L), and the extracellular potassium concentration at 3 to 5 mEq/L (mmol/L).

Electrical stimulation (or depolarization) of the cell will result in changes in membrane potential over time or a characteristic action potential (AP) curve (Fig. 40-2). The AP curve results from the transmembrane movement of specific ions and is divided into different phases. Phase 0 or initial, rapid depolarization of atrial and ventricular tissues is caused by an abrupt increase in the permeability of the membrane to sodium influx. This rapid depolarization more than equilibrates (overshoots) the electrical potential, resulting in a brief initial repolarization or phase 1. Phase 1 (initial repolarization) is caused by a transient and active potassium efflux (ie, the I_{Kto} current). Calcium begins to move into the intracellular space during phase 0, causing a slower depolarization. Calcium influx continues throughout phase 2 of the AP (plateau phase) and is balanced to some degree by potassium efflux. Calcium entrance (only through L channels in myocardial tissue) distinguishes cardiac conducting cells from nerve tissue and provides the critical ionic link to excitation–contraction coupling and the mechanical properties of the heart as a pump. The membrane remains permeable to potassium efflux during phase 3, resulting in cellular repolarization. Phase 4 of the action potential is the gradual depolarization of the cell and is related to a constant sodium leak into the intracellular space balanced by a decreasing (over time) efflux of potassium. As the cell is slowly depolarized during phase 4, an abrupt increase in sodium permeability occurs, allowing the rapid cellular depolarization of phase 0. The juncture of phase 4 and phase 0, where initiation of rapid sodium influx occurs, is referred to as the threshold potential of the cell.

FIGURE 40-2

Cardiac action potentials and responsible ion currents. While there are similarities between cardiac nodal and muscle action potentials there are many differences in how the phases are influenced by particular ion currents.



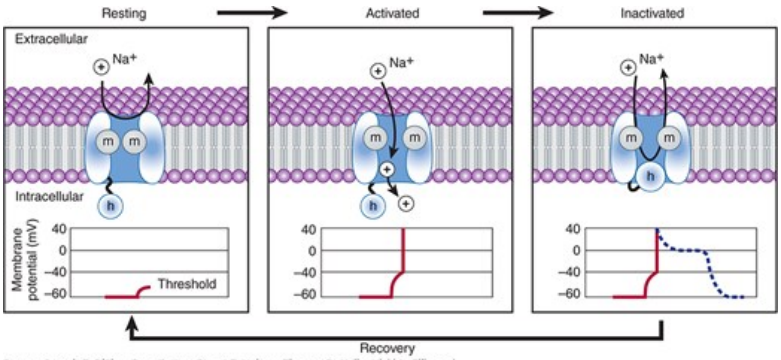
Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Not all cells in the cardiac conduction system rely on sodium influx for initial depolarization. Some tissues depolarize (phase 0) in response to a slower inward ionic current caused by calcium influx (L channels). These "calcium-dependent" tissues are found primarily in the SA and AV nodes (both L and T channels) and possess distinct conduction properties in comparison to "sodium-dependent" fibers (Fig. 40-2). Calcium-dependent cells generally have a slower conduction velocity and a less negative RMP. The RMP in nodal tissue is referred to as the slow depolarization phase or the pacemaker potential. This phase is initiated by the activation of funny current made up of sodium and potassium ions. It is referred to as the "funny" current because unlike most voltage-sensitive currents, it is activated by hyperpolarization. This phase is highly influenced by the autonomic system as seen in Fig. 40-1, panel C. Furthermore, in calcium-dependent tissues, recovery of excitability outlasts full repolarization, whereas in sodium-dependent tissues, recovery is prompt after repolarization. These two types of electrical tissues also differ dramatically in how medications modify their conduction properties.

Ion conductance across the lipid bilayer of the cell membrane occurs via the formation of membrane pores or "channels" (Fig. 40-3). Selective ion channels probably form in response to specific electrical potential differences between the inside and the outside of the cell (voltage dependence). Changes in equilibrium occur and permit the formation of activated ion channels. Besides channel formation and membrane composition, intrachannel proteins or phospholipids, referred to as gates, also regulate the transmembrane movement of ions. These gates are thought to be positioned strategically within the channel to modulate ion flow. Each ion channel conceptually has two types of gates: an activation gate and an inactivation gate (see Fig. 40-3). The activation gate opens during depolarization to allow the ion current to enter or exit from the cell, and the inactivation gate later closes to stop ion movement. When the cell is in a rested state, the activation gates are closed and the inactivation gates are open. The activation gates then open to allow ion movement through the channel, and the inactivation gates later close to stop ion conductance. Thus, the cell cycles between three states: resting, activated, and inactivated. Activation of SA and AV nodal tissue is dependent on a slow depolarizing current through calcium channels and gates, whereas the activation of atrial and ventricular tissues is dependent on a rapid depolarizing current through sodium channels and gates.

FIGURE 40-3

States of sodium (Na^+) channels cycling through the cardiac action potential. Transitions between resting, activated, and inactivated states are dependent on membrane potential and time. The activation gate is shown as m and the inactivation gate as h. Potentials typical for each state are shown under each channel schematic as a function of time. The dashed line indicates that part of the action potential during which most Na^+ channels are completely or partially inactivated and unavailable for reactivation. (*Reproduced, with permission, from Katzung BG, ed. Basic & Clinical Pharmacology. 15th ed. New York: McGraw Hill; 2021.*)



The impulse that is generated by the SA node disseminates to adjacent cells through gap junctions. The gap junctions provide a pathway for ions to travel to neighboring cells for AP propagation. The compilation of all the cardiac APs is presented on an ECG (Fig. 40-1, panel A). During a normal cardiac conduction cycle the ECG will have a P wave (atrial depolarization), QRS (ventricular depolarization and atrial repolarization), and T wave (ventricular repolarization). It is also important to note the PR interval, or the time from atrial depolarization to ventricular depolarization, and the QT interval, the duration of the ventricular AP (Fig. 40-1, panel B). Augmentation of the ECG is a product of alterations in the cardiac APs.

Abnormal Conduction

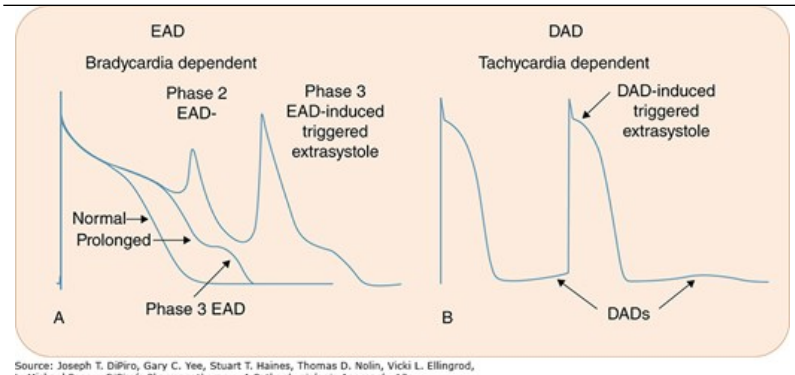
The mechanisms of tachyarrhythmias have been classically divided into two general categories: those resulting from an abnormality in impulse generation ("automatic" tachycardia and triggered automaticity) and those resulting from an abnormality in impulse conduction ("reentrant" tachycardias).[1]

Automatic tachycardias depend on spontaneous impulse generation in latent pacemakers and may be a result of several different mechanisms. Medications, such as digoxin or catecholamines, and conditions, such as hypoxia, electrolyte abnormalities (eg, hypokalemia), and fiber stretch (cardiac dilation), may lead to an increased slope of phase 4 depolarization in cardiac tissues other than the SA node.[1] These factors are associated with abnormal automaticity in experimental models and arrhythmogenesis in clinical situations. The increased slope of phase 4 causes heightened automaticity of these tissues and competition with the SA node for dominance of cardiac rhythm. If the rate of spontaneous impulse generation of the abnormally automatic tissue exceeds that of the SA node, then an automatic tachycardia may result. Automatic tachycardias have the following characteristics: (a) the onset of the tachycardia is unrelated to an initiating event such as a premature beat; (b) the initiating beat is usually identical to subsequent beats of the tachycardia; (c) the tachycardia cannot be initiated by programmed cardiac stimulation; and (d) the onset of the tachycardia is usually preceded by a gradual acceleration in rate and termination is usually preceded by a gradual deceleration in rate. Clinical tachycardias resulting from the classic forms of enhanced automaticity are not as common as once thought. Examples are sinus tachycardia and junctional tachycardia.

Triggered automaticity is also a possible mechanism for abnormal impulse generation. Briefly, triggered automaticity refers to transient membrane depolarizations that occur during repolarization (early afterdepolarizations [EADs]) or after repolarization (delayed afterdepolarizations [DADs]) but prior to phase 4 of the AP (Fig. 40-4).[1] Afterdepolarizations may be related to abnormal calcium and sodium influx during or just after full cellular repolarization. Experimentally, EADs may be precipitated by hypokalemia, class Ia AADs, or slow stimulation rates—any factor that blocks the ion channels (eg, potassium) responsible for cellular repolarization. EADs provoked by medications that block potassium conductance and delay repolarization are the underlying cause of TdP. DADs may be precipitated by digoxin or catecholamines and suppressed by non-dihydropyridine (non-DHP) calcium channel blockers (CCBs). DADs have been suggested as the mechanism for multifocal atrial tachycardia, digoxin-induced tachycardias, and exercise-provoked VT. Triggered automatic rhythms possess some of the characteristics of automatic tachycardias and some of the characteristics of reentrant tachycardias (description follows).

FIGURE 40-4

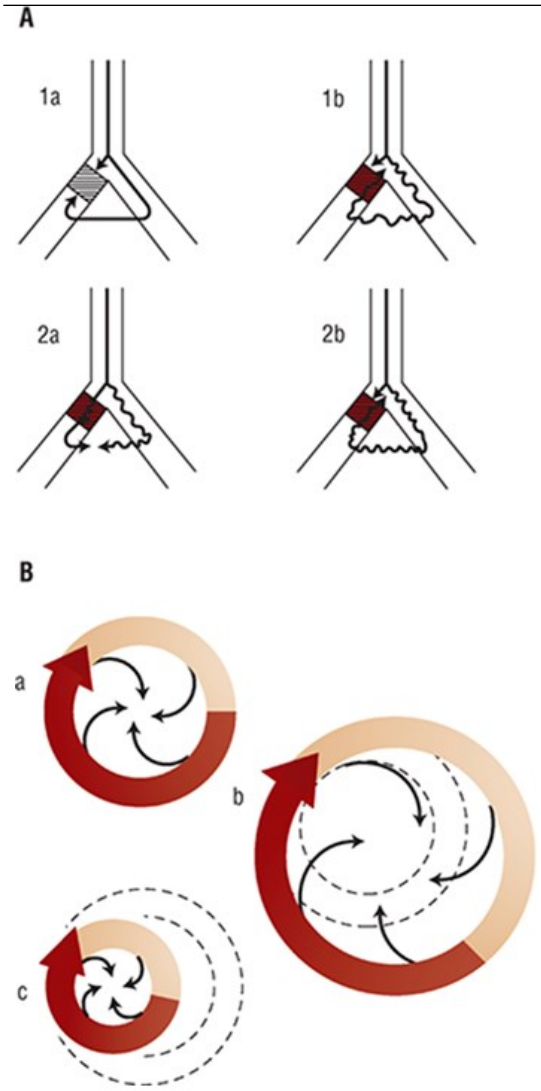
Afterdepolarizations. (EAD early afterdepolarization; DAD delayed afterdepolarization.)



Reentry is a concept that involves indefinite propagation of the impulse and continued activation of previously refractory tissue. There are three conduction requirements for the formation of a viable reentrant focus: (1) two pathways for impulse conduction, (2) an area of unidirectional block (prolonged refractoriness) in one of these pathways, and (3) slow conduction in the other pathway (Fig. 40-5, panel A).[1] Usually, a critically timed premature beat initiates reentry. This premature impulse enters both conduction pathways but encounters refractory tissue in one of the pathways at the area of unidirectional block. The impulse dies out because the tissue is still refractory from the previous (sinus) impulse. Although it fails to propagate in one pathway, the impulse may still proceed in a forward direction (antegrade) through the other pathway because of this pathway's relatively shorter refractory period. The impulse may then proceed through a loop of tissue and "reenter" the area of unidirectional block in a backward direction (retrograde). Because the antegrade pathway has slow conduction characteristics, the area of unidirectional block has time to recover its excitability. The impulse can proceed in a retrograde fashion through this previously refractory tissue and continue around the loop of tissue in a circular fashion. Thus, the key to the formation of a reentrant focus is crucial conduction discrepancies in the electrophysiologic characteristics of the two pathways. The reentrant focus may excite surrounding tissue at a rate greater than that of the SA node, leading to the formation of a clinical tachycardia. The above model is anatomically determined in that there is only one pathway for impulse conduction with a fixed circuit length.

FIGURE 40-5

(*A*) Possible mechanism of proarrhythmia in the anatomic model of reentry. (1a) Nonviable reentrant loop due to bidirectional block (*shaded area*). (1b) Instance where a medication slows conduction velocity without significantly prolonging the refractory period. The impulse is now able to reenter the area of unidirectional block (*shaded area*) because slowed conduction through the antegrade pathway allows recovery of the block. A new reentrant tachycardia may result. (2a) Nonviable reentrant loop due to a lack of a unidirectional block. (2b) Instance where a medication prolongs the refractory period without significantly slowing conduction velocity. The impulse moving antegrade meets refractory tissue (*shaded area*), allowing for unidirectional block. A new reentrant tachycardia may result. (*B*) Mechanism of functional reentry and proarrhythmia. (a) Functionally determined reentrant circuit. This model should be contrasted with anatomic reentry; here, the circuit is not fixed (it does not necessarily move around an anatomic obstacle), and there is no excitable gap. All tissue inside is held continuously refractory. (b) An instance where a medication prolongs the refractory period without significantly slowing conduction velocity. The tachycardia may terminate or slow in rate as shown as a consequence of a greater circuit length. The *dashed lines* represent the original reentrant circuit prior to medication treatment. (c) An instance where a medication slows conduction velocity without significantly prolonging the refractory period (ie, class Ic *antiarrhythmic medications*) and accelerates the tachycardia. The tachycardia rate may increase (proarrhythmia) as shown as a consequence of a shorter circuit length. The dashed lines represent the original reentrant circuit prior to medication treatment. (*Reprinted, with permission, from McCollam PL, Parker RB, Beckman KJ, et al. Proarrhythmia: A paradoxic response to antiarrhythmic agents. Pharmacotherapy 1989;9:146.*)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Another model of reentry, referred to as a functional reentrant loop, may also occur (Fig. 40-5, panel B).[1] In a functional reentrant focus, the length of the circuit may vary depending on the conduction velocity and recovery characteristics of the impulse. The area in the middle of the loop is continually kept refractory by the inwardly moving impulse. The length of the circuit is not fixed but is the smallest circle possible, such that the leading edge of the wave front is continuously exciting tissue just as it recovers. It differs from the anatomic model in that the leading edge of the impulse is not preceded by an excitable gap of tissue, and it does not have an obstacle in the middle or a fixed anatomic circuit.

Clinically, many reentrant foci probably have both anatomic and functional characteristics. All of these theoretical models require a critical balance of refractoriness and conduction velocity within the circuit and, as such, have helped to explain the effects of medications on terminating, modifying, and causing cardiac rhythm disturbances (eg, proarrhythmia).

What causes reentry to become clinically manifest? Reentrant foci may occur at any level of the conduction system: within the branches of the specialized atrial conduction system, within the Purkinje network, and even within portions of the SA and AV nodes. The anatomy of the Purkinje system appears to provide a suitable substrate for the formation of microreentrant loops and is often used as a model to facilitate the understanding of reentry concepts. Of course, because reentry does not usually occur in normal, healthy conduction tissue, various forms of heart disease or conduction abnormalities are typically present before reentry becomes manifest. An often-used example is reentry occurring as a consequence of ischemic or hypoxic damage. With inadequate cellular oxygenation, high-energy phosphate concentrations diminish, the activity of the transmembrane ion pumps declines, and RMP rises. This rise in RMP causes inactivation in the voltage-dependent sodium channel, and the tissue

begins to assume slow conduction characteristics. If changes in the tissue's conduction parameters occur in a discordant manner due to varying degrees of ischemia or hypoxia, then a reentry circuit may become manifest. Furthermore, an ischemic, dying cell releases intracellular potassium, which also causes a rise in RMP. In other cases, reentry may occur because of anatomic or functional variants in the normal conduction system. For instance, patients may possess two (instead of one) conduction pathways near or within the AV node or have an anomalous extranodal AV pathway that possesses different electrophysiologic characteristics from the normal AV nodal pathway. Reentry in these cases may occur within the AV node or encompass both atrial and ventricular tissues. Reentrant tachycardias have the following characteristics: (a) the onset of the tachycardia is usually related to an initiating event (ie, premature beat); (b) the initiating beat is usually different in morphology from subsequent beats of the tachycardia; (c) the initiation of the tachycardia can usually be incited with programmed cardiac stimulation; and (d) the initiation and termination of the tachycardia is usually abrupt without an acceleration or deceleration phase. There are many examples of reentrant tachycardias, including AF, atrial flutter (AFl), AV nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT), and recurrent VT (Table 40-1).

TABLE 40-1

Characteristics and Presumed Mechanisms of Arrhythmias

Tachycardia	Mechanism	Origin
Sinus tachycardia	Automatic (normal)	Sinus node
Atrial fibrillation	Reentry, automatic, triggered activity	Atria, thoracic veins, pulmonary veins, and superior vena cava
Atrial flutter	Reentry	Right (most common) and left atria
Atrial tachycardia	Reentry, automatic, triggered activity	Atria
AV nodal reentry tachycardia	Reentry	AV junction
AV reentry tachycardia	Reentry	Circuit includes accessory AV connection, atria, AV node, His-Purkinje system, ventricles
Ventricular tachycardia	Reentry, automatic, triggered	Ventricles
Torsades de Pointes	Reentry, triggered activity	Ventricles

AV, atrioventricular.

PHARMACOLOGIC THERAPY

In a theoretical sense, medications have antiarrhythmic activity by directly altering electrical conduction in several ways. First, a medication may depress the automatic properties of abnormal pacemaker cells. If the rate of spontaneous impulse generation of the abnormally automatic foci becomes less than that of the SA node, normal cardiac rhythm can be restored. Second, medications may alter the conduction characteristics of a reentrant loop (Fig. 40-5).[1,2] A medication may facilitate conduction (shorten refractoriness) in the area of unidirectional block, allowing antegrade conduction to proceed. On the other hand, a medication may further depress conduction (prolong refractoriness) either in the area of unidirectional block or in the pathway with slowed conduction and a relatively shorter refractory period. If refractoriness is prolonged in the area of unidirectional block, retrograde propagation of the impulse is not permitted, causing a "bidirectional" block. In the anatomic model, if refractoriness is prolonged in the pathway with slow conduction, antegrade conduction of the impulse is not permitted. In either case, medications that reduce the discordance and

cause uniformity in conduction properties of the two pathways may suppress the reentrant substrate. In the functionally determined model, if refractoriness is prolonged without significantly slowing conduction velocity, the tachycardia may terminate or slow in rate because of a greater circuit length (see Fig. 40-5, panel B). There are other theoretical ways to stop reentry: (a) a medication may eliminate the critically timed premature impulse that triggers reentry; (b) a medication may slow conduction velocity to such an extent that conduction is extinguished; or (c) a medication may reverse the underlying form of heart disease that was responsible for the conduction abnormalities that led to the arrhythmia (ie, “reverse remodeling”).

AADs have specific electrophysiologic actions that alter cardiac conduction in patients with or without heart disease. These actions form the basis of grouping AADs into specific categories based on their electrophysiologic actions in vitro. Vaughan Williams proposed the most frequently used classification system (Table 40-2).[2] This classification has been criticized for the following reasons: (a) it is incomplete and does not allow for the classification of medications such as digoxin or adenosine; (b) it is not pure, and many agents have properties of more than one class of medications; (c) it does not incorporate medication characteristics such as mechanisms of tachycardia termination/prevention, clinical indications, or side effects; and (d) medications become “labeled” within a class, although they may be distinct in many regards. Despite these criticisms, the Vaughan Williams classification remains the most frequently used for categorizing the electrophysiologic actions of AADs.

TABLE 40-2

Classification of Antiarrhythmic Medications

Class	Medication	Conduction Velocity[a]	Refractory Period	Automaticity	Ion Block
Ia	Quinidine	↓	↑	↓	Sodium (intermediate) Potassium
	Procainamide				
	Disopyramide				
Ib	Lidocaine	0/↓	↓	↓	Sodium (fast on–off)
	Mexiletine				
Ic	Flecainide	↓↓	↑ (atrial)	↓	Sodium (slow on–off)
	Propafenone[b]				
II[c]	β-blockers	↓	↑	↓	Calcium (indirect)
III	Amiodarone[d]	0	↑↑	0	Potassium
	Dofetilide				
	Dronedarone[d]				
	Sotalol[b]				
	Ibutilide				
IV[c]	Verapamil	↓	↑	↓	Calcium
	Diltiazem				

[a]Variables for normal tissue models in ventricular tissue.

[b]Also has β-blocking actions.

[c]Variables for sinoatrial (SA) and atrioventricular (AV) nodal tissue only.

[d]Also has sodium, calcium, and β-blocking actions; see Table 40-3.

TABLE 40-3

Time Course and Electrophysiologic Effects of Amiodarone

				IV		Oral	
Class	**Mechanism**	**EP**	**ECG**	**Minutes–Hours**	**Hours–Days**	**Days–Weeks**	**Weeks–Months**
Class I	Na^+ block	↑HV	↑QRS	0	+	+	++
Class II	β-block	↑AH	↑PR	++	++	++	++
			↓HR				
Class III	K^+ block	↑VERP	↑QT	0	+	++	++++
		↑AERP					
Class IV	Ca^{2+} block[a]	↑AH	↑PR	+	+	+	+
			↓HR				

AERP, atrial effective refractory period; AH, atria–His interval; ECG, electrocardiographic effects; EP, electrophysiologic actions; HR, heart rate; HV, His–ventricle interval; IV, intravenous; VERP, ventricular effective refractory period.

[a]Rate-dependent (for amiodarone).

Class I AADs are grouped together because of their common action in blocking sodium conductance. The receptor site for these AADs is probably inside the sodium channel so that, in effect, the medication plugs the pore. The AAD may gain access to the receptor either via the intracellular space through the membrane lipid bilayer or directly through the channel (Fig. 40-3). Several principles are inherent in antiarrhythmic sodium channel receptor theories[3,4]:

1. Class I AADs have predominant affinity for a particular state of the channel (eg, during activation or inactivation). For example, lidocaine blocks sodium current primarily when the cell is in the inactivated state, whereas quinidine, flecainide, and propafenone are predominantly open (or activated) channel blockers.

2. Class I AADs have specific binding and unbinding characteristics to the receptor, which has led to the subclassification (Ia, Ib, Ic) of these AADs. For example, lidocaine binds to and dissociates from the channel receptor quickly (“fast on–off”) but flecainide has very “slow on–off” properties. This explains why flecainide has such potent effects on slowing ventricular conduction, whereas lidocaine has little effect on normal tissue (at normal heart rates). In general, the class Ic AADs are “slow on–off,” the class Ib AADs are “fast on–off,” and the class Ia AADs are intermediate in their binding kinetics.

3. Class I AADs possess use dependence (ie, sodium channel blockade and slowed conduction are greatest at fast heart rates and least during bradycardia). For “slow on–off” medications, sodium channel blockade is evident at normal rates (60 to 100 beats/min), but for “fast on–off” agents, slowed conduction is only apparent at fast heart rates.

4. Class I AADs are weak bases with a pKa > 7 and block the sodium channel in their ionized form. Consequently, pH will alter these actions: acidosis accentuates, and alkalosis diminishes sodium channel blockade.

5. Class I AADs appear to share a single receptor site in the sodium channel. It should be noted, however, that a number of class I AADs have other electrophysiologic properties. For instance, quinidine has potent potassium channel blocking activity (manifests predominantly at low

concentrations) as does N-acetylprocainamide (manifests predominantly at high concentrations), the primary metabolite of procainamide. Additionally, propafenone has β-blocking actions.

The class Ia AADs, quinidine, procainamide, and disopyramide, slow conduction velocity, prolong refractoriness, and decrease the automatic properties of sodium-dependent (normal and diseased) conduction tissue. Although class Ia AADs are primarily considered sodium channel blockers, their electrophysiologic actions can also be attributed to blockade of potassium channels. In reentrant tachycardias, these medications generally depress conduction and prolong refractoriness, theoretically transforming the area of unidirectional block into a bidirectional block. Clinically, class Ia medications are broad-spectrum AADs that are indicated for both supraventricular and ventricular arrhythmias. However, their use tends to be infrequent in clinical practice because of their limited efficacy and significant toxicities.

The class Ib AADs, lidocaine and mexiletine were historically categorized separately from quinidine-like medications. Early work demonstrated that lidocaine had distinctly different electrophysiologic actions. In normal tissue models, lidocaine generally facilitates actions on cardiac conduction by shortening refractoriness and having little effect on conduction velocity. Thus, it was postulated that these agents could improve antegrade conduction, eliminating the area of unidirectional block. Arrhythmias do not usually arise from normal tissue. However, lidocaine possesses class Ia quinidine-like properties in diseased tissues. Therefore, it is probable that lidocaine acts in a similar fashion to the class Ia AADs (ie, prolongs refractoriness) in diseased ischemic tissues leading to bidirectional block in a reentrant circuit. Lidocaine and similar agents have accentuated effects in ischemic tissue caused by the local acidosis and potassium shifts that occur during cellular hypoxia. Changes in pH alter the time that local anesthetics, like lidocaine, occupy the sodium channel receptor, affecting the agent's electrophysiologic actions. In addition, the intracellular acidosis that ensues due to ischemia could cause lidocaine to become "trapped" within the cell, allowing increased access to the receptor. The class Ib AADs are considerably more effective in ventricular arrhythmias than supraventricular arrhythmias. As a group, these medications are relatively weak sodium channel blockers (at normal stimulation rates).

The class Ic AADs, propafenone and flecainide, are extremely potent sodium channel blockers, profoundly slowing conduction velocity while leaving refractoriness relatively unaltered. The class Ic AADs theoretically eliminate reentry by slowing conduction to a point where the impulse is extinguished and cannot propagate further. Although the class Ic AADs are effective for both ventricular and supraventricular arrhythmias, their use for ventricular arrhythmias has been limited by the risk of proarrhythmia.

The β-blockers are classified as class II AADs. For the most part, the clinically relevant acute antiarrhythmic mechanisms of the β-blockers result from their antiadrenergic actions.[4] Because the SA and AV nodes are heavily influenced by adrenergic innervation, β-blockers would be most useful in tachycardias in which these nodal tissues are abnormally automatic or are a portion of a reentrant loop. These medications are also helpful in slowing ventricular response in atrial arrhythmias (eg, AF) by their effects on the AV node. Furthermore, some tachycardias are exercise-related or precipitated by states of high sympathetic tone (perhaps through triggered activity), and β-blockers may be useful in these instances. Beta-adrenergic stimulation results in increased conduction velocity, shortened refractoriness, and increased automaticity of the nodal tissues; β-blockers will antagonize these effects. In the nodal tissues, β-blockers interfere with calcium entry into the cell by altering catecholamine-dependent channel integrity and gating kinetics. In sodium-dependent atrial and ventricular tissues, β-blockers shorten repolarization somewhat but otherwise have little direct effect. The antiarrhythmic properties of β-blockers observed with long-term, chronic therapy in patients with heart disease are less well understood. Although it is clear β-blockers decrease the likelihood of SCD (presumably arrhythmic death) after MI, the mechanism for this benefit remains unclear; this benefit may relate to the complex interplay of changes in sympathetic tone, damaged myocardium, and ventricular conduction. In patients with HF, medications such as β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers may prevent arrhythmias such as AF by attenuating the structural and/or electrical remodeling process in the myocardium.[5]

The class III AADs include those agents that specifically prolong refractoriness in atrial and ventricular tissues. This class includes amiodarone, dronedarone, sotalol, ibutilide, and dofetilide. These medications share the common effect of delaying repolarization by blocking potassium channels. Amiodarone and sotalol are effective in most supraventricular and ventricular arrhythmias. Amiodarone displays electrophysiologic characteristics of all four Vaughan Williams classes; it is a sodium channel blocker with relatively "fast on–off" kinetics, has nonselective β-blocking actions, blocks potassium channels, and has a small degree of calcium channel blocking activity (Table 40-3). At normal heart rates and with chronic use, its predominant effect is to prolong repolarization. With IV administration, its onset is relatively quick (unlike the oral form) and beta blockade predominates initially. Theoretically, amiodarone, like class I AADs, may interrupt the reentrant substrate by transforming an area of unidirectional block into an area of bidirectional block. However, amiodarone may leave the reentrant loop intact. The impressive effectiveness of amiodarone coupled with its low proarrhythmic potential has challenged the notion that selective ion channel blockade by AADs is preferable. Sotalol is a potent

inhibitor of outward potassium movement during repolarization and possesses nonselective β-blocking actions. Unlike amiodarone and sotalol, dronedarone, ibutilide, and dofetilide are only approved for the treatment of supraventricular arrhythmias. Both ibutilide (only available IV) and dofetilide (only available orally) can be used for the acute conversion of AF or AFl to SR. Dofetilide can also be used to maintain SR in patients with AF or AFl of longer than 1 week's duration who have been converted to SR. Dronedarone is approved to reduce the risk of hospitalization in patients with a history of paroxysmal or persistent AF who are currently in SR. Although structurally related to amiodarone, dronedarone's structure has been modified through the addition of a methylsulfonyl group and the removal of iodine. Dronedarone is also similar to amiodarone in exhibiting electrophysiologic characteristics of all four Vaughan Williams classes (sodium channel blocker with relatively "fast on–off" kinetics, nonselective β-blocker, potassium channel blocker, and calcium channel antagonist). However, amiodarone is more effective than dronedarone.

There are several different potassium channels that function during normal conduction; all approved class III AADs inhibit the delayed rectifier current (I_K) responsible for phase 2 and phase 3 repolarization. Subcurrents make up I_K: an ultrarapid component (I_{Kur}), a rapid component (I_{Kr}), and the slow component (I_{Ks}). Sotalol, ibutilide, and dofetilide selectively block I_{Kr}, whereas amiodarone and dronedarone block both I_{Kr} and I_{Ks}. Potassium channel blockers (particularly those with selective I_{Kr} blocking properties) display "reverse use dependence" (ie, their effects on repolarization are greatest at low heart rates). Sotalol and medications like it also appear to be much more effective in preventing VF (in dog models) than the traditional sodium channel blockers. The safety concern of all class III AADs is an extension of their underlying ionic mechanism; that is, by blocking potassium channels and delaying repolarization, these medications may also cause proarrhythmia in the form of TdP by provoking EADs.

The non-DHP CCBs, verapamil and diltiazem, are categorized as class IV AADs. They block L-type calcium channels in SA and AV nodal tissues, slowing conduction, prolonging refractoriness, and decreasing automaticity (eg, due to EADs or DADs). Thus, these agents are effective in automatic or reentrant tachycardias which arise from or use the SA or AV nodes. In supraventricular arrhythmias (eg, AF or AFl), these medications can slow ventricular response by slowing AV nodal conduction. Furthermore, because calcium entry seems to be integral to exercise-related tachycardias and/or tachycardias caused by some forms of triggered automaticity, these agents may be effective in the treatment of these types of arrhythmias. The DHP CCBs (eg, nifedipine) do not have significant antiarrhythmic activity as they do not affect AV nodal conduction.

2 All AADs currently available have an impressive side effect profile (Table 40-4). A considerable percentage of patients cannot tolerate long-term therapy with these medications and will have to discontinue therapy because of adverse drug reactions. Flecainide, propafenone, quinidine, procainamide, disopyramide, sotalol, non-DHP CCBs, and dronedarone may worsen HF symptoms in patients with underlying LV systolic dysfunction. Consequently, these medications should be avoided in patients with HFrEF. The class Ib AAD, mexiletine, causes neurologic and/or gastrointestinal toxicity in a high percentage of patients. One of the most frightening adverse effects related to AADs is the aggravation of underlying ventricular arrhythmias or the precipitation of new, life-threatening ventricular arrhythmias.[4]

TABLE 40-4

Adverse Drug Reactions of Class I and III Antiarrhythmic Medications

Disopyramide	Anticholinergic symptoms (dry mouth, urinary retention, constipation, blurred vision), nausea, anorexia, HF, conduction disturbances, ventricular arrhythmias (eg, TdP)
Procainamide	Hypotension, worsening HF, conduction disturbances, ventricular arrhythmias (eg, TdP)
Quinidine	Cinchonism, diarrhea, abdominal cramps, nausea, vomiting, hypotension, worsening HF, conduction disturbances, ventricular arrhythmias (eg, TdP), fever
Lidocaine	Dizziness, sedation, slurred speech, blurred vision, paresthesia, muscle twitching, confusion, nausea, vomiting, seizures, psychosis, sinus arrest, conduction disturbances
Mexiletine	Dizziness, sedation, anxiety, confusion, paresthesia, tremor, ataxia, blurred vision, nausea, vomiting, anorexia, conduction disturbances, ventricular arrhythmias
Flecainide	Blurred vision, dizziness, dyspnea, headache, tremor, nausea, worsening HF, conduction disturbances, ventricular arrhythmias
Propafenone	Dizziness, fatigue, blurred vision, bronchospasm, headache, taste disturbances, nausea, vomiting, bradycardia or AV block, worsening HF, ventricular arrhythmias
Amiodarone	Tremor, ataxia, paresthesia, insomnia, corneal microdeposits, optic neuropathy/neuritis, nausea, vomiting, anorexia, constipation, TdP (<1%), bradycardia or AV block (IV and oral use), pulmonary fibrosis, liver function test abnormalities, hypothyroidism, hyperthyroidism, photosensitivity, blue-gray skin discoloration, hypotension (IV use), phlebitis (IV use)
Dofetilide	Headache, dizziness, TdP
Dronedarone	Nausea, vomiting, diarrhea, serum creatinine elevations, bradycardia, worsening HF, hepatotoxicity, pulmonary fibrosis, acute renal failure, TdP (<1%)
Ibutilide	Headache, TdP, bradycardia or AV block, hypotension
Sotalol	Dizziness, weakness, fatigue, nausea, vomiting, diarrhea, bradycardia or AV block, TdP, bronchospasm, worsening HF

AV, atrioventricular; HF, heart failure; IV, intravenous; TdP, torsades de pointes.

3 Amiodarone has assumed a prominent place in the treatment of both acute and chronic supraventricular and ventricular arrhythmias and is the most commonly prescribed AAD.[6] Once considered a medication of last resort, it is often the first AAD considered for the treatment of many arrhythmias. Yet amiodarone is a peculiar and complex medication, displaying unusual pharmacologic effects, pharmacokinetics, dosing regimens, and multiorgan adverse drug reactions. Amiodarone has an extremely long elimination half-life (approximately 60 days) and a large volume of distribution. Consequently, the onset of action with the oral form is delayed (days to weeks) despite the use of a loading regimen, and the duration of effect may persist for months after discontinuation. Amiodarone is a substrate of the cytochrome P450 (CYP) 3A4 isoenzyme, a moderate inhibitor of many CYP isoenzymes (eg, CYP2C9, CYP2D6, CYP3A4), and a P-glycoprotein (P-gp) inhibitor, which can result in numerous medication interactions.[7] By inhibiting P-gp, amiodarone can increase digoxin concentrations by approximately twofold; therefore, the digoxin dose should be empirically reduced by 50% when initiating amiodarone. By inhibiting CYP2C9 and CYP3A4, amiodarone can increase warfarin concentrations and the international normalized ratio (INR). Consequently, when amiodarone and warfarin are initiated concurrently, an empiric warfarin dose reduction is necessary. When amiodarone is initiated in a patient already receiving warfarin, close INR monitoring is needed and the dose of warfarin may need to be reduced by approximately 30%.[8]

Acute administration of amiodarone is usually well tolerated by patients; however, severe organ toxicities may result with chronic use. Severe bradycardia, hyperthyroidism, hypothyroidism, peripheral neuropathy, gastrointestinal discomfort, and photosensitivity are common. Fulminant hepatitis (uncommon) and pulmonary fibrosis (2% of patients) have caused death.[6] While amiodarone can cause benign corneal microdeposits in virtually every patient, it has also been associated with the development of optic neuropathy/neuritis which can lead to blindness. Even though amiodarone may markedly prolong the QT interval, proarrhythmia (ie, TdP) is rare. All of these adverse drug reactions mandate close, continued monitoring (liver enzymes, thyroid function tests, eye examinations, chest radiographs, pulmonary function tests), leading to a proliferation of "amiodarone clinics" designed for patients treated chronically with amiodarone (Table 40-5).[6]

TABLE 40-5

Amiodarone Monitoring

Adverse Drug Reaction	Monitoring Recommendations	Management of Adverse Drug Reactions
Pulmonary fibrosis	Chest radiograph (baseline, and then every 12 months)	Discontinue amiodarone immediately; may consider corticosteroid therapy
	Pulmonary function tests (baseline, and then if symptoms develop)	
	High-resolution CT (if symptoms develop)	
Hypothyroidism	TFTs (baseline, and then every 6 months)	Thyroid hormone supplementation (eg, levothyroxine)
Hyperthyroidism	TFTs (baseline, and then every 6 months)	Antithyroid medications (eg, methimazole, propylthiouracil) or corticosteroids; may need to discontinue amiodarone
Optic neuritis/neuropathy	Ophthalmologic examination (baseline [only if visual impairment present], and then if symptoms develop)	Discontinue amiodarone immediately
Corneal microdeposits	Slit-lamp examination (routine monitoring not necessary)	No treatment necessary
Hepatotoxicity	LFTs (baseline, and then every 6 months)	Lower the dose or discontinue amiodarone if LFTs >2× the upper limit of normal
Bradycardia/heart block	ECG (baseline, and then every 6 months or as clinically indicated)	Lower the dose, if possible, or discontinue amiodarone if severe (or continue amiodarone and implant permanent pacemaker)
Tremor, ataxia, peripheral neuropathy	History/physical examination (each office visit)	Lower the dose, if possible, or discontinue amiodarone if severe
Photosensitivity	History/physical examination (each office visit)	Lower the dose; advise patients to wear sunblock while outdoors

ECG, electrocardiogram; LFTs, liver function tests; TFTs, thyroid function tests.

Dronedarone has a considerably shorter half-life (approximately 24 hours) when compared with amiodarone which allows for steady state to be achieved in 5 to 7 days without the need for loading doses. Like amiodarone, dronedarone is a substrate of the CYP3A4 isoenzyme and a moderate

inhibitor of the CYP2D6 and CYP3A4 isoenzymes. Its use with potent CYP3A4 inhibitors or inducers should be avoided. Dronedarone may increase plasma concentrations of (*S*)-warfarin; therefore, the INR should be closely monitored with concurrent use of these medications. Dronedarone also inhibits P-gp and can increase digoxin concentrations by about 2.5-fold. Consequently, when concomitantly using dronedarone and digoxin, the digoxin dose should be empirically reduced by 50%. Additionally, dronedarone can increase dabigatran concentrations in patients with renal impairment. To minimize the risk of bleeding when concomitantly using dronedarone and dabigatran in patients with moderate renal impairment (creatinine clearance [CrCl] 30-50 mL/min [0.5-0.83 mL/s]), the dose of dabigatran should be reduced to 75 mg twice daily. The concomitant use of dronedarone and dabigatran should be avoided in patients with severe renal impairment (CrCl less than 30 mL/min [0.5 mL/s]).

Modifications to the chemical structure of dronedarone (addition of a methylsulfonyl group, deletion of the iodine moiety) result in it being less lipophilic than amiodarone. Consequently, dronedarone is supposed to be less likely to accumulate in tissues and cause various organ toxicities. However, like amiodarone, several post-marketing reports have linked dronedarone to significant organ toxicities, including severe hepatic injury, interstitial lung disease (ie, pulmonary fibrosis), and acute kidney injury.[9-11]

Table 40-6 summarizes potential sites/mechanisms for drug interactions with the AADs and Table 40-7 lists recommended dosages of the oral dosage forms of the AADs. Table 40-8 lists the dosing recommendations for the IV forms of various AADs.

TABLE 40-6

Potential Mechanisms for Drug-Drug Interactions with Antiarrhythmic Medications

Medication	Substrate	Inhibitor
Disopyramide	CYP3A4 (M)	—
Procainamide	NAT CYP2D6 (M)	—
Quinidine	CYP3A4 (M) CYP2C9	CYP2D6 (S) CYP3A4 (S) CYP2C9 P-gp
Lidocaine	CYP3A4 (M) CYP2D6 (M) CYP1A2 CYP2C9	CYP1A2 (S) CYP2D6
Mexiletine	CYP2D6 (M) CYP1A2 (M)	CYP1A2 (S)
Flecainide	CYP2D6 (M) CYP1A2	CYP2D6
Propafenone[a]	CYP2D6 (M) CYP1A2 CYP2D6	CYP1A2 CYP2D6
Amiodarone	CYP3A4 (M) CYP1A2 CYP2C19 CYP2D6	CYP2C9 CYP2D6 CYP3A4 CYP1A2

		CYP2C19 P-gp
Dofetilide	CYP3A4	—
Dronedarone	CYP3A4	CYP2D6 CYP3A4
Ibutilide	—	—
Sotalol	—	—
Diltiazem	CYP3A4 (M) CYP2C9 CYP2D6	CYP3A4 CYP2C9 CYP2D6 P-gp
Verapamil	CYP3A4 (M) CYP1A2 CYP2C9	CYP3A4 CYP1A2 CYP2C9 CYP2D6 P-gp

[a]Variables for parent compound (not 5-OH-propafenone).

CYP, cytochrome P450 isoenzyme; M, major; NAT, N -acetyltransferase; P-gp, P-glycoprotein; S, strong.

TABLE 40-7

Typical Maintenance Doses of Class I and Class III Oral Antiarrhythmic Medications

Medication	Dose	Dose Adjustments
Disopyramide	Immediate-release: 100-150 mg every 6 hours Controlled-release: 200-300 mg every 12 hours	**Chronic kidney disease** CrCl 30-40 mL/min (0.5-0.67 mL/s): 100 mg every 8 hours CrCl 15-30 mL/min (0.25-0.5 mL/s): 100 mg every 12 hours CrCl < 15 mL/min (0.25 mL/s): 100 mg daily *Note:* Avoid controlled release formulation if CrCl <40 mL/min (0.67 mL/s) **Hepatic impairment** Immediate-release: 100 mg every 6 hours Controlled-release: 200 mg every 12 hours
Quinidine	200-600 mg sulfate every 6 hours 324-648 gluconate every 8-12 hours	**Chronic kidney disease** No dosage adjustment. Use with caution. The following guidelines have been used by some clinicians[12]: CrCl ≥10 mL/min (0.17 mL/s): No dosage adjustment CrCl <10 mL/min (0.17 mL/s): Administer 75% of normal dose. Hemodialysis: Dose following hemodialysis. **Hepatic impairment** No dosage adjustment. Use with caution due to reduced clearance.

Mexiletine	200-300 mg every 8 hours	**Hepatic impairment** No dose adjustment provided. Use caution as half-life doubles with hepatic impairment.
Flecainide	50-200 mg every 12 hours	**Chronic kidney disease** CrCl >35 mL/min (0.58 mL/s): Initial: 100 mg every 12 hours. Dose increases should be made very cautiously at intervals >4 days. CrCl ≤35 mL/min (0.58 mL/s): Initial: 100 mg once daily or 50 mg every 12 hours. Dose increases should be made very cautiously at intervals >4 days. **Hepatic impairment** No dose adjustment provided. Use caution.
Propafenone	150-300 mg every 8 hours 225-425 mg every 12 hours (SR form)	**Chronic kidney disease** No dose adjustment provided. Use caution. **Hepatic impairment** No dose adjustment provided. Use caution.
Amiodarone	400 mg one to three times daily until 10 g total, then 100-400 mg daily	None
Dofetilide	500 µg every 12 hours	**Chronic kidney disease** CrCl >60 mL/min (1.0 mL/s): No dosage adjustment. CrCl 40 to 60 mL/min (0.67-1.0 mL/s): 250 µg twice daily. CrCl 20 to 39 mL/min (0.33-0.65 mL/s): 125 µg twice daily. CrCl <20 mL/min (0.33 mL/s): Use is contraindicated. **Hepatic impairment** Child-Pugh class A or B: No dosage adjustment. Child-Pugh class C: Use caution.
Dronedarone	400 mg twice daily (with meals)	**Hepatic impairment** Severe impairment: Contraindicated.
Sotalol	80-320 mg every 12 hours	**Chronic kidney disease** *Atrial fibrillation/flutter* CrCl >60mL/min: No dosage adjustment CrCl 40 to 60 mL/min: Administer every 24 hours CrCl <40 mL/min: Avoid use *Ventricular arrhythmia* CrCl >60 mL/min: No dosage adjustment CrCl 30 to 60 mL/min: Administer every 24 hours CrCl 10 to 29 mL/minute: Administer every 36 to 48 hours CrCl <10 mL/min: Individualized **Hepatic impairment** No dosage adjustment

SR, sustained release.

TABLE 40-8

Typical Doses of IV Antiarrhythmic Medications

Medication	Clinical Situation	Dose
Amiodarone	Pulseless VT/VF	300 mg IV/IO push (can give additional 150 mg IV/IO push if persistent VT/VF or if VT/VF recurs), followed by infusion of 1 mg/min for 6 hours, and then 0.5 mg/min × 18 hours
	Stable VT (with a pulse)	150 mg IV over 10 minutes, followed by infusion of 1 mg/min for 6 hours, and then 0.5 mg/min × 18 hours
	AF (termination)	150 mg IV over 10 minutes, followed by infusion of 1 mg/min for 6 hours, and then 0.5 mg/min × 18 hours
	AF (rate control)	300 mg IV over 1 hour, then 10-50 mg/hour over 24 hours
Diltiazem	PSVT; AF (rate control)	0.25 mg/kg IV over 2 minutes (may repeat with 0.35 mg/kg IV over 2 minutes), followed by infusion of 5-15 mg/hr
Ibutilide	AF (termination)	1 mg IV over 10 minutes (may repeat once, if needed, 10 minutes after initial dose)
Lidocaine	Pulseless VT/VF	1-1.5 mg/kg IV/IO push (can give additional 0.5-0.75 mg/kg IV/IO push every 5-10 minutes if persistent VT/VF [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1-4 mg/min (1-2 mg/min if liver disease or HF)
	Stable VT (with a pulse)	1-1.5 mg/kg IV push (can give additional 0.5-0.75 mg/kg IV push every 5-10 minutes if persistent VT [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1-4 mg/min (1-2 mg/min if liver disease or HF)
Procainamide	AF (termination); stable VT (with a pulse)	15-18 mg/kg IV over 60 minutes, followed by infusion of 1-4 mg/min
Verapamil	PSVT; AF (rate control)	2.5-5 mg IV over 2 minutes (may repeat up to maximum cumulative dose of 20 mg); can follow with infusion of 2.5-10 mg/hr

AF, atrial fibrillation; HF, heart failure; IO, intraosseous; IV, intravenous; PSVT, paroxysmal supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Supraventricular Arrhythmias

The common supraventricular tachycardias that often require medication treatment are: (a) AF or AFl; (b) PSVT; and (c) automatic atrial tachycardias. Other common supraventricular arrhythmias that usually do not require medication therapy include premature atrial complexes and sinus tachycardia. For example, premature atrial complexes rarely cause symptoms and never cause hemodynamic compromise; therefore, medication therapy is usually not indicated. Likewise, the cause of sinus tachycardia is often an underlying metabolic or hemodynamic disorder (eg, infection, dehydration, hypotension); therapy should focus on treating the underlying cause, not the tachycardia. Of course, there are exceptions to these suggestions. For example, sinus tachycardia may be deleterious in patients after cardiac surgery or MI. Therefore, AADs, such as β-blockers, may be indicated in these situations. Stated in another way, although many arrhythmias generally do not require therapy, clinical judgment and patient-specific variables play an important role in this decision. AF, AFl, and PSVT tend to be the most common supraventricular arrhythmias seen in clinical practice; therefore, this discussion will focus only on these arrhythmias.

Clinical Presentation

CLINICAL PRESENTATION: Superventricular Tachycardias

Atrial Fibrillation/Flutter

General

- These arrhythmias are usually not directly life-threatening and do not generally cause hemodynamic collapse or syncope; 1:1 AFl (ventricular response approximately 300 beats/min) is an exception. Also, patients with underlying forms of heart disease who are heavily reliant on atrial contraction to maintain adequate cardiac output (eg, mitral stenosis, obstructive cardiomyopathy) display more severe symptoms of AF or AFl.

Symptoms

- Most often, patients complain of rapid heart rate/palpitations, chest pain, dyspnea, dizziness, and fatigue. Medical emergencies are severe HF (ie, pulmonary edema, hypotension) or AF occurring in the setting of acute MI.

ECG Findings

- AF is an irregularly irregular supraventricular rhythm with no discernible, consistent atrial activity (P waves). Ventricular rate is usually 90 to 170 beats/min and the pulse is irregular (Fig. 40-6).
- AFl is (usually) a regular supraventricular rhythm with characteristic flutter waves (or sawtooth pattern) reflecting more organized atrial activity. Commonly, the ventricular rate 150 beats/min (Fig. 40-6).

Paroxysmal Supraventricular Tachycardia Caused by Reentry

General

- This arrhythmia can be transient.

Symptoms

- Patients can complain of intermittent episodes of rapid heart rate/palpitations that abruptly start and stop, usually without provocation (but occasionally as a result of exercise). Severe symptoms include syncope. Often (in particular, those with AV nodal reentry), patients complain of a chest pressure or neck sensation. This is caused by simultaneous AV contraction with the right atrium contracting against a closed tricuspid valve. Life-threatening symptoms (syncope, hemodynamic collapse) are associated with an extremely rapid heart rate (eg, greater than 200 beats/min) and AF associated with an accessory pathway.

ECG Findings

- Most commonly, PSVT is a rapid, narrow QRS tachycardia (regular in rhythm) that starts and stops abruptly (Fig. 40-6). Atrial activity, although present, is difficult to ascertain on surface ECG because P waves are “buried” in the QRS complex or T wave.

Atrial Fibrillation and Atrial Flutter

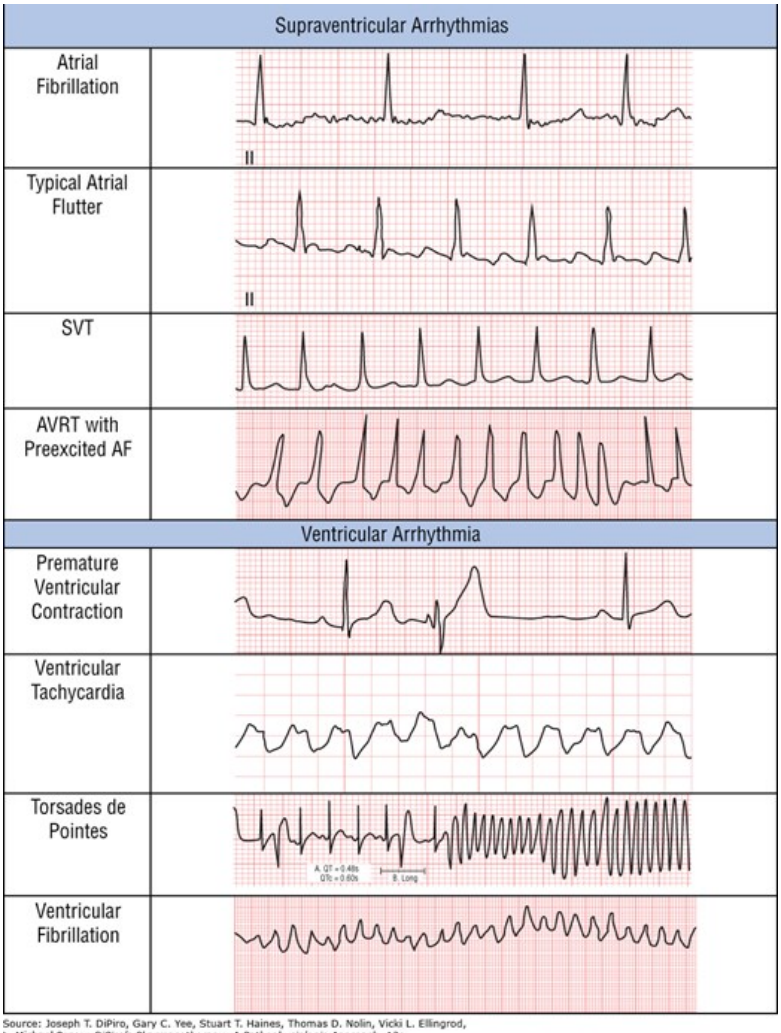
AF continues to be the most common sustained arrhythmia encountered in clinical practice, affecting approximately 5 million Americans.[13] The overall prevalence of AF is 2% to 4%, and increases with age (eg, approximately an 8% prevalence in patients greater than 65 years old). The prevalence of AF is expected to increase dramatically to an estimated 12 million by the year 2030. The general lifetime risk for AF in White people is 1 in 3 and 1 in 5 among Black people. Hypertension carries the highest risk of developing AF, followed by obesity, smoking, cardiac disease, diabetes, CKD, alcohol consumption, and sleep apnea.[13]

AF and AFl may present as a chronic, established tachycardia, an acute tachycardia, or a self-terminating, paroxysmal form. The following terms may be used to further define AF: first diagnosed AF (never diagnosed before, irrespective of its duration or symptoms), paroxysmal AF (terminates

spontaneously or with intervention within 7 days of onset), persistent AF (duration longer than 7 days), long-standing persistent AF (duration longer than 12 months), and permanent AF (patient and provider jointly decide to stop attempts to restore or maintain SR).[14] AF is characterized by extremely rapid (atrial rate of 400-600 beats/min) and disorganized atrial activation. With this disorganized atrial activity, the contribution of synchronized atrial contraction (atrial kick) is lost, potentially decreasing forward cardiac output. Moreover, the impulses penetrate the AV conduction system in variable degrees, resulting in an irregular activation of the ventricles and an irregularly irregular pulse (Fig. 40-6). The AV node will not conduct most of the supraventricular impulses, causing the ventricular response to be considerably slower than the atrial rate. It is sometimes stated that "AF begets AF," that is, the arrhythmia tends to perpetuate itself. Long episodes are more difficult to terminate, perhaps because of tachycardia-induced changes in atrial function (mechanical and/or electrical "remodeling").

FIGURE 40-6

Electrocardiographic findings of common arrhythmias. (SVT, supraventricular tachycardia; AVRT, atrioventricular reentrant tachycardia; AF, atrial fibrillation.)



AFl occurs less frequently than AF but is similar in its precipitating factors, consequences, and medication therapy approach. This arrhythmia is characterized by rapid (atrial rate of 270 to 330 beats/min) but regular atrial activation. The slower and regular electrical activity results in a regular ventricular response that is in approximate factors of 300 beats/min (ie, 1:1 AV conduction = ventricular rate of 300 beats/min; 2:1 AV conduction = ventricular rate of 150 beats/min; 3:1 AV conduction = ventricular rate of 100 beats/min). AFl may be characterized as "typical" or "atypical." "Typical" flutter is the more common form, which involves the cavotricuspid isthmus. The characteristic "sawtooth" pattern of atrial activation is seen on the surface ECG (Fig. 40-6). The ventricular rate for "atypical" flutter can vary. There are times when a coarse AF can regularize into AFl and then

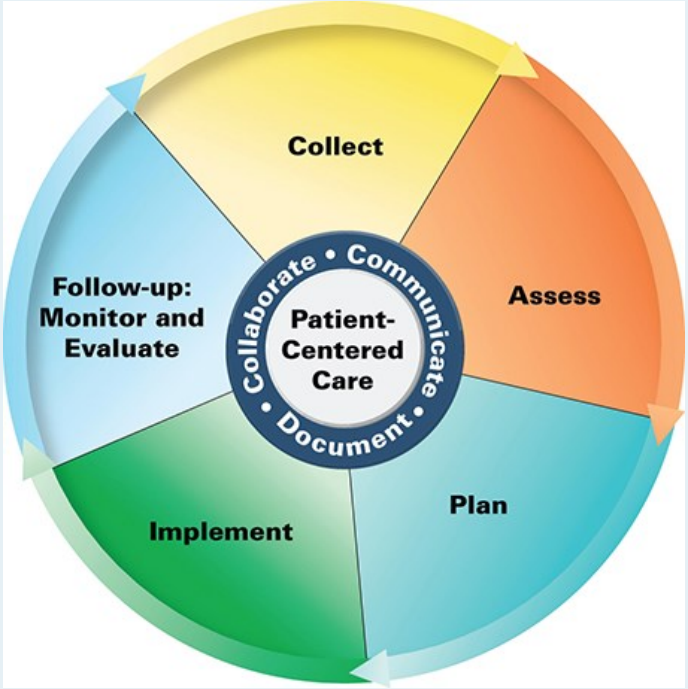
degenerates into AF.

AF may result from multiple atrial reentrant loops (or wavelets), triggered, or abnormal automaticity, whereas AFl is caused by a single, dominant, reentrant substrate ("typical" AFl counterclockwise or clockwise circus movement in the right atrium around the tricuspid annulus). AF or AFl usually occurs in association with various forms of structural heart disease (SHD) that cause left atrial distension, including myocardial ischemia or infarction, hypertensive heart disease, valvular disorders such as mitral stenosis or mitral insufficiency, congenital abnormalities such as septal defects, dilated or hypertrophic cardiomyopathy, and obesity. Disorders that cause right atrial stretch and are associated with AF or AFl include acute pulmonary embolism and chronic lung disease resulting in pulmonary hypertension and right-sided heart failure. AF may also occur in association with states of high adrenergic tone, such as thyrotoxicosis, surgery, alcohol withdrawal, sepsis, and excessive physical exertion. Other states in which patients are predisposed to episodes of AF are the presence of an accessory pathway and sinus node dysfunction (SND).

Patients with AF or AFl may experience the entire range of symptoms associated with other supraventricular tachycardias, although syncope as a presenting symptom is uncommon. Because left atrial kick is lost with the onset of AF, patients with HFrEF, HF with preserved ejection fraction (HFpEF) or critical valvular heart disease, particularly mitral stenosis, may develop worsening signs and symptoms of HF as they often depend on the contribution of their atrial kick to maintain an adequate cardiac output. Thromboembolic (TE) events resulting from atrial stasis, predominantly in the left atrial appendage (LAA), and poorly adherent mural thrombi are an additional complication of AF. The risk of stroke is increased fivefold in patients with AF.[14] Stroke can precede the onset of documented AF, probably because of undetected paroxysms prior to the onset of established AF. The risk of stroke significantly increases with age, with the annual attributable risk increasing from 1.5% in individuals 50 to 59 years of age to almost 24% in those 80 to 89 years of age.[15] The risk of stroke in patients with only AFl has been traditionally believed to be lower than AF. Yet, the same risk stratification scheme and antithrombotic recommendations used in patients with AF should also be applied to those with AFl.[14]

Patient Care Process

Patient Care Process: Atrial Fibrillation



Collect

- Patient characteristics (eg, age, sex)
- History of present illness (eg, signs/symptoms of AF, duration of AF symptoms) and patient medical history

- Social history (eg, tobacco/ethanol use) and dietary habits including intake of vitamin K–containing foods (for warfarin)
- Current and previous medications including prescription, over-the-counter, aspirin/nonsteroidal anti-inflammatory medications, herbal products, and dietary supplements
- Objective data
  - Blood pressure (BP), ventricular rate (ie, heart rate), height, weight
  - Labs: electrolytes (potassium, magnesium), serum creatinine (SCr), hemoglobin, hematocrit, platelets, activated partial thromboplastin time, prothrombin time (PT), international normalized ratio (INR), thyroid function tests
  - 12-lead electrocardiogram and echocardiogram

Assess

- Hemodynamic instability (eg, systolic BP <90 mm Hg), evidence of decompensated heart failure, or angina
- Duration of AF symptoms (unknown, less than 48 hours, or greater than 48 hours)
- Left ventricular systolic function (ie, left ventricular ejection fraction)
- Risk of stroke (CHA_2DS_2-VASc score) and risk of bleeding (HAS-BLED score)
- Presence of potentially reversible causes of AF (eg, thyrotoxicosis, alcohol withdrawal, infection, electrolyte abnormalities [hypokalemia, hypomagnesemia])
- Ability/willingness to pay for anticoagulation treatment options
- Ability/willingness to obtain laboratory monitoring tests (eg, PT/INR [warfarin], SCr [direct oral anticoagulants (DOACs)])
- Potential medication interactions with anticoagulants and/or antiarrhythmics

Plan*

- Medication therapy regimen including anticoagulant, and/or antiarrhythmic as well as dose, route, frequency, and duration; see Figs. 40-7 and 40-8 and Tables40-7, 40-8, 40-10, and 40-11.
- Monitoring parameters including efficacy (eg, ventricular rate, rhythm, PT/INR [warfarin], signs/symptoms of stroke) and safety (eg, proarrhythmia [ventricular tachycardia, torsades de pointes], sign/symptoms of bleeding, SCr); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, medication-specific information, monitoring/follow-up)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, PT/INR [warfarin], SCr [DOACs], adherence assessment (all medications), bleeding risk assessment [warfarin and DOACs], serum digoxin concentration [digoxin], pertinent laboratory/radiologic tests [amiodarone])

Follow-up: Monitor and Evaluate

- Ventricular rate and rhythm
- Symptoms

- Presence of adverse medication reactions (eg, bradycardia [ventricular rate control medications], bleeding [warfarin and DOACs], organ toxicities [antiarrhythmics]) (see Table 40-4)
- INR [warfarin only] (adjust warfarin dose as needed to maintain target INR in range of 2-3) and determine time in therapeutic range (TTR)
- Patient adherence to treatment plan using multiple sources of information

Collaborate with patient, caregivers, and other healthcare professionals.

General Approach to Treatment

The Atrial Fibrillation Better Care (ABC) approach to the treatment of AF can be organized into several sequential goals: "A" Anticoagulation/Avoid stroke; "B" Better symptom management; "C" Cardiovascular and Comorbidity optimization. This approach improves outcomes and reduces cardiovascular events and health-related costs.[5] A review of the management of AF and AFl follows, organized according to the ABCs.

A—Anticoagulation/Avoid Stroke

Historically, warfarin has been the standard of care for stroke prevention in patients considered to be at moderate or high risk for stroke due to AF. However, while warfarin is undoubtedly effective in preventing strokes in patients with AF, its use is associated with several potential limitations, including a narrow therapeutic window, requirement for routine INR monitoring, food and drug interactions, and pharmacogenetic influences. Over the past decade, the Food and Drug Administration (FDA) has approved several oral antithrombotic therapies for stroke prevention in patients with AF not due to valvular heart disease (moderate-to-severe mitral stenosis or mechanical heart valve). These oral anticoagulant medications, commonly referred to as direct oral anticoagulants (DOAC), include the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors, apixaban, edoxaban, and rivaroxaban.

When initiating chronic antithrombotic therapy in patients with AF, the CHEST and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend assessing the patient's risk for stroke and bleeding before selecting the most appropriate regimen.[16,17] The CHA_2DS_2-VASc risk scoring system is used for stroke risk stratification in patients with AF.[16] CHA_2DS_2-VASc is an acronym for each of these risk factors as seen in Fig. 40-7. The points are added up, and the total score is then used to determine the most appropriate antithrombotic therapy for the patient. No antithrombotic therapy is recommended for males with a CHA_2DS_2-VASc score of 0 and females with a CHA_2DS_2-VASc score of 1, as these patients are considered to be at low risk for stroke.[16] For patients with one non-sex CHA_2DS_2-VASc stroke risk factor (ie, CHA_2DS_2-VASc score of 1 in males or 2 in females), oral anticoagulant therapy is suggested by the ACC/AHA and recommended by the CHEST guidelines over no antithrombotic therapy.[16,17] For patients with 2 or more non-sex CHA_2DS_2-VASc stroke risk factors (ie, CHA_2DS_2-VASc score of 2 or higher in males or 3 or higher in females), oral anticoagulant therapy is recommended. If anticoagulation is indicated, the patient's risk for bleeding should also be evaluated. There are several tools to assess bleeding risk, but the most predictive is the HAS-BLED score (Table 40-09).[16] A score of 3 or more is considered high-risk for bleeding. The score should be used to manage modifiable bleeding risk factors and increase surveillance for bleeding in patients with nonmodifiable risk factors.

TABLE 40-9

HAS-BLED Score to Predict Bleeding Risk in Patients with Atrial Fibrillation

Letter	Risk Factor	Points
H	Uncontrolled hypertension (systolic blood pressure >160 mm Hg)	1
A	Abnormal renal +/− hepatic function (dialysis, transplant, serum creatinine >2.26 mg/dL (200 µmol/L), cirrhosis, bilirubin >2× normal with AST/ALT/AP >3× normal)	1 point each
S	Stroke (ischemic or hemorrhagic)	1
B	Bleeding (history of major hemorrhage or anemia or severe thrombocytopenia)	1
L	Labile INR on warfarin (TTR <60%)	1
E	Elderly (>65 years old or extremely frail)	1
D	Drugs or alcohol use (concomitant use of antiplatelet or NSAID and/or ≥8 alcoholic drinks/week)	1 point each

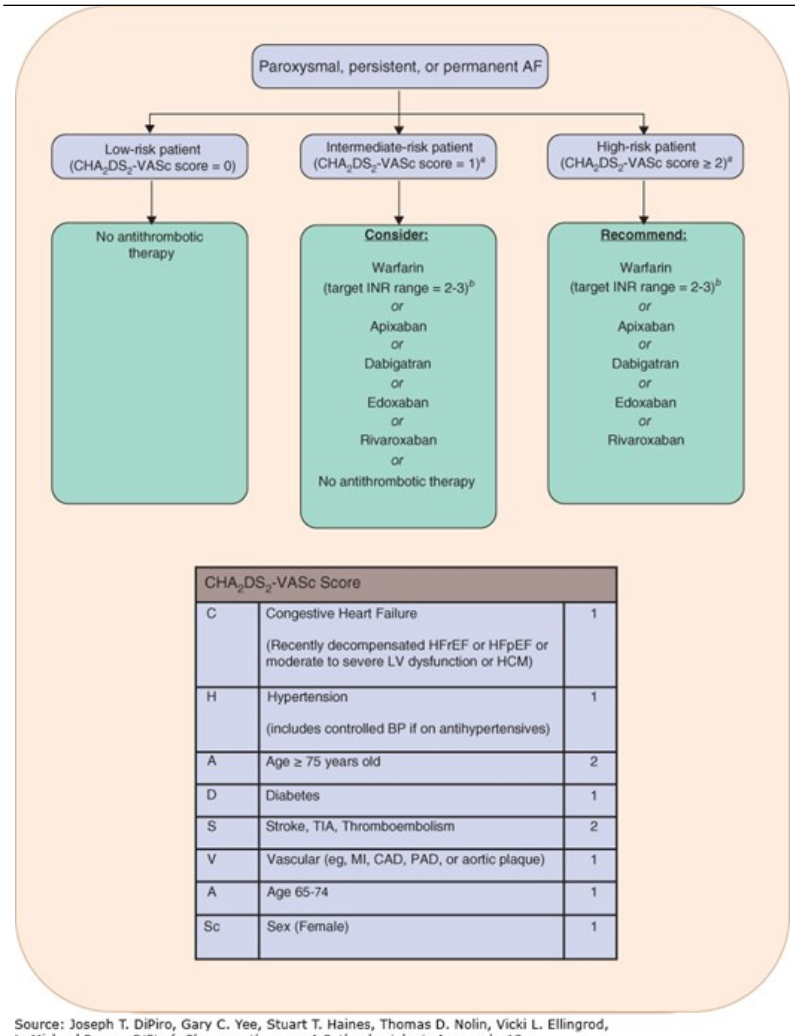
HAS-BLED score assesses a patient's 1-year risk of major bleeding when taking anticoagulants for atrial fibrillation. A score of 3 or greater is considered high risk for bleeding. The maximum score is 9. (AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; TTR, time in therapeutic range.)

FIGURE 40-7

Algorithm for the prevention of thromboembolism in atrial fibrillation.

[a] Score based on non-sex risk factors.

[b] The target INR for patients with prosthetic heart valves should be based on the type of valve that is present. (AF, atrial fibrillation; INR, international normalized ratio; MI, myocardial infarction; PAD, peripheral arterial disease.)



CHA_2DS_2-VASc Score		
C	Congestive Heart Failure (Recently decompensated HFrEF or HFpEF or moderate to severe LV dysfunction or HCM)	1
H	Hypertension (includes controlled BP if on antihypertensives)	1
A	Age ≥ 75 years old	2
D	Diabetes	1
S	Stroke, TIA, Thromboembolism	2
V	Vascular (eg, MI, CAD, PAD, or aortic plaque)	1
A	Age 65-74	1
Sc	Sex (Female)	1

The efficacy and safety of two dabigatran doses (110 mg and 150 mg twice daily) were compared with those of warfarin in patients with AF.[18] For the primary endpoint of stroke or systemic embolism, both dabigatran groups were shown to be noninferior to warfarin. Furthermore, the dabigatran 150-mg group was shown to be superior to warfarin in reducing this endpoint. The rate of major bleeding was similar between the dabigatran 150-mg and warfarin groups, while the rate of major bleeding was significantly lower in the dabigatran 110-mg group than in the warfarin group. The rate of intracranial hemorrhage (ICH) was significantly lower in both dabigatran groups than in the warfarin group. Even though the 110- and 150-mg dosing regimens of dabigatran were evaluated in this trial, only the 150-mg dose was initially approved by the FDA for AF. A lower 75-mg dose was also approved for patients with a CrCl of 15 to 30 mL/min (0.25 to 0.5 mL/s) even though this dose has not been evaluated in a randomized, prospective clinical trial in patients with AF; this dose has only pharmacokinetic data to support its use.[19] It is important to note that the trial excluded patients with a CrCl less than 30 mL/min (0.5 mL/s). A 110-mg dose of dabigatran has been approved for prophylaxis of venous thromboembolism in patients following hip replacement surgery. Although this dose has not been FDA-approved for stroke prevention in AF, the CHEST guidelines suggest using this dose (or apixaban or edoxaban) in patients with a history of or who are at high risk of bleeding.[16] Dabigatran is contraindicated in patients with mechanical heart valves because its use in this population has been associated with an increased risk of TE complications and bleeding.[20]

The efficacy and safety of rivaroxaban were compared with those of warfarin in patients with AF in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF).[21] In this study, patients were randomized to receive rivaroxaban 20 mg daily or adjusted-dose warfarin. For the primary endpoint of stroke or systemic embolism, rivaroxaban was shown to be noninferior to warfarin. The rate of major and nonmajor clinically relevant bleeding was similar between the rivaroxaban and warfarin groups. Significantly fewer ICHs occurred in the rivaroxaban group compared with the warfarin group.

The efficacy and safety of apixaban were compared with those of warfarin in patients with AF in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.[22] Overall, apixaban was shown to be noninferior and superior to warfarin with regard to the primary endpoint of stroke or systemic embolism. The rate of major bleeding in this trial was significantly lower in the apixaban group than in the warfarin group. Additionally, significantly fewer ICHs occurred in the apixaban group compared with the warfarin group.

The efficacy and safety of edoxaban were compared with those of warfarin in patients with AF in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction (ENGAGE AF-TIMI) 48 trial.[23] In this study, patients were randomized to receive edoxaban 60 mg daily, edoxaban 30 mg daily, or adjusted-dose warfarin. Overall, both doses of edoxaban were shown to be noninferior to warfarin with regard to the primary endpoint of stroke or systemic embolism. However, the edoxaban 60-mg dosing regimen was also shown to be superior to warfarin with regard to this endpoint. The rate of major bleeding and the risk of ICH were significantly lower in both edoxaban groups than in the warfarin group. However, the risk of major gastrointestinal bleeding was significantly higher in the edoxaban 60-mg group, but significantly lower in the edoxaban 30-mg group when compared to the warfarin group.

Guidelines recommend therapy with a DOAC over warfarin.[16,17] However, it is essential that anticoagulant therapy be individualized for each patient, with consideration given to medication cost, insurance coverage, INR monitoring options, patient preference, drug interaction potential, anticipated medication adherence, and necessary follow-up. Specifically with warfarin, the target INR range should be 2 to 3, and the time in therapeutic range (TTR) should ideally be greater than 70%.[16] The TTR is an important metric when evaluating the efficacy of warfarin therapy as the risk of TE events, major bleeding, and death is lower in patients with a TTR of at least 65% compared to patients with a TTR of less than 65%.[24] The CHEST guidelines have recommended the use of the SAMe-TT_2R_2 score to assist in the identification of patients who are likely or not likely to achieve good anticoagulation control with warfarin (ie, TTR of at least 65%).[16] With this scoring system, patients with AF are given two points each if they use tobacco or are of a non-white race. Patients are given one point each for being female, being younger than 60 years of age, having at least two of the specified medical conditions (hypertension, diabetes, CAD/MI, congestive HF, previous stroke, pulmonary disease, hepatic disease, or renal disease), or receiving treatment with a medication that interacts with warfarin. SAMe-TT_2R_2 is an acronym for each of these risk factors. Once the points for this scoring system are added up, a score of 0 to 2 suggests that patients are likely to achieve a TTR of at least 65%. Patients with a score of more than 2 are less likely to achieve a TTR of at least 65% and should be educated on strategies that could improve their TTR, including more frequent INR monitoring and medication reviews, adherence counseling, and dietary guidance. Alternatively, these patients could be considered for DOAC therapy. Additionally, if a patient has previously taken warfarin, the time that his/her INR has been within the therapeutic range should also be considered before making the decision to switch the patient to a DOAC.

If a patient is unable to maintain a therapeutic INR while on warfarin, therapy with a DOAC is recommended. Strict adherence with the DOACs is important because missing a single dose could result in an increased risk of TE events.[25] If treatment with warfarin must be temporarily interrupted for the patient to undergo a medical procedure, coverage with a parenteral anticoagulant (eg, unfractionated heparin, low molecular weight heparin [LMWH]) should be considered in patients with a high risk of stroke and/or have a mechanical heart valve. Moreover, warfarin is the anticoagulant of choice for patients with moderate to severe mitral stenosis or a mechanical heart valve; the INR should be based on the type and location of the valve placed. Dabigatran, edoxaban, and rivaroxaban should be avoided in patients with a CrCl less than 15 mL/min (0.25 mL/s). In this particular population, anticoagulant options are warfarin and apixaban. Edoxaban should also be avoided in patients with a CrCl greater than 95 mL/min (1.58 mL/s) because of the potential for reduced efficacy.

Although it was previously an acceptable practice to discontinue antithrombotic therapy 4 weeks after successful cardioversion (with the belief that a patient's risk for thromboembolism had abated since he/she was in SR), data from the RACE and AFFIRM trials strongly suggest that patients with AF and other risk factors for stroke continue to be at risk for stroke even when maintained in SR.[26,27] It is possible that these patients may be having undetected episodes of paroxysmal AF, placing them at risk for stroke. Consequently, the decision regarding chronic antithrombotic therapy should be based on a patient's risk for stroke using the CHA_2DS_2-VASc scoring system.[14]

Should a patient have an increased risk of stroke but have a contraindication to long-term anticoagulation, a LAA occluder may be an alternative.[5,14,17] The Watchman, the only FDA-approved device, is deployed into the left atrial appendage and designed to conform to the anatomy of the LAA, permanently sealing it off and reducing the risk of emboli. Although postimplantation antithrombotic practice patterns vary, patients should initiate aspirin the day before the procedure and an oral anticoagulant upon implantation. If an adequate seal has been formed at 45 days postimplant, oral

anticoagulation should be discontinued, aspirin should be continued, and a $P2Y_{12}$ inhibitor should be started. At 6 months postimplant, the $P2Y_{12}$ inhibitor is stopped while aspirin is continued lifelong.

B—Better Symptom Management

Should patients receive rate control (regulate only the ventricular rate and remain in AF) or rhythm control (restoring and maintaining normal sinus rhythm)? Six landmark clinical trials have compared the efficacy of rate control and rhythm control treatment strategies in patients with AF.[26-31] The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial is the largest rate control versus rhythm control study conducted to date in patients with AF.[27] In this trial, patients with AF and at least one risk factor for stroke were randomized to either a rate control or a rhythm control group. Rate-control treatment involved AV nodal blocking medications (digoxin, β-blockers, and/or non-DHP CCBs) first, and then nonpharmacologic treatment (AV nodal ablation with pacemaker implantation), if necessary. All patients in this group were anticoagulated. In the rhythm control group, class I or III AADs were used to maintain SR. The choice of AAD therapy was left up to each patient's physician. By the end of the trial, more than 60% of patients had received at least one trial of amiodarone, and approximately 40% of patients had received at least one trial of sotalol. In the rhythm control group, anticoagulation was encouraged but could be discontinued if SR had been maintained for at least 4 weeks. Overall mortality was not statistically different between the two strategies. However, patients in the rhythm-control group were significantly more likely to be hospitalized or experience an adverse drug reaction. The results of the other four trials were consistent with those of the AFFIRM trial.[26,28-30] In addition, a meta-analysis of these data demonstrated no significant difference in overall mortality between rate control and pharmacological rhythm control strategies, which persisted even when the results from the AFFIRM trial were excluded from this analysis.[32]

Collectively, these trials demonstrate that a rate control strategy is a viable alternative to a rhythm control strategy in patients with persistent AF. However, only a small proportion of patients enrolled in these trials had HFrEF. Thus, a trial was conducted to specifically evaluate the safety and efficacy of rate control and rhythm control strategies in patients with HFrEF.[31] Consistent with other rate control versus rhythm control studies, no significant difference in the primary endpoint of death from cardiovascular (CV) causes was observed between treatment groups. Though not statistically significant, patients in the rhythm control group tended to have more hospitalizations, primarily due to repeated cardioversions and adjustment of AAD therapy. It is important to note that the results of this trial should not be applied to patients with HFpEF. Together, these trials suggest that a pharmacological rhythm control strategy does not confer any advantage over a rate control strategy in patients with AF, with or without HFrEF.

4 Clearly, these important findings temper the old approach of aggressively attempting to maintain SR. Because a rhythm control strategy does not offer any significant advantage over a rate control strategy in the management of patients with AF, the decision to utilize one strategy over another is primarily driven by the goal of improving a patient's quality of life (Table 40-10).

TABLE 40-10

Considerations for Selecting a Rate-Control Versus Rhythm-Control Strategy in Patients with Atrial Fibrillation

Rate-Control	Rhythm-Control
No or minimal symptoms	Paroxysmal or persistent AF
Treatment of choice for permanent AF	Symptomatic despite adequate rate control
	Hemodynamically unstable
	Exacerbating heart failure
	Tachycardia-mediated cardiomyopathy
	Other factors • Younger age • First episode of AF • Patient preference

AF, atrial fibrillation.

Rate Control

Once the decision has been made to rate control a patient, the next important question is: What defines “adequate” ventricular rate control? A lenient rate control strategy targeting a resting heart rate less than 110 beats/min is recommended for asymptomatic patients with a preserved LV systolic function (LVEF greater than 40% [0.40]).[14,33] In patients who are symptomatic or have LV systolic dysfunction (LVEF less than or equal to 40% [0.40]), a stricter rate control approach targeting a resting heart rate less than 80 beats/min should be considered.

The selection of an AV nodal-blocking medication to control ventricular rate is primarily based on the patient’s LV function.[14] In patients with preserved LV function or in patients with stable HFpEF, a β-blocker or non-DHP CCB (diltiazem or verapamil) is preferred over digoxin because of their relatively quick onset and maintained efficacy during exercise. When adequate ventricular rate control cannot be achieved with one of these medications, the addition of digoxin may result in an additive lowering of the heart rate. However, digoxin tends to be ineffective for controlling ventricular rate under conditions of increased sympathetic tone (ie, surgery, thyrotoxicosis) because it slows AV nodal conduction primarily through vagotonic mechanisms. Verapamil and diltiazem should be avoided in patients with HFrEF (LVEF less than or equal to 40% [0.40]) because of their potent negative inotropic effects.[14] Instead, β-blockers and digoxin are preferred. Specifically, in patients with NYHA class II or III HF, β-blockers should be considered over digoxin because of their survival benefits in patients with HFrEF. If patients are having an episode of decompensated HF (NYHA class IV), digoxin is preferred as first-line therapy to achieve ventricular rate control because of the potential for worsening HF symptoms with the initiation and subsequent titration of β-blocker therapy. Several analyses have associated digoxin with a significant increase in the risk of mortality in patients with AF.[34] The risk is highest when serum digoxin concentrations are 1.2 ng/mL (mcg/L; 1.5 nmol/L) or greater.[35]

If adequate ventricular rate control during rest and exercise cannot be achieved with β-blockers, non-DHP CCBs, and/or digoxin in patients with normal or depressed LV function, amiodarone can be used as an alternative therapy to control the heart rate (Table 40-11). However, clinicians should be aware that the use of amiodarone for controlling ventricular rate may also stimulate the conversion of AF to SR and place the patient at risk for a TE event, especially if the AF has persisted for at least 48 hours or is of unknown duration.

TABLE 40-11

Evidence-Based Pharmacologic Treatment Recommendations for Controlling Ventricular Rate, Restoring Sinus Rhythm, and Maintaining Sinus

Rhythm in Patients with Atrial Fibrillation

Treatment Recommendations	ACC/AHA Guideline Recommendation
Ventricular rate control (acute setting)	
In the absence of an accessory pathway, an IV β-blocker or IV non-DHP CCB is recommended for patients without HF.	Class I
In the absence of an accessory pathway, IV digoxin or IV amiodarone is recommended to control the ventricular rate in patients with HF.	Class I
In the absence of an accessory pathway, an IV β-blocker is recommended to control the ventricular rate in patients with stable HFrEF.	Class I
In the absence of an accessory pathway, an IV non-DHP CCB is recommended to control the ventricular rate in patients with stable HFpEF.	Class I
In the absence of an accessory pathway, IV amiodarone is recommended to control the ventricular rate in critically ill patients.	Class IIa
IV amiodarone can be useful to control the ventricular rate when other measures are unsuccessful or contraindicated.	Class IIa
Digoxin, non-DHP CCBs, or IV amiodarone should not be used in patients with an accessory pathway.	Class III
IV β-blockers or IV non-DHP CCBs are not recommended in patients with decompensated HF.	Class III
Ventricular rate control (chronic setting)	
An oral β-blocker or non-DHP CCB is recommended to control the ventricular rate in patients with paroxysmal, persistent, or permanent AF.	Class I
An oral β-blocker or non-DHP CCB is recommended to control the ventricular rate in patients with persistent or permanent AF and compensated HFpEF.	Class I
Digoxin is effective for controlling resting heart rate in patients with HFrEF.	Class I
A combination of digoxin and a β-blocker is reasonable to control resting and exercise heart rate in patients with HFrEF.	Class IIa
A combination of digoxin and a non-DHP CCB is reasonable to control resting and exercise heart rate in patients with HFpEF.	Class IIa
Oral amiodarone can be used when the ventricular rate cannot be adequately controlled at rest and during exercise with an oral β-blocker, non-DHP CCB, and/or digoxin.	Class IIb
Oral non-DHP CCBs and dronedarone are not recommended to control the ventricular rate in patients with decompensated HF.	Class III
Dronedarone should not be used to control the ventricular rate in patients with permanent AF.	Class III
Restoration of sinus rhythm	
In the absence of contraindications, flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacologic	Class I

cardioversion of AF.	
Oral amiodarone is a reasonable option for pharmacologic cardioversion of AF.	Class IIa
The "pill-in-the-pocket" approach with flecainide or propafenone can be used to terminate persistent AF on an outpatient basis once the treatment has been used safely in the hospital, in patients without sinus or AV node dysfunction, bundle-branch block, QT interval prolongation, Brugada syndrome, or SHD (*Note*: AV node must be adequately blocked with β-blocker or non-DHP CCB therapy before initiating this therapy).	Class IIa
Dofetilide should not be initiated on an outpatient basis.	Class III
Maintenance of sinus rhythm	
The following AADs are recommended for maintaining SR, depending on underlying SHD and other comorbidities: amiodarone, dofetilide, dronedarone, flecainide, propafenone, and sotalol.	Class I
Because of its potential toxicities, amiodarone should only be used after consideration of its risks and when other agents have failed or are contraindicated.	Class I
The risk of the AAD, including proarrhythmia, should be considered before initiating treatment with that medication.	Class I
Antiarrhythmic therapy can be useful for maintaining SR for the treatment of tachycardia-induced cardiomyopathy.	Class IIa
It may be reasonable to continue current AAD therapy in the setting of infrequent, well-tolerated recurrences of AF when the medication has reduced the frequency or symptoms of AF.	Class IIb
An AAD should not be continued when the AF becomes permanent.	Class III
Dronedarone should not be used in patients with class III or IV HF or patients who have had an episode of decompensated HF in the last 4 weeks.	Class III

AAD, antiarrhythmic medication; ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; AV, atrioventricular; CCB, calcium channel blocker; DHP, dihydropyridine; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HRS, Heart Rhythm Society; IV, intravenous; SHD, structural heart disease; SR, sinus rhythm.

Data from Reference 36.

Rhythm Control

In those whose decision has been made to restore SR, one must consider that this very act (regardless of whether an electrical or pharmacologic method is chosen) places the patient at risk for a TE event. The heightened risk is because the return of SR restores effective contraction in the atria, which may dislodge poorly adherent thrombi. Administering anticoagulant therapy prior to cardioversion not only prevents clot growth and the formation of new thrombi but also allows existing thrombi to become organized and adhere to the atrial wall. It is a generally accepted principle that the risk of thrombus formation and a subsequent embolic event increases if the duration of the AF exceeds 48 hours. Therefore, it is vital for clinicians to estimate the duration of the patient's AF so that appropriate anticoagulant therapy can be administered prior to cardioversion if needed.

For patients undergoing elective cardioversion (electrical or pharmacologic) for AF lasting at least 48 hours or for an unknown duration, guidelines recommend that therapeutic anticoagulation with warfarin or DOAC should be given for at least 3 weeks before cardioversion is performed; this recommendation applies to patients regardless of their CHA_2DS_2-VASc score.[16,37] If 3 weeks of therapeutic oral anticoagulant therapy is not feasible in these patients, a screening transesophageal echocardiogram (TEE) can be performed prior to cardioversion to evaluate for the presence of thrombus

in the heart chambers (particularly the atria or atrial appendage). Overall, there is no difference in the efficacy and safety between DOACs and warfarin in patients undergoing TEE-guided cardioversion.[38]

If cardioversion is successful (ie, the patient is now in SR), therapeutic anticoagulation with warfarin (INR target range 2 to 3) or a DOAC should be continued for at least 4 weeks, regardless of the patient's baseline risk of stroke.[16,37] The reason for continuing anticoagulation for this additional 4-week time period is that after the restoration of SR, full atrial contraction does not occur immediately. Rather, it returns gradually to a maximum contractile force over a 3- to 4-week period. Decisions regarding long-term antithrombotic therapy after this 4-week period should be based on the patient's risk for stroke and not on whether the patient is in SR. If a thrombus is seen on TEE, cardioversion should not be performed and the patient should be anticoagulated for another 4 to 12 weeks.[16]

In patients with AF that is less than 48 hours in duration, a prolonged period of anticoagulation prior to cardioversion is unnecessary because there has not been sufficient time to form atrial thrombi. However, an oral anticoagulant, LMWH or unfractionated heparin should be started as soon as possible.[5,16,37]

After anticoagulation needs and/or TEE have been addressed, the process of restoring SR can be considered. There are two methods of restoring SR in patients with AF or AFl: pharmacologic cardioversion and DCCV. The decision to use either of these methods is generally based on clinical preference and the hemodynamic stability of the patient. In situations of hemodynamic instability (eg, severe hypotension, angina, or pulmonary edema), direct current cardioversion is indicated as first-line therapy in an attempt to immediately restore SR (without regard to the risk of thromboembolism). The disadvantages of pharmacologic cardioversion are the risk of significant adverse drug reactions (eg, drug-induced TdP), the potential for drug-drug interactions (eg, digoxin–amiodarone), and the lower efficacy of AADs when compared with DCCV. The advantages of DCCV are that it is quick and more often successful (80% to 90% success rate) compared to pharmacologic cardioversion. The disadvantages of DCCV are the need for periprocedural sedation/anesthesia and the risk (albeit small) of serious complications such as sinus arrest or ventricular arrhythmias.

Nonetheless, despite the relatively high success rate associated with DCCV, clinicians and patients may elect to use AADs first and then resort to DCCV if these medications fail. Pharmacologic cardioversion appears to be most effective when initiated within 7 days after the onset of AF.[14] There is relatively strong evidence for the efficacy of class III pure I_K blockers (ibutilide and dofetilide), the class Ic AADs (flecainide and propafenone), and amiodarone (oral or IV) for cardioversion of AF.[14] Class Ia AADs have limited efficacy or have not been adequately studied in this setting. Sotalol is not effective for cardioversion of paroxysmal or persistent AF. Single, oral loading doses of propafenone (body weight greater than 70 kg: 600 mg; less than 70 kg: 450 mg) and flecainide (body weight greater than 70 kg: 300 mg; less than 70 kg: 200 mg) are effective compared with placebo for conversion of recent-onset AF and have been incorporated into the "pill-in-the-pocket" approach endorsed by treatment guidelines.[14,39] With this method, patient-controlled, self-administration of a single, oral loading dose of flecainide or propafenone in the outpatient setting is relatively safe and effective for the termination of recent-onset AF in the absence of sinus or AV node dysfunction, bundle-branch block, or SHD.[39] This approach should be considered in patients who have previously been successfully cardioverted with these medications on an inpatient basis.

Overall, when considering pharmacologic cardioversion, the selection of an AAD should be based on whether the patient has SHD (eg, LV dysfunction, CAD, valvular heart disease, LV hypertrophy).[14] In the absence of any type of SHD, the use of a single, oral loading dose of flecainide or propafenone is a reasonable approach for cardioversion. Ibutilide can also be used as an alternative in this patient population; however, the use of this agent is restricted to a monitored setting in the hospital because it requires QT interval monitoring. In patients with underlying SHD, flecainide, propafenone, and ibutilide should be avoided because of the increased risk of proarrhythmia; amiodarone or dofetilide should be used instead. Although amiodarone can be administered safely on an outpatient basis because of its low proarrhythmic potential, dofetilide therapy can only be initiated in the hospital (for QT interval monitoring and assessment of renal function). Additionally, a patient's ventricular rate should be adequately controlled with AV nodal blocking medications prior to administering a class Ic AAD for cardioversion. The class Ic AADs may paradoxically increase ventricular response. The most likely mechanism for this effect is that by slowing atrial conduction, the class Ic AADs decrease the number of impulses reaching the AV node. Consequently, the AV node paradoxically allows more impulses to gain entrance to the ventricular conduction system, thereby increasing ventricular rate.

Class Ic or III AADs are reasonable to consider to maintain patients in SR (Table 40-12).[14] The role of the class Ia AADs for maintenance of SR has been deemphasized compared with the class Ic and III AADs. While a systematic review of AADs for the maintenance of SR after cardioversion in patients with AF demonstrated that AF recurrences were significantly reduced with the use of class Ia, Ic, and III AADs, mortality was significantly increased with the

class Ia medications.[40] The class Ic AADs, flecainide and propafenone, are effective for maintaining SR. However, because of the increased risk for proarrhythmia, these medications should be avoided in patients with SHD.

TABLE 40-12

Guidelines for Selecting Antiarrhythmic Medication Therapy to Maintain Sinus Rhythm in Patients with Recurrent Paroxysmal or Recurrent Persistent Atrial Fibrillation

No structural heart disease[a] (absence of heart failure, coronary artery disease, or significant LVH) First line[b]: dofetilide, dronedarone, flecainide, propafenone, or sotalol Second line[c]: amiodarone
Heart failure[a] First line[b]: amiodarone or dofetilide Second line: catheter ablation
Coronary artery disease[a] First line[b]: dofetilide, dronedarone,[d] or sotalol[d] Second line[c]: amiodarone

LVH, left ventricular hypertrophy.

[a]Medications are listed alphabetically and not in order of suggested use.

[b]Catheter ablation may also be considered first-line therapy in select patients with paroxysmal atrial fibrillation.

[c]Catheter ablation may also be considered when patients are refractory or intolerant to at least one antiarrhythmic medication.

[d]Should only be used in this situation if the patient has normal left ventricular systolic function.

Although all oral class III AADs have demonstrated efficacy in preventing AF recurrences, amiodarone is clearly the most effective agent and the most frequently used AAD despite its potential for causing significant organ toxicity.[41] The superiority of amiodarone over other AADs for maintaining patients in SR has been demonstrated in a number of clinical trials. Amiodarone was significantly more effective than sotalol or propafenone in maintaining SR in patients with persistent or paroxysmal AF.[42] Amiodarone was also found to be significantly more effective than sotalol at maintaining SR in all patient subgroups, except for those with CAD where the efficacy of these two medications was comparable.[43] Furthermore, amiodarone appears to be the most effective AAD in maintaining SR.[44]

Although sotalol is not effective for the conversion of AF, it is an effective medication for maintaining SR. Sotalol appears to be at least as effective as propafenone in preventing recurrences of AF.[42] However, treatment with sotalol is associated with TdP. Because TdP occurs primarily with higher doses of sotalol, it may be easier to predict and avoid. Nonetheless, sotalol may increase mortality in patients with AF.[45]

Dofetilide is effective in preventing AF recurrences but has not been directly compared with either amiodarone or sotalol. In a large, multicenter trial, dofetilide was more effective than placebo in maintaining SR (approximately 35% to 50% at 1 year).[46] The efficacy of dofetilide for the maintenance of SR has also specifically been demonstrated in patients with HFrEF.[47] Like sotalol and quinidine, dofetilide also has significant potential to cause TdP (in a dose-related fashion).

In two similarly designed trials, dronedarone was more effective than placebo in maintaining SR in patients with paroxysmal or persistent AF or AFl.[48] In another trial, the use of dronedarone in patients with persistent or paroxysmal AF or AFl was associated with significantly fewer hospitalizations due to CV events or death when compared with placebo.[49] In another study, dronedarone was shown to be significantly less effective than amiodarone in

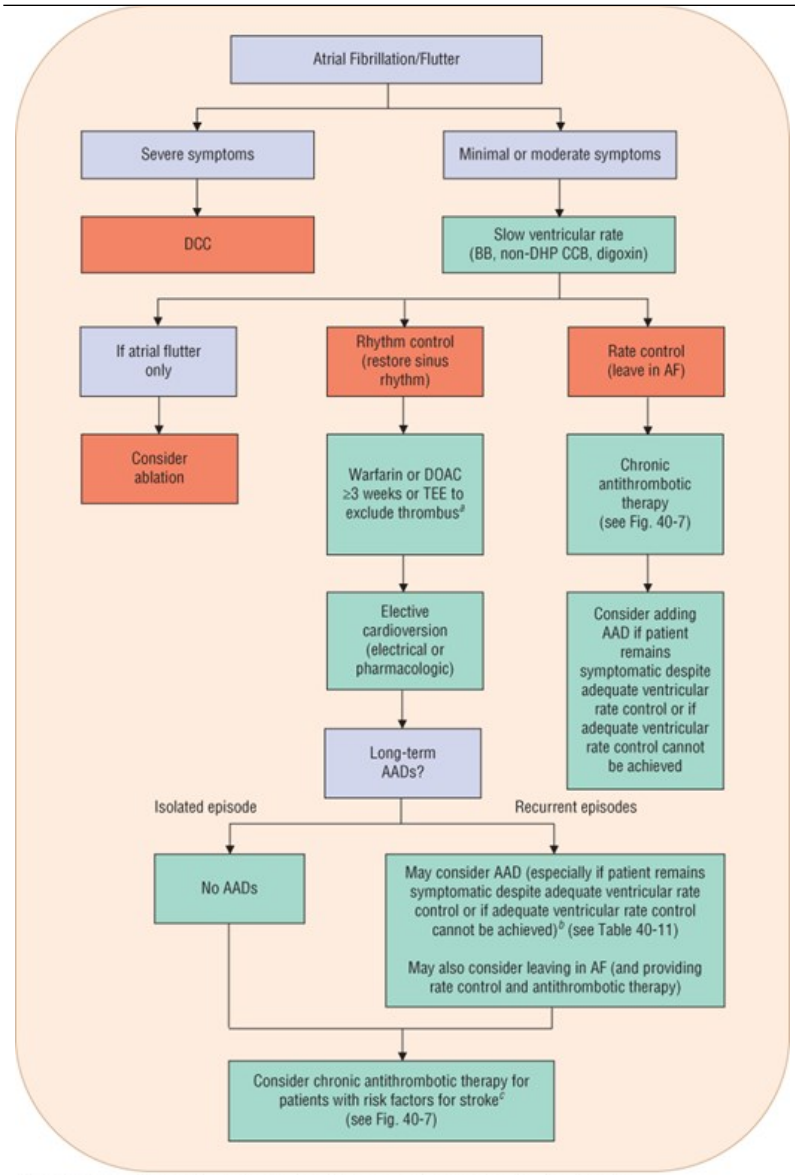
reducing AF recurrences.[50] However, tolerability was significantly better in the dronedarone group than the amiodarone group as evidenced by higher rates of premature medication discontinuation due to adverse events in the amiodarone group.[50] Most recently, a trial that enrolled patients with permanent AF and risk factors for major vascular events was terminated prematurely after significantly more patients in the dronedarone group died (primarily from CV causes), or hospitalized for HF, or suffered a stroke compared with the placebo group.[51] Based on the results of this trial, dronedarone is contraindicated (black box warning) in patients with permanent AF. One study evaluated the safety and efficacy of dronedarone to prevent death and heart failure hospitalizations in patients with NYHA class III or IV HFrEF (presumably due to decreasing arrhythmia occurrence).[52] This trial was prematurely terminated because all-cause mortality (primarily due to worsening HF) was significantly higher in the dronedarone group compared with the placebo group. Consequently, dronedarone is contraindicated (black box warning) in advanced HF (NYHA class IV or NYHA class II or III with a recent hospitalization for decompensated HF).

Overall, the selection of an AAD to maintain SR should be primarily based on whether the patient has SHD.[14] However, other factors, including renal and hepatic function, concomitant disease states and medications, and the AAD's side effect profile also need to be considered. Dofetilide, dronedarone, flecainide, propafenone, or sotalol should be considered initially for those patients with no underlying SHD because these medications have the most optimal long-term safety profile in this setting.[14] However, amiodarone could be used as an alternative therapy if the patient fails or does not tolerate one of these initial AADs. In the presence of SHD, flecainide and propafenone should be avoided because of the risk of proarrhythmia. For those patients with HFrEF (LVEF less than or equal to 40% [0.40]), amiodarone or dofetilide should be considered the AADs of choice. Only amiodarone and dofetilide have been shown to be mortality-neutral in patients with AF and HFrEF. Both dronedarone and sotalol should be avoided in patients with HFrEF because of the risk for increased mortality (dronedarone) or worsening HF (dronedarone and sotalol). In patients with CAD, dofetilide, dronedarone, or sotalol can be used initially. Amiodarone could be used as an alternative therapy if the patient fails or does not tolerate one of these initial AADs. The presence of LV hypertrophy may predispose the myocardium to proarrhythmic events. Because of their low proarrhythmic potential, amiodarone or dronedarone should be considered first-line AAD therapy in these patients.

Figure 40-8 shows an algorithm for the management of AF and AFl.

FIGURE 40-8

Algorithm for the treatment of AF and AFl. [a]If AF is less than 48 hours in duration, anticoagulation prior to cardioversion is unnecessary; initiate anticoagulation with unfractionated heparin, a low-molecular-weight heparin, apixaban, dabigatran, edoxaban, or rivaroxaban as soon as possible either before or after cardioversion for stroke prevention (this anticoagulant regimen or no antithrombotic therapy may be considered in low-risk patients). [b]Ablation may be considered for patients who fail or do not tolerate at least one AAD or as first-line therapy (before AAD therapy) for select patients with recurrent symptomatic paroxysmal AF or any classification of AF and heart failure with reduced left ventricular ejection fraction. [c]Chronic antithrombotic therapy should be considered in all patients with AF and risk factors for stroke regardless of whether or not they remain in sinus rhythm. (AAD, antiarrhythmic medication; AF, atrial fibrillation; AFl, atrial flutter; BB, beta-blocker; non-DHP CCB, non-dihydropyridine calcium channel blocker; DCCV, direct current cardioversion; DOAC, direct oral anticoagulant; TEE, transesophageal echocardiogram.)



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Nonpharmacologic forms of therapy, designed to maintain SR, are becoming increasingly popular options for patients with AF or AFl. For patients who have "typical" AFl, not associated with concurrent AF, ablation of the reentrant substrate with radiofrequency current is highly effective (more than 90%) and should be the first-line treatment of AFl to prevent recurrences.[53] Catheter ablation for patients with AF is much more technically difficult for a variety of reasons, including the lack of a single, identifiable, and ablatable reentrant focus (as in AFl). Patients with AF have been found to have arrhythmogenic foci that occur in atrial tissue near and within the pulmonary veins. The ablation procedure most commonly used is a pulmonary vein isolation (PVI) ablation, where the foci originating in these areas are abolished by locally delivering heat (radiofrequency energy) or freezing the tissue (cryoablation). Historically, PVI ablation was often considered last-line therapy for patients who had failed all AADs, including amiodarone. However, in some trials, the use of PVI ablation in patients with AF has been associated with a significant reduction in recurrent episodes of AF and an improvement in quality of life when compared with AAD therapy.[54,55] In patients with AF and concomitant HFrEF who did not respond to, were intolerant of, or were unwilling to take AADs, the use of PVI ablation has been associated with a significant reduction in all-cause mortality or hospitalization for worsening HF.[56] There is also evidence to suggest that this procedure may be superior to AADs as first-line therapy of symptomatic AF.[57,58] Moreover, ablation is an appropriate option for patients with tachycardia-induced cardiomyopathy. Controlling comorbidities (ie, OSA, obesity, HTN) highly contributes to the success of maintaining normal sinus rhythm post-ablation. This procedure is not without risks, as major complications, such as pulmonary vein stenosis, TE events, cardiac tamponade, and new AFl, have been reported in 4.5% of patients.[59]

C—Cardiovascular and Comorbidity Optimization

Cardiovascular burden and comorbidities, such as obesity, hypertension, diabetes, and sleep apnea, play a role in atrial structural and electrical remodeling; thus, the development of AF.[5] Weight loss can reduce AF episodes and reoccurrence after ablation. Furthermore, weight loss can reduce blood pressure, Hgb A1C, and cholesterol, which leads to better cardiovascular health. Other lifestyle interventions a patient should engage in are abstaining from alcohol and incorporating physical activity, except for endurance training, as this can precipitate AF.

Patients with hypertension have a 1.7-fold higher risk of AF than a patient with normal blood pressure and should be treated to a goal blood pressure of ≤130/80 mm Hg.[5] Patients with diabetes have a twofold higher prevalence of AF than those without diabetes. Moreover, diabetes places patients at a higher risk for stroke. Roughly 50% of patients with AF have sleep apnea. When managed with continuous positive airway pressure, the recurrence of AF may be ameliorated. Controlling these disease states reduces a patient's risk of developing AF, the number of occurrences the patient experiences, and the success of rhythm control management.

Paroxysmal Supraventricular Tachycardia

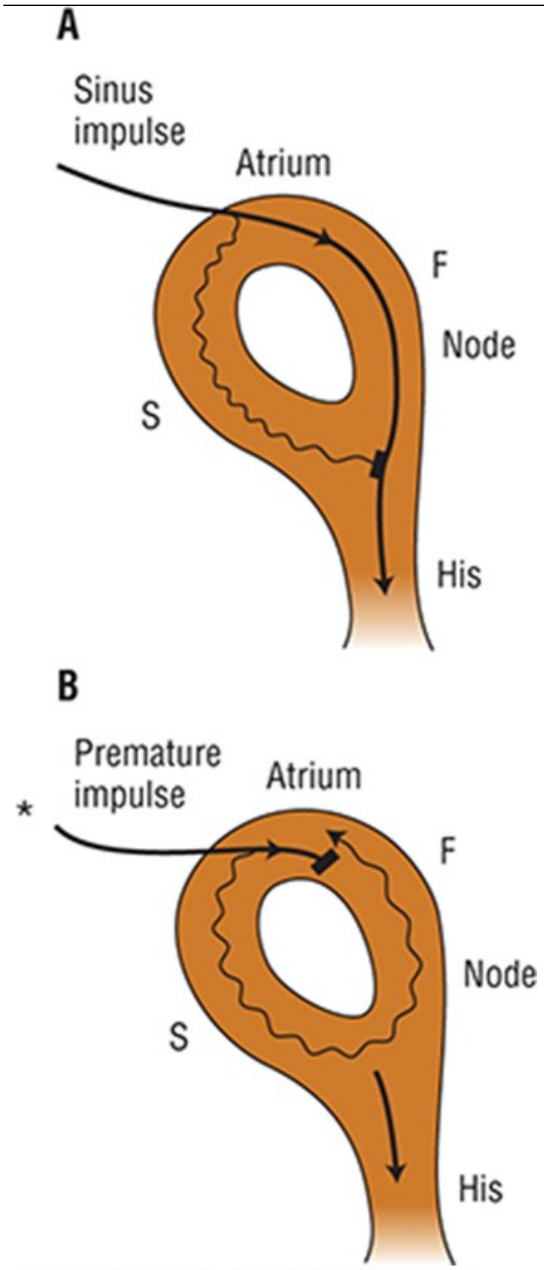
5 PSVT generated by reentrant mechanisms includes AV nodal reentry (ie, AVNRT), AV reentry incorporating an accessory pathway (ie, AVRT), SA nodal reentry, and intra-atrial reentry. AVNRT and AVRT are, by far, the most common of these tachycardias.

AVNRT is usually seen in middle-aged adults without heart disease and more than 60% of cases occur in females.[60] The ventricular rate can range from 110 beats/min to more than 250 beats/min. This arrhythmia can spontaneously occur or be provoked by exertion, coffee, tea, or alcohol. Patients generally tolerate AVNRT hemodynamically; however, many are highly symptomatic.[53]

The underlying substrate of AVNRT is the functional division of the AV node into two (or more) longitudinal conduction pathways or "dual" AV nodal pathways.[61] There are not two distinct anatomic pathways inside the AV node itself; rather, it is likely that a fan-like network of perinodal fibers inserts into the AV node and represents the second pathway. The pathways possess key differences in conduction characteristics: one is a fast-conducting pathway with a relatively long refractory period (fast pathway) and the other is a slower-conducting pathway with a shorter refractory period (slow pathway). The presence of dual pathways does not necessarily imply that the patient will have clinical PSVT. In fact, it is estimated that between 10% and 50% of patients have discernible dual pathways, but the incidence of AVNRT is considerably lower.[61] Sustenance of the tachycardia depends on the critical electrophysiologic discrepancies and the ability of one pathway (usually the slow) to allow repetitive antegrade conduction, and the ability of the other pathway (usually the fast) to allow repetitive retrograde conduction. During SR, a patient with dual pathways conducts the impulses antegrade through both pathways but reaches the distal common pathway first through the fast AV nodal route and continues to depolarize the ventricles in an antegrade direction (Fig. 40-9).

FIGURE 40-9

Reentry mechanism of dual AV nodal pathway PSVT. (*A*) Sinus rhythm: the impulse travels from the atrium through the fast pathway, F, and then to the distal common pathway and the His-Purkinje system (*His*). The impulse also travels through the slow pathway, S, but is stopped when refractory tissue is encountered. (*B*) Dual AV nodal reentry: a critically timed premature impulse, *, is stopped in the fast pathway, F (because of prolonged refractoriness) but is able to travel antegrade down the slow pathway, S, and retrograde through the fast pathway. (AV, atrioventricular; PSVT, paroxysmal supraventricular tachycardia.)



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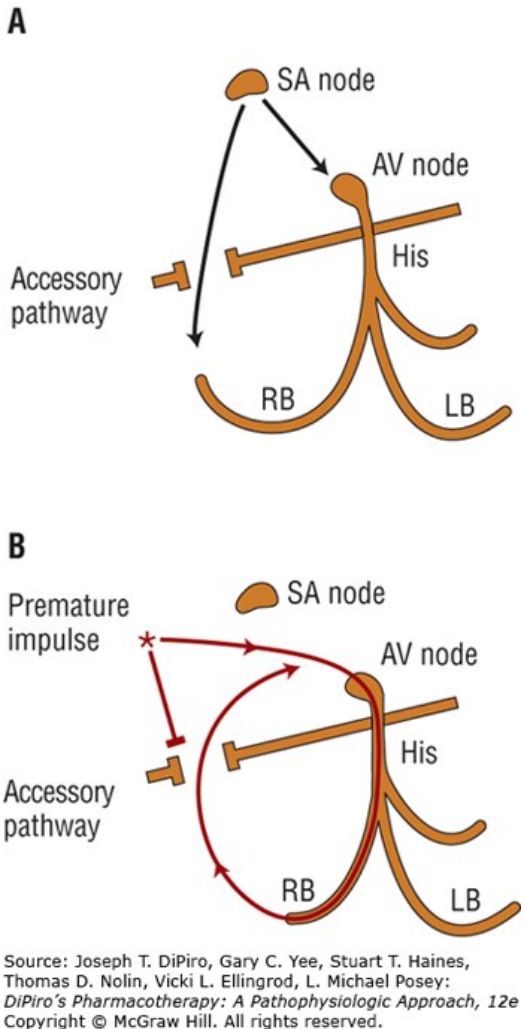
The mechanism behind AVNRT may occur by the following sequence of events. The occurrence of a properly timed premature atrial impulse penetrates the AV node but is blocked in the fast pathway that is still refractory from the previous beat. However, the slow pathway, which has a shorter refractory period, permits antegrade conduction of the premature impulse. By the time the impulse has reached the distal common pathway, the fast pathway has recovered its excitability and now will permit retrograde conduction. The impulse then reaches the common proximal pathway, reenters the slow pathway, and the tachycardia is initiated. This reentrant circuit does not require atrial or ventricular tissue; it is completed within the AV node. The common form of this tachycardia uses the slow pathway for antegrade conduction and the fast pathway for retrograde conduction; an uncommon form exists in which the reentrant impulse travels in the opposite direction.

AVRT is generally seen in young adults, and like AVNRT, it is generally well tolerated. However, it can be less benign than AVNRT as it can cause syncope. AVRT depends on the presence of an accessory pathway that bypasses the normal AV conduction pathway. Several different types of accessory pathways have been described, depending on the specific anatomic areas they connect (eg, AV or nodoventricular tracts). During SR (Fig. 40-10), patients with an accessory pathway that can conduct antegrade depolarize the ventricles simultaneously through both the AV nodal and accessory

pathway, causing ventricular preexcitation and creating a fusion pattern on the early portion of the QRS complex (known as a delta wave). Patients may have an accessory pathway that is not evident on ECG, which is referred to as a “concealed” accessory pathway. These concealed accessory pathways are often incapable of antegrade conduction and can only accept electrical stimulation in a retrograde fashion. The electrocardiographic expression of a delta wave depends on the location of the accessory pathway, the distance from the wave front of sinus activation, and the conduction characteristics of the various structures involved. Similar to patients with dual AV nodal pathways, not all patients with an accessory AV pathway are capable of having clinical PSVT, characterized as Wolff-Parkinson-White (WPW) syndrome.

FIGURE 40-10

Reentry mechanism for AV accessory pathway PSVT in Wolff-Parkinson-White syndrome. (*A*) Sinus rhythm: the impulse travels from the atrium to the ventricle by two pathways—the AV node and an accessory bypass pathway. (*B*) AV reentry: a critically timed premature impulse (*) is stopped in accessory pathway (because of prolonged refractoriness) but travels antegrade through the AV node and retrograde through accessory pathway. (AV, atrioventricular; His, His-Purkinje system; LB, left bundle branch; PSVT, paroxysmal supraventricular tachycardia; RB, right bundle branch; SA, sinoatrial.)



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6 WPW syndrome can occur as orthodromic AVRT, antidromic AVRT, and/or AF. AVRT usually occurs by the following sequence of events. Analogous to AVNRT, two pathways (eg, the normal AV nodal pathway and the accessory AV pathway) exist that have different electrophysiologic characteristics. The AV nodal pathway usually has a relatively slower conduction velocity and shorter refractory period, and the accessory pathway has a faster conduction velocity and a longer refractory period. A critically timed premature atrial impulse may be blocked in the accessory pathway because this area is still refractory from the previous sinus beat. However, the AV nodal pathway, with a relatively shorter refractory period, may accept antegrade conduction of the premature atrial impulse. Meanwhile, the accessory pathway may recover its excitability and now allow retrograde conduction. A

macroreentrant tachycardia is thereby initiated in which the antegrade pathway is the AV nodal pathway, the distal common pathway is the ventricle, the retrograde pathway is the accessory pathway, and the proximal common pathway is the atrium (see Fig. 40-10). Additionally, this macroreentrant tachycardia could also be initiated by a premature ventricular impulse that first conducts retrograde over the accessory pathway, then antegrade through the AV nodal pathway. This sequence of events (down the AV node, up the accessory pathway), termed *orthodromic AVRT*, is the common variety of reentry in patients with an accessory AV pathway, resulting in a narrow QRS tachycardia (Fig. 40-6). In the uncommon variety, conduction proceeds in the opposite direction (down the accessory pathway, up the AV node), resulting in a wide QRS tachycardia, which is termed *antidromic AVRT*. Patients with WPW syndrome can have a third type of tachycardia, namely, AF. The occurrence of AF in the setting of an accessory AV pathway can be extremely serious. As AF is an extremely rapid atrial tachycardia, conduction can proceed down the accessory AV pathway, resulting in a very fast ventricular response or even VF and SCD. Unlike the AV nodal pathway, the refractory period of the accessory pathway shortens in response to rapid stimulation rates.

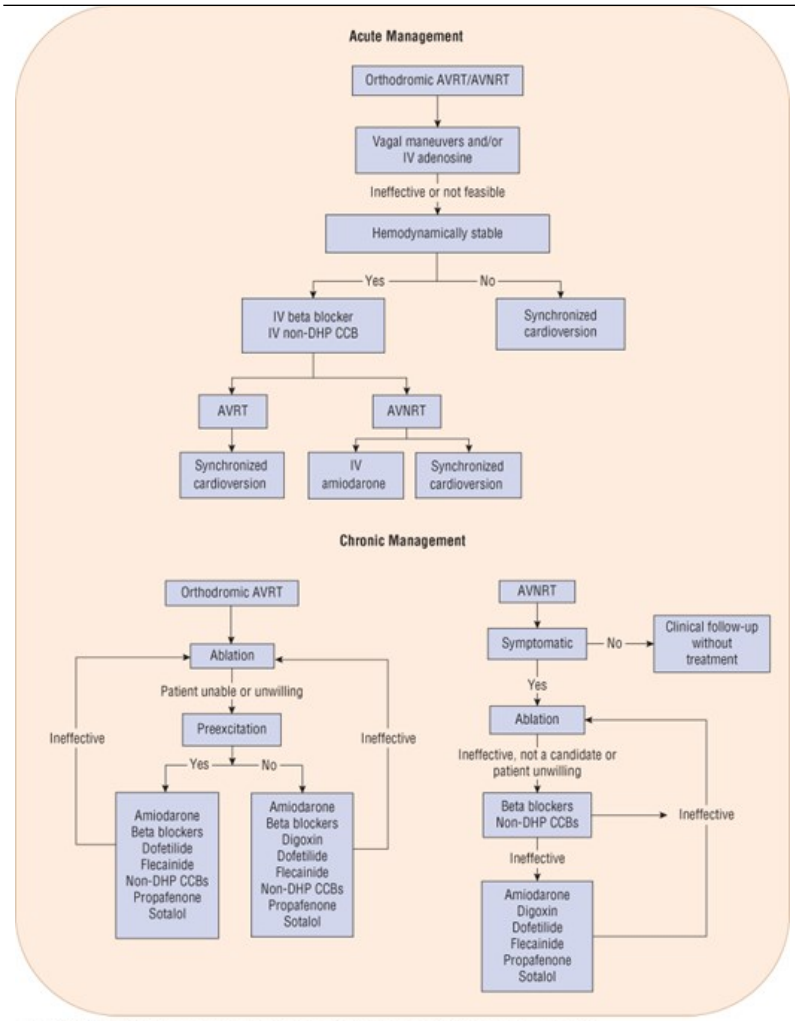
General Approach to Treatment

Both pharmacologic and nonpharmacologic methods have been used to treat patients with PSVT. Medications used in the treatment of these arrhythmias can be divided into three broad categories: (a) those that directly or indirectly increase vagal tone to the AV node (eg, digoxin); (b) those that depress conduction through slow, calcium-dependent tissue (eg, adenosine, β-blockers, and non-DHP CCBs); and (c) those that depress conduction through fast, sodium-dependent tissue (eg, quinidine, procainamide, disopyramide, and flecainide). Medications within these categories alter the electrophysiologic characteristics of the reentrant substrate so that PSVT cannot be sustained. In PSVT caused by AVNRT, class I AADs, such as flecainide, act primarily on the retrograde fast pathway. Digoxin and β-blockers may work on either the retrograde fast or the antegrade slow pathway. Verapamil, diltiazem, and adenosine prolong conduction time and increase refractoriness, primarily in the slow antegrade pathway of the reentrant loop. In PSVT caused by AVRT, class I AADs increase refractoriness in the fast accessory pathway or within the His-Purkinje system. β-Blockers, digoxin, adenosine, and verapamil all act by their effects on the AV nodal (antegrade, slow) portion of the reentrant circuit. Regardless of the mechanism, treatment measures are directed first at terminating an acute episode of PSVT and then at preventing symptomatic recurrences of the arrhythmia.

Acute management (Fig. 40-11) for patients with AVNRT or orthodromic AVRT includes vagal maneuvers and/or adenosine.[53] Vagal techniques, such as unilateral carotid sinus massage, Valsalva maneuver, ice water facial immersion, or induced retching, are about 20% successful in terminating these PSVTs. Carotid massage and Valsalva maneuver are the simplest, least obtrusive, and most frequently used of these techniques. Should these techniques and/or adenosine be ineffective or unfeasible in a hemodynamically unstable patient (ie, syncope, pre-syncope, angina, or severe HF), synchronized DCCV is the next step. Even at low energy levels (such as 25 J), DCCV is almost always effective in quickly restoring SR and correcting symptomatic hypotension. If vagal techniques and/or adenosine are ineffective or unfeasible in patients who are hemodynamically stable, the next course of action would be to administer IV β-blockers or non-DHP CCBs (oral could be used with AVNRT). Approximately 80% to 98% of patients with a narrow QRS, regular arrhythmia (AVNRT or orthodromic AVRT) given adenosine (6 to 12 mg) will revert to SR within seconds; and those given IV verapamil (5 to 10 mg), IV diltiazem (15 to 25 mg) will revert to SR within 5 minutes.[62] However, if AVNRT is unable to be corrected with these measures, IV amiodarone can be utilized.[53] For patients with AVRT, the next step would be synchronized cardioversion.

FIGURE 40-11

Algorithm for the treatment of acute (*top panel*) orthodromic AVRT/AVNRT and chronic prevention of recurrences (*bottom panel*). (AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; IV, intravenous; non-DHP CCBs, non-dihydropyridine calcium channel blockers.) *Note*: Medications are listed in alphabetical order, not in order of preference.



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Should a patient have preexcited AF, synchronized cardioversion should be used if hemodynamically unstable.[53] If the patient is hemodynamically stable, IV ibutilide or procainamide can be administered. IV digoxin, IV amiodarone, oral or IV β-blockers, diltiazem, and verapamil should be avoided in patients with preexcited AF as they may increase conduction over the accessory pathway leading to an increase in the ventricular rate and enhance the risk of provoking a life-threatening ventricular arrhythmia.

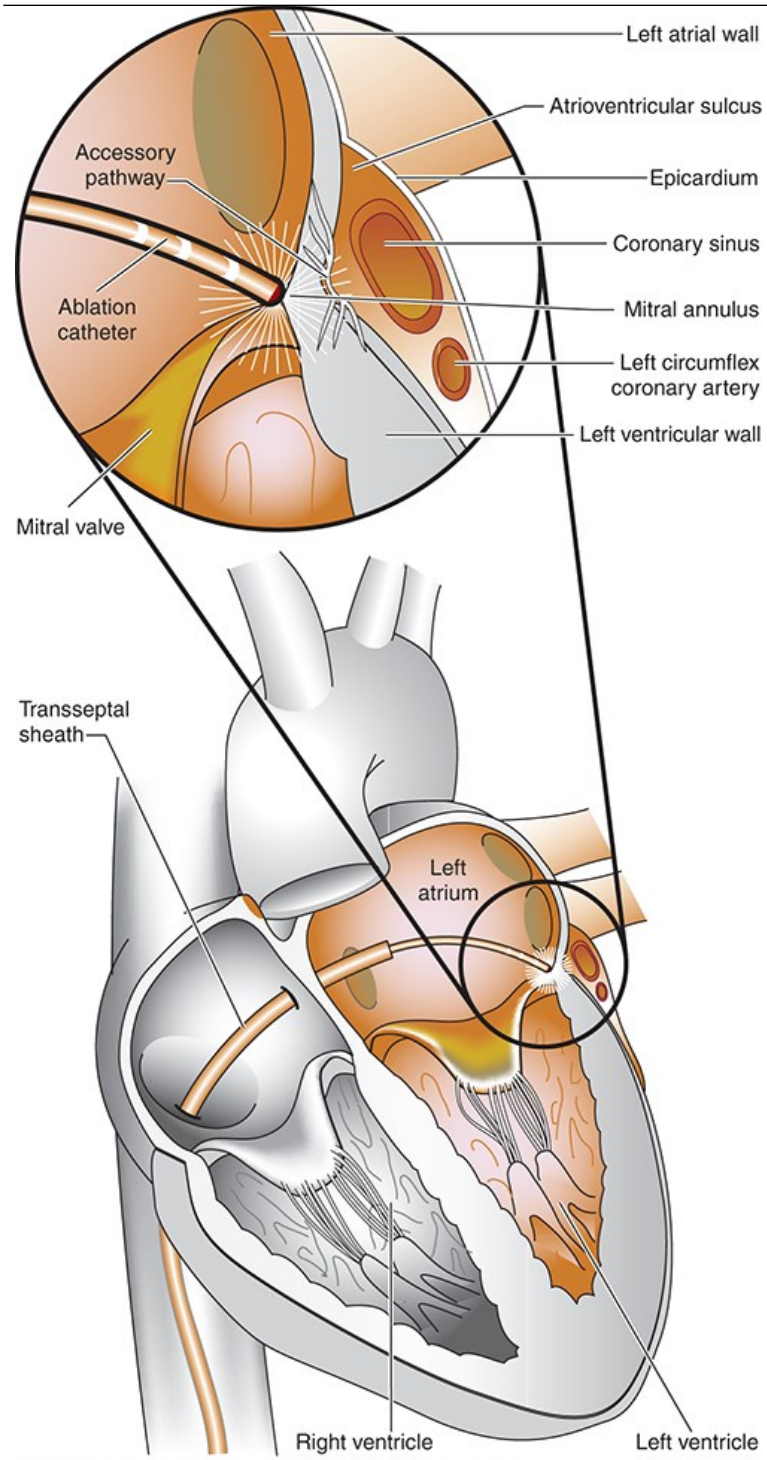
Once the acute episode of AVNRT or AVRT is terminated, a decision on long-term preventive therapy must follow (Fig. 40-11). Preventive treatment is indicated if: (a) frequent episodes occur that necessitate therapeutic intervention (ie, emergency department visits) or cause symptoms that interfere with the patient's lifestyle; or (b) episodes are infrequent but cause severe symptoms. If preventive treatment is deemed necessary, either medication therapy or catheter ablation can be used.

AADs are no longer the treatment of choice to prevent recurrences of reentrant PSVT for the following reasons: (a) lifelong treatment is necessary in these generally young but otherwise healthy individuals; (b) there are few, if any, large controlled or comparative trials to assist the clinician in rationally choosing effective agents; and (c) most importantly, other nonpharmacologic treatments are clearly more effective. Nevertheless, medication therapy may occasionally be necessary in some patients, particularly those with mild symptoms and infrequent recurrences. A trial-and-error approach may be used, complemented by the use of ambulatory electrocardiographic recordings (Holter) or telephonic transmissions of cardiac rhythm (event monitors) to objectively document the efficacy or failure of the chosen medication regimen. Medications known to be effective in preventing recurrences of these arrhythmias are the AV nodal blocking medications (digoxin, β-blockers, non-DHP CCBs, and combinations of these agents) and the class Ic AADs (flecainide, propafenone).[53] Sotalol, dofetilide, and amiodarone can be considered alternatives. Although rarely used, digoxin is only indicated in orthodromic AVRT without preexcitation.

Catheter ablation using radiofrequency current on the PSVT substrate has dramatically altered the traditional treatment of these patients (Fig. 40-12). Radiofrequency ablation is highly effective, preventing the recurrences of PSVT in more than 90% of patients.[63,64] The procedure was originally used in patients with WPW syndrome.[63] In these patients, the extranodal pathway is most often located at the left lateral free wall between the left atrium and ventricle at the level of the mitral valve (see Fig. 40-12). During invasive electrophysiologic studies, portions of the reentrant circuit can be located (or mapped) using several catheters. Once this is completed, either radiofrequency or cryo ablation is performed, causing cell death in the tissue necessary for reentry. In this way, the substrate for reentry is destroyed, "curing" the patient of recurrent episodes of PSVT and obviating the need for chronic medication therapy. Thereafter, a similar approach was developed for patients with AVNRT, placing the catheter just anterior to the coronary sinus, below the His bundle and in the region of the slow pathway.[64] The preferred method in these individuals is to apply lesions to the slow pathway of the reentrant circuit in order to modify its properties enough so that AVNRT cannot recur. Complications, although unusual, include cardiac tamponade, pericarditis, valvular insufficiency, and AV block. Ablation of the extranodal connection occurs promptly, and evidence of preexcitation (delta waves) disappears.

FIGURE 40-12

Drawing showing catheter placement for radiofrequency ablation of a left lateral free wall accessory pathway. Here, a venous (atrial) transseptal puncture to gain access to accessory pathway is shown; a retrograde arterial approach has also been used. (*Reprinted with permission from Lerman BB, Basson CT. High risk patients with ventricular preexcitation: A pendulum in motion. N Engl J Med 2003;349:1787–1789. Copyright © 2003 Massachusetts Medical Society. All rights reserved.*)



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Catheter ablation is the preferred treatment strategy (over AADs) for patients with symptomatic PSVT because the procedure is highly effective and curative, rarely results in complications, and obviates the need for chronic AAD therapy.[53]

Ventricular Arrhythmias

The common ventricular arrhythmias include (a) premature ventricular complexes (PVCs), (b) VT, and (c) VF. These arrhythmias may result in a wide

variety of symptoms. PVCs often cause no symptoms or only mild palpitations. VT may be a life-threatening situation associated with hemodynamic collapse or may be totally asymptomatic. VF, by definition, is an acute medical emergency necessitating cardiopulmonary resuscitation (CPR).

Premature Ventricular Complexes and Sudden Cardiac Death

PVCs (Fig. 40-6) are very common ventricular rhythm disturbances that occur in patients with or without SHD. Experimental models show that PVCs may be elicited by abnormal automaticity, triggered activity, or reentrant mechanisms. PVCs are commonly observed in healthy individuals; in these patients, the PVCs seem to have little, if any, prognostic significance. PVCs occur more frequently and in more complex forms in patients with SHD than in healthy individuals. The prognostic meaning of PVCs has been well studied in patients with MI (acute or remote) with several consistent themes. Patients with some forms of PVCs (ie, multifocal or couplets) are at higher risk for SCD, defined as unexpected death (without an obvious noncardiac cause) occurring in a patient within 1 hour of experiencing symptoms (witnessed episodes) or within 24 hours of last being observed in normal health (unwitnessed episodes).[65] Studies of patients who experienced SCD (and happened to be wearing an electrocardiographic monitor at the time) often demonstrate the cause to be VF preceded by a short run of VT and frequent PVCs.[66]

Clinical Presentation

CLINICAL PRESENTATION: Ventricular Arrhythmias

Premature Ventricular Contractions (PVCs)

General

- PVCs are not acutely life-threatening in a patient with a structurally normal heart and usually asymptomatic. A high frequency of PVCs (>20% of all beats) can cause ventricular dysfunction.

Symptoms

- Occasionally, patients will complain of palpitations or uncomfortable heartbeats. Since the PVC, by definition, occurs early and the ventricle contracts when it is incompletely filled, often the aortic valve will not open. The ensuing compensatory pause allows for an increase in left ventricular filling causing the next sinus beat have a more forceful contraction which can result in symptoms.

ECG Findings

- Premature, oddly shaped QRS complex that is unusually wide (Fig. 40-6).

Ventricular Tachycardia (VT)

General

- Patients can be asymptomatic or become hemodynamically compromised depending on their degree of underlying structural heart disease and rate of tachycardia.

Symptoms

- The symptoms of VT (monomorphic VT or TdP), if prolonged (ie, sustained), can vary from nearly completely asymptomatic to pulseless, hemodynamic collapse. Fast heart rates and underlying poor LV function will result in more severe symptoms. Symptoms of nonsustained, self-terminating VT also correlate with duration of episodes (eg, patients with 15-second episodes will be more symptomatic than those with three-beat episodes).

ECG Findings

- Wide QRS complexes at a rate >100 beats/min (Fig. 40-6).

Ventricular Vibrillation (VF)

General

- Cardiac output and blood pressure are not recordable.

Symptoms

- By definition, VF results in hemodynamic collapse, syncope, and cardiac arrest.

ECG Findings

- Lack of organized electrical activity, coarse fibrillation waves are seen. (Fig. 40-6).

General Approach to Treatment

Historically, investigators promoted the concept that patients in the acute phase of MI may have types of PVCs that are predictive of VF and SCD. These types of PVCs were referred to as “warning arrhythmias” and included frequent ventricular ectopy (more than 5 beats/min), multiform configuration

(different morphology), couplets (two in a row), and R-on-T phenomenon (PVCs occurring during the repolarization phase of the preceding sinus beat in the vulnerable period of ventricular recovery). However, as a result of using continuous electrocardiographic monitoring techniques, it is apparent that almost all patients have warning arrhythmias in the acute MI setting. In those patients who experience VF, warning arrhythmias are no more common than in those without VF. Consequently, warning arrhythmias observed during acute MI are neither sensitive nor specific for determining which patients will have VF. Thus, there is little need to direct medication therapy specifically at PVC suppression in these patients. Studies show that effective prevention of VF in the acute MI setting may be achieved without the abolition of PVCs.

Conversely, data strongly imply that PVCs documented in the convalescence period of MI do carry important long-term prognostic significance.[67] PVCs occurring after an MI seem to be a risk factor for patient death that is independent of the degree of LV dysfunction or the extent of coronary atherosclerosis. Using a classification of PVCs (simple or benign [infrequent and monomorphic] versus complex [at least 5 PVCs/min, couplets, R-on-T beats, and multiform]), investigators found that complex (but not simple) ventricular ectopy in the setting of CAD was associated with a higher incidence of overall mortality and cardiac death.[67]

PVCs carry little or no risk when the frequency is low and individuals are without SHD; thus, medication therapy is unnecessary. However, because of the prognostic significance of complex PVCs in patients with SHD, the use of AAD therapy to suppress them has been controversial. Historically, many supported the aggressive use of AAD therapy to suppress PVCs, based on the underlying premise of eliminating a risk factor for SCD in patients with CAD (namely, the presence of complex PVCs). However, others favored a more conservative approach and disregarded the use of AAD therapy in the absence of significant symptoms. An important study, the Cardiac Arrhythmia Suppression Trial (CAST), abruptly put an end to this debate. This trial was conducted to determine if suppression of ventricular ectopy with encainide, flecainide, or moricizine could decrease the incidence of death from arrhythmia in patients who had suffered an MI.[68] In the trial, patients with an LVEF less than or equal to 55% (0.55) (if recruited within 90 days of the MI) or an LVEF less than or equal to 40% (0.40) (if recruited at least 90 days after the MI) were randomized to receive encainide, flecainide, moricizine, or placebo. Compared with placebo, treatment with encainide or flecainide was associated with a significantly higher rate of total mortality and death due to arrhythmia, presumably caused by proarrhythmia. Analysis of the moricizine arm indicated neither harm nor benefit; therefore, only this portion of the study was allowed to continue as CAST II.[69] However, CAST II was also prematurely discontinued because there was a trend toward an increase in mortality in moricizine-treated patients. Quinidine and sotalol have also been shown to increase the risk of death in patients with a HFrEF and PVCs.[70]

Currently, only two AADs have been shown *not* to increase mortality in post-MI patients with long-term use: amiodarone and dofetilide. A number of trials have shown amiodarone to decrease the incidence of sudden (or arrhythmic) death, but not total mortality, in post-MI patients with complex ventricular ectopy.[71,72] Clearly, because of its impressive side effect profile and its inability to improve survival, amiodarone should not routinely be recommended in patients with heart disease such as remote MI and complex PVCs. Two randomized controlled trials have also shown that chronic therapy with dofetilide has no effect on overall mortality in post-MI patients with LV dysfunction.[73,74]

These results have clearly had a negative influence on the long-term use of all AADs, causing a broad skepticism in the risk-versus-benefit analysis of these medications. Consequently, pharmaceutical companies have shifted their medication discovery and investigative efforts away from potent sodium channel blockers. The findings of the CAST have also provided additional fuel for the pursuit of nonpharmacologic therapies for arrhythmias, such as catheter ablation and implantable devices.

7 How should the clinician approach the patient with documented asymptomatic PVCs? Clearly, attempts to suppress asymptomatic PVCs should *not* be made with any AAD. Indeed, those patients who are at risk for arrhythmic death (recent MI, LV dysfunction, complex PVCs) should also *not* be routinely given *any* class I or III AAD.[70] In post-MI patients, the use of β-blockers is associated with a reduction in mortality and SCD, especially in the presence of LV dysfunction. β-Blockers and non-DHP CCBs can be used in patients without underlying SHD to suppress symptomatic PVCs. If neither is effective in reducing recurrence and symptoms, class Ic AADs, amiodarone, or sotalol can be used. Uncommonly, patients have such frequent PVCs that are either extremely bothersome or result in the development of cardiomyopathy leading to a decline in left ventricular function (usually when the PVCS greater than 20% of all beats).[70] In these patients, ablation of the PVCs can be pursued.

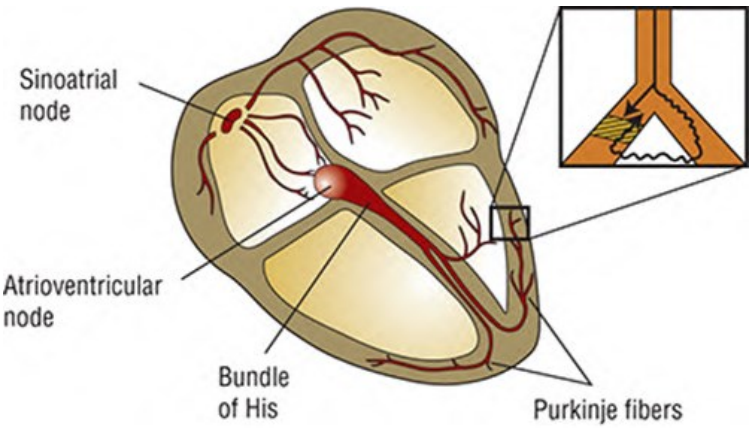
Ventricular Tachycardia

VT is a wide QRS tachycardia (Fig. 40-6) that may acutely occur because of metabolic abnormalities, ischemia, or medication toxicity, or chronically recur as a paroxysmal form. On the ECG, VT may appear as repetitive monomorphic or polymorphic ventricular complexes. The definition of VT is three

or more consecutive PVCs occurring at a rate of greater than 100 beats/min. An acute episode of VT may be precipitated by severe electrolyte abnormalities (hypokalemia or hypomagnesemia), hypoxia, or digoxin toxicity, or (most commonly) may occur in patients presenting with acute MI or myocardial ischemia complicated by HF. In these cases, correction of the underlying precipitating factors will usually prevent further recurrences of VT. As an example, if VT occurs during the first 24 hours of an acute MI, it will probably not reappear on a chronic basis after the infarcted area has been reperfused or healed with scar formation. This form of acute VT may be caused by a transient reentrant mechanism within temporarily ischemic or dying ventricular tissue. In contrast, some patients have a chronic, recurrent form of VT that is almost always associated with some type of underlying SHD. Common examples are paroxysmal VT associated with idiopathic dilated cardiomyopathy or remote MI with an LV aneurysm. In chronic, recurrent VT, microreentry within the distal Purkinje network and myocardium is responsible for the underlying substrate in a large majority of patients (see Fig. 40-13). Theoretically, electrophysiologic abnormalities occur as a result of structural damage and heart disease within the ventricular conducting system. The reentrant circuit may possess both anatomically determined and functional properties coursing through normal tissue, damaged (but not dead) tissue, and islands of necrosed tissue. In a minority of patients, macroreentrant circuits may be responsible for recurrent VT, including reentry incorporating the bundle branches. Patients with acute VT associated with a precipitating factor often suffer severe symptoms, requiring immediate treatment measures. Chronic, recurrent VT may also cause severe hemodynamic compromise but may also be associated with only mild symptoms that are generally well tolerated. The severity of symptoms is reliant upon the rate of the tachycardia and the patient's underlying heart disease and ventricular function.

FIGURE 40-13

Conduction system of the heart. The magnified portion shows a bifurcation of a Purkinje fiber traditionally explained as the etiology of reentrant VT. A premature impulse travels to the fiber which is damaged by heart disease or ischemia. It encounters a zone of prolonged refractoriness (area of unidirectional block; *cross-hatched area*) but fails to propagate because the fiber remains refractory to stimulation from the previous impulse. However, the impulse may slowly travel (*squiggly line*) through the other portion of the Purkinje twig and will "reenter" the cross-hatched area if the refractory period is concluded and the fiber is now excitable. Thus, the premature impulse never meets refractory tissue; circus movement ensues. If this site stimulates the surrounding ventricle repetitively, clinical reentrant VT results. (VT, ventricular tachycardia.)



Sustained VT is that which requires therapeutic intervention to restore a stable rhythm or persists for a relatively long time (usually more than 30 seconds). Nonsustained VT is that which self-terminates after a brief duration (usually less than 30 seconds). Patients who experience VT more frequently than SR (ie, VT is the dominant rhythm) are considered to have incessant VT. In monomorphic 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. A characteristic type of polymorphic VT, in which the QRS complexes appear to undulate around a central axis and that is associated with evidence of delayed ventricular repolarization (long QT interval or prominent U waves), is referred to as TdP.

Most, but not all forms of recurrent VT occur in patients with extensive SHD. VT occurring in a patient without SHD is sometimes referred to as idiopathic VT and may take several forms, including fascicular VT and ventricular outflow tract VT.[75-77] Fascicular VT arises from a fascicle of the left bundle branch (usually posterior) and is usually not associated with severe underlying SHD. Non-DHP CCBs are effective in terminating an acute

episode of fascicular VT. Ventricular outflow tract VT (usually originating from the right ventricular outflow tract) originates from near the pulmonic valve (or uncommonly the aortic valve or LV outflow tract) and also occurs in patients with normal LV function without discernible SHD.[77] Unlike other forms of VT, right ventricular outflow tract VT often terminates with adenosine and may be prevented with β-blockers and/or non-DHP CCBs.

Some unusual forms of VT are congenital or heritable. TdP can be associated with heritable defects in the flux of ions that govern ventricular repolarization. Although multiple syndromes and genetic mutations have been described, the more common examples are long QT syndrome 1 (depressed I_{Ks}), long QT syndrome 2 (depressed I_{Kr}), and long QT syndrome 3 (enhanced, inward sodium ion flux during repolarization).[78] Polymorphic VT (without a prolonged QT interval) or VF may also occur due to a heritable defect in the sodium channel. This is the case in Brugada syndrome, which is described as a typical ECG pattern (ST-segment elevation in leads V_1 to V_3) in SR that is associated with SCD, and commonly occurs in young males.[70]

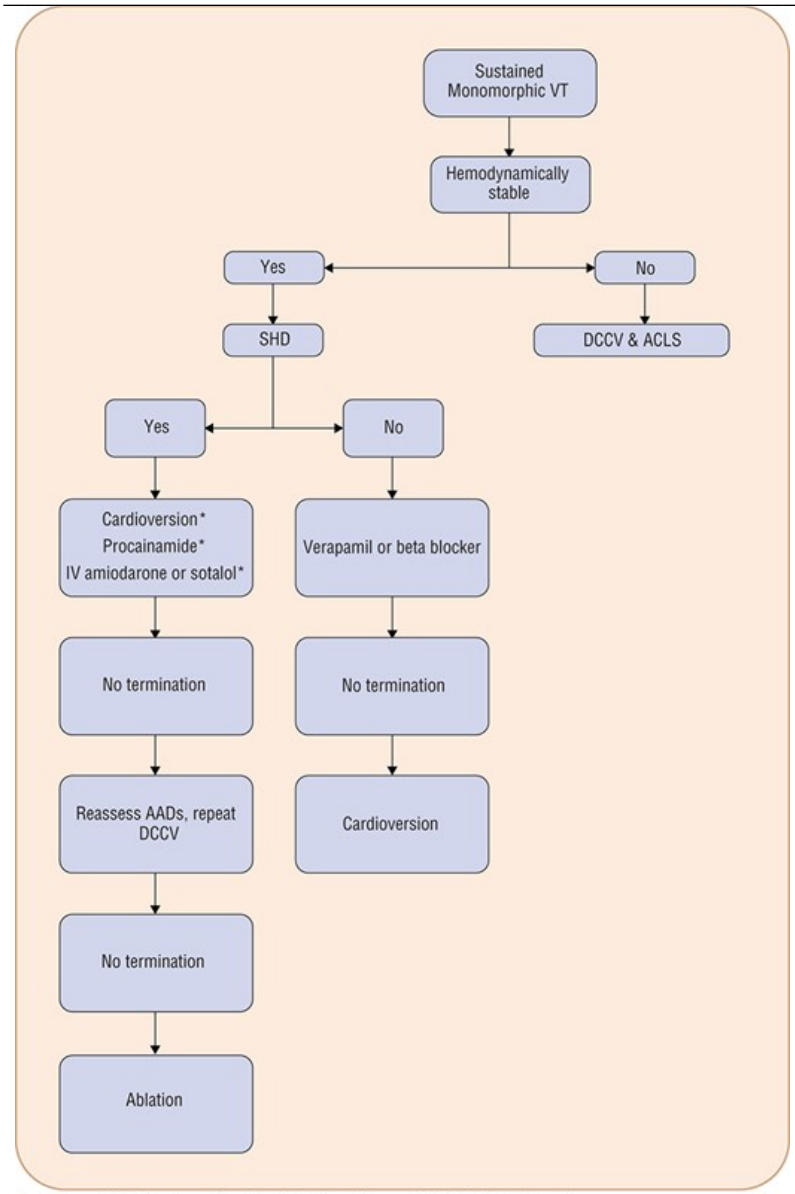
General Approach to Treatment

Consider the patient with the more common form of sustained monomorphic VT (ie, those with SHD, usually ischemic in nature). Like other rapid tachycardias, the initial management of an acute episode of VT (with a pulse) requires a quick assessment of the patient's signs and symptoms. An investigation should be made into possible precipitating factors, which should be corrected if possible. The diagnosis of acute MI should always be entertained. If the episode of VT is thought to be an isolated electrical event associated with a transient initiating factor (such as acute myocardial ischemia or digoxin toxicity), there is no need for long-term AAD therapy once the precipitating factors are corrected (eg, an MI has been reperfused and healed and the patient is stable). Nevertheless, the patient should be monitored closely for possible recurrences of VT.

Patients presenting with an acute episode of sustained monomorphic VT and hemodynamically instability should have advanced cardiovascular life support (ACLS) initiated immediately, including DCCV to restore SR.[79] In patients with stable monomorphic VT, treatment is driven by the presence of SHD. If a patient has SHD, cardioversion should be implemented and IV procainamide, amiodarone, or sotalol can be considered. For patients without SHD, verapamil and β-blockers are first-line options. See Fig. 40-14 for an algorithm to acutely manage monomorphic VT.

FIGURE 40-14

Acute management of ventricular tachycardia. *Treatment listed in order of level of evidence. (ACLS, acute cardiovascular life support; AAD, antiarrhythmic drug; DCCV, direct current cardioversion; SHD, structural heart disease; VT, ventricular tachycardia.) (*Data from Reference 70.*)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Once an acute episode of sustained VT has been successfully terminated by electrical or pharmacologic means and an acute MI has been ruled out, the possibility of a patient having recurrent episodes of VT should be considered. Evidence for the possibility of VT recurrence can often be gleaned from invasive electrophysiologic studies using programmed ventricular stimulation. Patients who survive an acute episode of sustained VT are at extremely high risk for death and the yield for finding an effective AAD via electrophysiologic testing is low. Amiodarone is the most effective (approximately 50% effective after 2 years) AAD in patients with recurrent VT. However, nonpharmacologic approaches have demonstrated impressive effectiveness in the treatment of recurrent VT/VF.[70] For instance, some forms of recurrent VT are amenable to catheter ablation therapy using radiofrequency current. This approach is highly effective (approximately 90%) in idiopathic VT (right ventricular outflow tract or fascicular VT), but less so in recurrent VT associated with a cardiomyopathic process or remote MI with LV aneurysm. In the latter patients, ablation is usually regarded as second-line therapy after other methods have failed.[80] Numerous trials have established ICDs as a superior treatment over AADs not only for the prevention of SCD in patients who have been resuscitated from an episode of cardiac arrest or had sustained VT ("secondary prevention") but also for the prevention of an initial episode of SCD in certain high-risk patient populations ("primary prevention").

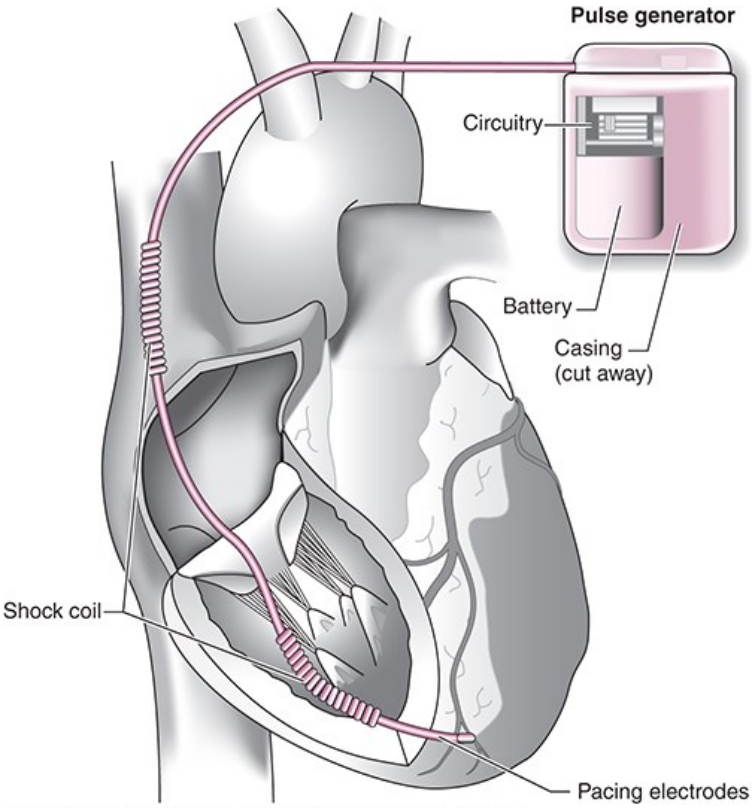
Implantable Cardioverter-Defibrillator

8 The introduction of and advances in the ICD (Fig. 40-15) have obviated the need for AADs to prevent episodes of life-threatening ventricular

arrhythmias.[70,81] Numerous advancements in device technology have allowed the ICD to become smaller, less invasive to implant, and programmable with advanced functions. Early ICDs required a thoracotomy to place the generator in the abdomen, whereas with the newer, smaller models, the leads are implanted transvenously with the generator placed into the pectoral region in a manner similar to cardiac pacemakers. Modern ICDs now employ a "tiered-therapy approach," meaning that overdrive or anti-tachycardia pacing (stimulates the heart to go faster than the rate induced by the VT) can be attempted first to terminate the tachyarrhythmia (no shock delivered), followed by low-energy cardioversion, and, finally, by high-energy defibrillation shocks. In addition, backup anti-bradycardia pacing and extended battery lives have made these newer devices much more attractive. All models store recordings during the delivery of pacing shocks, which is extremely important in discerning appropriate shocks (ie, delivers shock for serious ventricular arrhythmia) from inappropriate shocks (ie, delivers shock for AF with rapid ventricular rate) and in documenting true recurrences of the patient's tachycardia.

FIGURE 40-15

Drawing showing implantable cardioverter-defibrillator. (*Data from Reference 82.*)



Although ICDs are highly effective for preventing SCD due to recurrent VT or VF, several problems remain. First, the device itself, the implantation procedure, electrophysiologic studies, hospitalization, and physician fees are costly. Second, many patients with ICDs end up receiving concomitant AAD therapy (usually amiodarone or sotalol).[81,83] AADs can be initiated in these patients for a number of reasons including: (a) decreasing the frequency of VT/VF episodes to subsequently reduce the frequency of appropriate shocks; (b) reducing the rate of VT so that it can be terminated with anti-tachycardia pacing; and (c) decreasing episodes of concomitant supraventricular arrhythmias (eg, AF, AFl) that may trigger inappropriate shocks. As a result of these potential benefits, the concomitant use of AADs can minimize patient discomfort and prolong the battery life of the ICD. The decision to initiate concomitant AAD therapy should be individualized, with treatment usually being reserved for those patients with frequent shocks because of VT or AF.

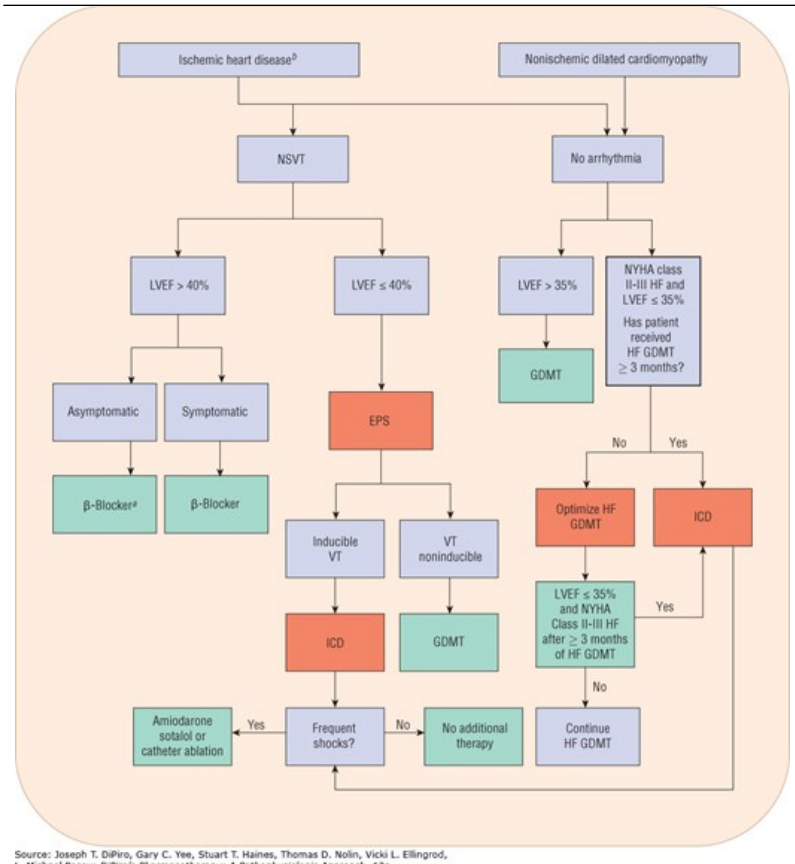
Prevention of Sudden Cardiac Death

First-line therapy for the secondary prevention of SCD is ICD implantation as the rate of survival is superior to that of AADs in patients who are at high risk for recurrent, life-threatening ventricular arrhythmias.[84-86] Patient populations at high risk for a first episode of SCD include those with a prior MI, HFrEF, and nonsustained VT. The use of AADs to prevent SCD in this high-risk group has been significantly limited by the results of the CAST and similar trials that have collectively demonstrated that these medications may increase mortality in these patients. As a result of these trials, clinicians have sought a more clearly defined strategy for risk stratification in these patients before initiating medication therapy.

9 For patients with nonsustained VT, there are four treatment strategies based upon symptoms and underlying comorbidities: (a) conservative (ie, no AAD treatment beyond β-blockers); (b) empiric amiodarone or sotalol; (c) ablation; and (d) aggressive (ie, electrophysiologic studies with possible insertion of an ICD) (Fig. 40-16).[70] A number of early studies suggested that tests such as electrophysiologic studies could be used to determine long-term risk in patients with nonsustained VT.[87,88] For instance, one study demonstrated that post-MI patients with nonsustained VT and inducible sustained VT after programmed stimulation were at increased risk for subsequent VT/VF or SCD compared with those in whom sustained VT could not be induced.[87] These data led to the evaluation of the efficacy of ICD therapy in this high-risk patient population.[89,90] The first trial to test this hypothesis randomized patients with a previous MI, HFrEF, asymptomatic nonsustained VT, and inducible VT that was not suppressed with the use of IV procainamide to receive an ICD or conventional medical therapy (74% received amiodarone).[89] This trial was terminated prematurely after a significant survival benefit was detected in the ICD group. A subsequent study randomized patients with a history of MI, HFrEF, and either asymptomatic nonsustained VT or inducible sustained VT to treatment using a conservative approach (no AAD therapy beyond β-blockers) or electrophysiologically guided therapy (AADs and/or ICD).[90] The conservative approach had a significantly higher event rate (cardiac arrest or death from arrhythmia). Furthermore, patients in the electrophysiologically guided group receiving only AADs (no ICD) had similar event rates to the conservative therapy group. In other words, only those treated with an ICD had a significantly lower event rate and greater survival. Based on the results of these trials, it is reasonable for patients with CAD, HFrEF, and nonsustained VT to undergo electrophysiologic testing.[70] If these patients do have inducible sustained VT/VF, implantation of an ICD is warranted.

FIGURE 40-16

Algorithm for the primary prevention of SCD in patients with a history of MI or with a nonischemic dilated cardiomyopathy. LVEF of 35% is equivalent to 0.35 expressed as a fraction. (a) In these patients, the β-blocker is being used to reduce post-MI mortality. (b) Patients should be >40 days post-MI and at least 90 days postrevascularization prior to insertion of the ICD. (EPS, electrophysiologic study; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained VT; SCD, sudden cardiac death; VT, ventricular tachycardia.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The effectiveness of ICDs in patients with nonsustained VT led to the study of their benefit in patients at high risk for but no prior history of ventricular arrhythmias. In a study of patients with a prior MI and HFrEF (prior history of ventricular arrhythmia or electrophysiologic testing not required), those treated with an ICD experienced a significant reduction in mortality compared with the conventional therapy group (routine post-MI and HF therapy).[91] The reduction in the ICD group was primarily due to a reduction in arrhythmic death. A similar study randomized patients with NYHA class II or III HFrEF (of either ischemic or nonischemic etiology) to receive placebo, amiodarone, or an ICD in addition to standard HF therapies.[92] Implantation of an ICD resulted in a significantly lower mortality rate compared with both placebo and amiodarone (there was no difference between placebo and amiodarone). The survival benefits of the ICD were observed regardless of the etiology of the HF.

9 Overall, as the ICD trials have evolved over the past decade, the indications for implanting these devices have significantly expanded, and many patients are eligible for an ICD.[70,93]

Ventricular Proarrhythmia

All AADs have the potential to aggravate existing arrhythmias or to cause new arrhythmias. AADs may cause proarrhythmia in nearly 30% of patients.[94] Many definitions for proarrhythmia have been proposed; however, in the simplest terms, it indicates the development of a significant new arrhythmia (such as VT, VF, or TdP) or worsening of an existing arrhythmia (episodes are longer, faster, or more frequent). As with all arrhythmias, the consequences of proarrhythmia are varied. Some patients who develop proarrhythmia may be totally asymptomatic, others may notice a worsening of symptoms, and some may die suddenly. The development of proarrhythmia results from the same mechanisms that cause arrhythmias in general (eg, quinidine-induced TdP due to EADs) or from an alteration in the underlying substrate due to the AAD (eg, development of an accelerated tachycardia caused by flecainide, which decreases conduction velocity without significantly altering the refractory period).[67] The diagnosis of proarrhythmia is sometimes difficult to make because of the variable nature of the underlying arrhythmias. However, in all cases, the AAD should be discontinued if proarrhythmia is detected or suspected.

Monomorphic Ventricular Tachycardia

The prototypical form of proarrhythmia caused by the class Ic AADs is a rapid, sustained, monomorphic VT with a characteristic sinusoidal QRS pattern that is often resistant to resuscitation with cardioversion or overdrive pacing. It is sometimes referred to as sinusoidal or incessant VT and is the result of excessive sodium channel blockade and slowed conduction. Sinusoidal VT caused by the class Ic AADs was thought to occur within the first several days of medication initiation. However, the results of the CAST indicate that the risk for this type of proarrhythmia may exist as long as the AAD is continued. Factors that can predispose a patient to this form of proarrhythmia include: (a) the presence of underlying ventricular arrhythmias; (b) CAD; and (c) LV dysfunction. Provocation of proarrhythmia by the class Ic AADs is sometimes reported during exercise, which is most likely a result of augmented slowed conduction at rapid heart rates (ie, rate-dependent sodium blockade). The incidence of proarrhythmia caused by class Ic AADs is greatest in patients with all three of the above risk factors (approximately 10%-20%) and extremely uncommon in those without these risk factors, such as patients with supraventricular tachycardias and normal LV function. Other factors that have a less well-defined association with proarrhythmia are elevated AAD serum concentrations and rapid dosage escalation of the AAD. The presence of underlying ventricular conduction delays may also pose a risk for proarrhythmia. As mentioned earlier, incessant monomorphic VT is often resistant to resuscitation. However, some have had success with lidocaine ("fast on–off" AAD, which successfully competes with a "slow on–off" agent such as flecainide for sodium channel receptor) or sodium bicarbonate (reverses the excessive sodium channel blockade).

Torsades de Pointes

TdP is a rapid form of polymorphic VT (Fig. 40-6) that is associated with evidence of delayed ventricular repolarization (long QT interval) on ECG. Most forms of polymorphic VT occurring in the setting of a normal QT interval are similar to monomorphic VT in terms of etiology and treatment strategies (thus, a long QT interval is crucial to the diagnosis of TdP). Much has been learned about the underlying etiology of TdP. Basic defects (genetic, medications, or diseases) that delay repolarization by influencing ion movement (usually by blocking potassium efflux) provoke EADs preferentially in cells deep in the heart muscle, which, in turn, trigger reentry and TdP. Drugs that cause TdP usually delay ventricular repolarization in an inhomogeneous way (termed *dispersion of refractoriness*), which facilitates the formation of multiple reentrant loops in the ventricle.[95] TdP may occur in association with hereditary syndromes or as an acquired form (ie, a result of medications or diseases). The underlying etiology in both cases is delayed ventricular repolarization due to blockade of potassium conductance. It is possible, however, that some individuals have a partially expressed form of these congenital syndromes but never suffer TdP unless some other external factor (eg, medications, diseases, electrolyte disturbances, abrupt heart rate changes) further delays ventricular repolarization. Specifically, acquired forms of TdP are associated with electrolyte disturbances (hypokalemia or hypomagnesemia), subarachnoid hemorrhage, myocarditis, liquid protein diets, arsenic poisoning, severe hypothyroidism, or, most commonly, medication therapy (notably phenothiazines, antibiotics, antihistamines, antidepressants, and AADs) (Table 40-13).

TABLE 40-13

Potential Causes of QT Interval Prolongation and Torsades de Pointes

Conditions

Congenital long QT syndromes
Heart failure
Hypokalemia
Hypomagnesemia
Myocardial ischemia/infarction
Myocarditis
Severe bradycardia (<50 beats/min)
Severe hypothermia
Severe starvation/liquid protein diets
Subarachnoid hemorrhage

Medications

Antiarrhythmic medications

- Amiodarone (<1%)
- Disopyramide
- Dofetilide
- Dronedarone
- Ibutilide
- Procainamide
- Quinidine
- Sotalol

Antiinfectives

- Azole antifungals (eg, fluconazole, voriconazole)
- Fluoroquinolones (eg, levofloxacin, moxifloxacin, gemifloxacin)
- Macrolides
- Pentamidine
- Chloroquine

Cancer chemotherapy or biologic agents

- Oxaliplatin
- Vandetanib

Methadone
Ondansetron (IV)
Psychotropics

- Citalopram
- Escitalopram
- Droperidol
- Haloperidol
- Phenothiazines (eg, thioridazine, chlorpromazine)
- Pimozide

Toxins

- Arsenic
- Organophosphate insecticides

IV, intravenous

Note: For a complete list, see www.crediblemeds.org.

The class Ia AADs (especially quinidine) and class III I_{Kr} blockers are most notorious for precipitating TdP; the class Ib and Ic AADs rarely, if ever, cause TdP as they do not appreciably delay repolarization. Most AADs with I_{Kr} blocking activity cause TdP in approximately 2% to 4% of patients, with the exceptions being amiodarone and dronedarone (less than 1%). Risk factors and associated features of medication-induced TdP have been identified and summarized in Table 40-14.[96] However, none of these associations are absolute prerequisites to the development of medication-induced TdP. For instance, although TdP is usually documented early in the course of quinidine therapy, patients may develop this arrhythmia anytime during chronic treatment.[97] The reason for quinidine's unique propensity for causing TdP at relatively low dosages and plasma concentrations requires explanation. Quinidine's ability to block I_{Kr} is clinically manifest at low plasma concentrations; at higher plasma concentrations, its sodium channel blocking properties predominate. Other medications that block I_{Kr} usually do so in a concentration-dependent fashion. The observation that most patients who suffer medication-induced TdP have evidence of mildly delayed repolarization (long QT intervals) even before they are prescribed the offending medication has stimulated a search for a potential genetically linked risk. Indeed, it appears that at least some patients with acquired medication-induced TdP possess mutations of genes that encode for I_{Kr} or I_{Ks}.[96]

TABLE 40-14

Risk Factors Associated with Drug-Induced Torsades de Pointes

High dosages or plasma concentrations of the offending medication
Concurrent SHD (eg, CAD, HF, and/or LV hypertrophy)
Prolonged QT interval at baseline
Prolonged QT interval shortly after initiation of the offending medication
Concomitant electrolyte disturbances (ie, hypokalemia or hypomagnesemia)
Female gender
A characteristic long-short initiating sequence of the TdP episode ()
Bradycardia
Concomitant QT interval prolonging medications

CAD, coronary artery disease; HF, heart failure; LV, left ventricular; SHD, structural heart disease; TdP, torsades de pointes.

The common underlying electrophysiologic cause of TdP is a delay in ventricular repolarization (provoking EADs), which usually results from inhibition (medication-induced or genetic) of the I_K current and manifests as QT interval prolongation on the ECG. Therefore, the extent of QT interval prolongation has been used as a measurement of risk of TdP. However, considerable controversy exists regarding this practice. Amiodarone, for example, commonly causes significant QT prolongation but is a relatively infrequent cause of TdP. Nonetheless, the QT interval should be measured and monitored in all patients prescribed medications that have a high potential for causing TdP (see Table 40-3). Patients with a prolonged QT_c interval at baseline (QT interval corrected for heart rate, which can be calculated using Bazett's formula: $QT_c = QTmeasured/\sqrt{R - RInterval}$QTc=QTmeasured/R−RInterval) (ie, greater than 450 msec in men; greater than 470 msec in women) should not be given medications that have a high potential for causing TdP. The development of clinically significant QTc interval prolongation (ie, QTc interval greater than 500 msec or an increase in the QTc interval of more than 60 to 70 msec from baseline) after initiation of a medication is an indication to discontinue the agent or, at least, to reduce its dosage and carefully

monitor.[98]

Drug-induced TdP has become an extremely visible hazard plaguing new medications, sometimes resulting in public health disasters. For instance, several medications (cisapride, astemizole, levomethadyl, grepafloxacin, sparfloxacin, terfenadine, and high-dose [32 mg] IV ondansetron) have been withdrawn from the market in the United States because of their significant potential for causing TdP. Thus, all new medication entities under investigation are screened for their ability to block I_K and cause significant QT prolongation.

Acute treatment of TdP is different than treatment for the more common acute monomorphic VT. For an acute episode of TdP, most patients will require and respond to defibrillation. However, TdP tends to be paroxysmal in nature and often will rapidly recur after defibrillation. Therefore, after the initial restoration of a stable rhythm, therapy designed to prevent recurrences of TdP should be instituted. AADs that further prolong repolarization, such as IV procainamide, are absolutely contraindicated. Lidocaine is usually ineffective. Although there are no true efficacy trials, IV magnesium sulfate, by suppressing EADs, is considered the medication of choice in preventing recurrences of TdP.[70] If IV magnesium sulfate is ineffective, treatment strategies designed to increase heart rate, shorten ventricular repolarization, and prevent the pause dependency should be initiated. Either temporary transvenous pacing (105-120 beats/min) or pharmacologic pacing (isoproterenol) can be initiated for this purpose. All medications that prolong the QT interval should be discontinued, and exacerbating factors (eg, hypokalemia or hypomagnesemia) should be corrected.

Ventricular Fibrillation

VF (Fig. 40-6) is electrical anarchy of the ventricle, resulting in no cardiac output and CV collapse. Death will ensue rapidly if effective treatment measures are not taken. Patients who die abruptly (within 1 hour of initial symptoms) and unexpectedly (ie, “sudden death”) usually have VF recorded at the time of death.[99] SCD accounts for more than 360,000 deaths per year in the United States.[13] It occurs most commonly in patients with CAD or LV dysfunction but occasionally in those without associated heart disease (eg, Brugada syndrome). When a patient experiences sudden cessation of cardiac activity with no normal breath or signs of circulation, they are said to have sudden cardiac arrest. CPR, medications, and defibrillation can be corrective measures to prevent SCD. If the event is not associated with acute MI, sustained VT and/or VF during electrophysiologic studies are often inducible. These individuals are at high risk for the recurrence of VT and/or VF. In contrast, patients who have VF associated with acute MI (ie, within 48 hours of hospital presentation) usually have little risk of recurrence.

In the presence of acute coronary syndrome, CAD should be treated. The patient’s LVEF should be reevaluated 40 days post-MI and 90 days post-revascularization.[70] If the LVEF is greater than 35% (0.35), the patient should be treated with medical management; however, if the LVEF is less than 35% (0.35), an ICD should be considered. Without acute coronary syndrome, the patient should be evaluated for SHD and inherited arrhythmia syndrome. Regardless, reversible causes should be eliminated (ie, discontinue the offending medication or correct electrolytes) and avoided. If no reversible cause is identified, an ICD can be considered.

Acute Management

A patient with pulseless VT or VF should have advanced cardiovascular life support (ACLS) initiated immediately, including defibrillation to restore SR.[100] A detailed discussion regarding the acute management of pulseless VT/VF can be found in Chapter 41, “Cardiopulmonary Arrest.”

Bradyarrhythmias

For the most part, the symptoms of bradyarrhythmias result from a decline in cardiac output. Because cardiac output decreases as heart rate decreases (to a point), patients with bradyarrhythmias may experience symptoms in association with hypotension, such as dizziness, syncope, fatigue, and confusion. If LV dysfunction exists, patients may experience worsening HF symptoms. Except in the case of recurrent syncope, symptoms associated with bradyarrhythmias are often subtle and nonspecific.

Sinus Bradycardia

Sinus bradyarrhythmias (heart rate less than 60 beats/min) are a common finding, especially in young, athletically active individuals, and usually are neither symptomatic nor in need of therapeutic intervention. On the other hand, some patients, particularly the elderly, have SND. This may be the result of underlying SHD and the normal aging process that attenuates SA nodal function over time, resulting in symptomatic sinus bradycardia and/or

periods of sinus arrest.[93] SND is usually reflective of diffuse conduction disease and accompanying AV block is relatively common. Furthermore, symptomatic bradyarrhythmias may be accompanied by alternating periods of paroxysmal tachycardias such as AF. In this instance, AF sometimes presents with a rather slow ventricular response (in the absence of AV nodal blocking medications) because of diffuse conduction disease. The occurrence of alternating bradyarrhythmias and tachyarrhythmias is referred to as the tachy-brady syndrome. The occurrence of paroxysmal AF in a patient with SND may be a result of underlying SHD with atrial dysfunction or atrial escape in response to reduced sinus node automaticity. In fact, because the rate of impulse generation by the sinus node is generally depressed or may fail altogether, other automatic pacemakers within the conduction system may "rescue" the sinus node. These rescue rhythms often present as paroxysmal atrial rhythms (eg, AF) or as a junctional escape rhythm.

The treatment of SND involves eliminating the symptomatic bradycardia and potentially managing alternating tachycardias such as AF. In general, the long-term therapy of choice is permanent pacemaker implantation.[81,93] Pacing clearly improves symptoms and overall quality of life and decreases the incidence of paroxysmal AF and systemic embolism. Drugs commonly employed to treat supraventricular tachycardias should be used with caution, if at all, in the absence of a functioning pacemaker. AADs prescribed to prevent AF recurrences may also suppress the escape or rescue rhythms that appear in severe sinus bradycardia or sinus arrest. Consequently, these medications may transform an asymptomatic patient with bradycardia into a symptomatic one. Other medications that depress SA or AV nodal function, such as β-blockers, non-DHP CCBs, and ivabradine, may also significantly exacerbate bradycardia. Drugs with indirect sympatholytic actions, such as methyldopa and clonidine, may also worsen SND. The use of digoxin in these patients is controversial; however, in most cases, it can be used safely.

Another reason for paroxysmal bradycardia and sinus arrest, not directly due to SND, is carotid sinus syndrome.[101,102] This syndrome occurs commonly in the elderly with underlying SHD and may precipitate falls and hip fractures. Symptoms occur when the carotid sinus is stimulated, resulting in an accentuated baroreceptor reflex. Often, however, symptoms are not well correlated with the obvious physical manipulation of the carotid sinus (in the lateral neck region). Patients may experience intermittent episodes of dizziness or syncope because of sinus arrest caused by increased vagal tone (the cardioinhibitory type), a drop in systemic blood pressure caused by sympathetic withdrawal (the vasodepressor type), or both (mixed cardioinhibitory and vasodepressor types). The diagnosis can be confirmed by performing carotid sinus massage with ECG and blood pressure monitoring in a controlled setting. Symptomatic carotid sinus hypersensitivity should be treated with permanent pacemaker therapy.[93] However, some patients, particularly those with a significant vasodepressor component, still experience syncope or dizziness even after pacemaker implantation.

Vasovagal syndrome, by causing bradycardia, sinus arrest, and/or hypotension, is the cause of syncope in many patients who present with recurrent fainting of unknown origin.[102] Many individuals can recount rare instances of fainting spells at times of duress or fear while others may have extremely frequent, unexpected syncopal episodes that interfere with the patient's quality of life and cause physical danger (sometimes referred to as neurocardiogenic syncope syndrome or malignant vasovagal syndrome). Although the true mechanism is uncertain, vasovagal syncope is presumed to be a neurally mediated, paradoxical reaction involving stimulation of cardiac mechanoreceptors, forceful contraction of the ventricle (eg, as with adrenergic stimulation), and low ventricular volumes (eg, with upright posture or dehydration) leading to transient hypotension (sympathetic withdrawal), bradycardia (vagotonia), and syncope. Patients believed to have frequent episodes of vasovagal syncope may undergo an upright body-tilt test to establish the diagnosis, although the value of this test has been questioned.[102]

Patients with vasovagal syncope should receive education targeting awareness and trigger avoidance (ie, prolonged standing or warm environments).[102] First-line treatment includes counter-pressure maneuvers (ie, laying on the ground, squatting, etc.), followed by increasing salt and fluid intake when not contraindicated. The drug of choice is midodrine, which has been associated with a 43% reduction in syncope recurrence. Midodrine is an alpha-agonist that reduces the peripheral sympathetic neural outflow that causes venous pooling and vasodepression. Although it may seem inappropriate to treat a syndrome resulting from vasodilation and bradycardia with a medication that slows heart rate and reduces blood pressure, β-blockers are used to prevent episodes of vasovagal syncope in patients 42 years of age and older. The rationale for their use is that they inhibit the sympathetic surge that causes forceful ventricular contraction and precedes the onset of hypotension and bradycardia. Other medications that have been used successfully include mineralocorticoids as volume expanders (fludrocortisone) and selective serotonin receptor antagonists (sertraline, paroxetine). Dual-chamber pacemakers can be used but should be reserved for at least 40 years of age with recurrent episodes and prolonged spontaneous pauses.

Atrioventricular Block

Conduction delay or block may occur in any area of the AV conduction system: the AV node, the His bundle, or the bundle branches. AV block is usually categorized into three different types based on ECG findings (Table 40-15). First-degree AV block is 1:1 AV conduction with a prolonged PR interval. Second-degree AV block is divided into two forms: Mobitz I AV block (Wenckebach periodicity) is less than 1:1 AV conduction with progressively lengthening PR intervals until a ventricular complex is dropped; Mobitz II AV block is intermittently dropped ventricular beats in a random fashion without progressive PR lengthening. Third-degree AV block is complete heart block where AV conduction is totally absent (AV dissociation). First-degree AV block usually represents prolonged conduction in the AV node. Mobitz I, second-degree AV block is also usually caused by prolonged conduction in the AV node. In contrast, Mobitz II, second-degree AV block is usually caused by conduction disease below the AV node (ie, His bundle). Third-degree AV block may be caused by disease at any level of the AV conduction system: complete AV nodal block, His bundle block, or trifascicular block. In this situation, the ventricle beats independently of the atria (AV dissociation), and the rate of ventricular activation and QRS configuration are determined by the site of the AV block. The usual degree of automaticity of ventricular pacemakers progressively declines as the site of impulse generation moves down the ventricular conduction system. Therefore, the ventricular escape rate in cases of trifascicular block will be significantly less than complete AV nodal block. Consequently, trifascicular block is a much more dangerous form of AV block. For instance, complete AV block at the level of the AV node usually results in the ventricular rhythm being controlled by the stable AV junctional pacemaker (rate approximately 40 beats/min). In contrast, in complete AV block due to trifascicular or His bundle block, a much less reliable pacemaker with slower rates below the site of block controls ventricular rhythm.

TABLE 40-15

Forms of Atrioventricular Block

Type	Criteria	Site of Block
First-degree block	Prolonged PR interval (>0.2 second)	Usually AVN
	1:1 AV conduction	
Second-degree block: Mobitz I	Progressive PR prolongation until QRS is dropped; <1:1 AV conduction	AVN
Second-degree block: Mobitz II	Random nonconducted beats (absence of QRS); <1:1 AV conduction	Below AVN
Third-degree block	AV dissociation; absence of AV conduction	AVN or below

AV, atrioventricular; AVN, atrioventricular node.

AV block may be found in patients without underlying SHD, such as trained athletes or during sleep when vagal tone is high. Also, AV block may be transient where the underlying etiology is reversible such as in myocarditis, myocardial ischemia, after CV surgery, or during medication therapy. β-Blockers, digoxin, or non-DHP CCBs may cause AV block, primarily in the AV nodal area. Class I AADs may exacerbate conduction delays below the level of the AV node (sodium-dependent tissue). In other cases, AV block may be irreversible, such as that caused by acute MI, rare degenerative diseases, primary myocardial disease, or congenital heart disease.

If patients with second-degree or third-degree AV block develop signs or symptoms of poor perfusion (eg, altered mental status, chest pain, hypotension, shock), IV atropine (0.5 mg given every 3-5 minutes, up to 3 mg total dose) should be administered.[79] If these patients do not respond to atropine, transcutaneous or transvenous pacing can be initiated. Sympathomimetic infusions such as epinephrine (2-10 µg/min) or dopamine (2-10 µg/kg/min) can also be used in the event of atropine failure and are particularly effective in sinus bradycardia/arrest and AV nodal block. An isoproterenol infusion (2-10 µg/min) may be considered if the patient does not respond to dopamine or epinephrine; however, this medication should be used with caution because of its vasodilating properties and ability to increase myocardial oxygen consumption (particularly during active MI). As would be expected, these medications usually do not help when the site of the AV block is below the AV node (eg, Mobitz II or trifascicular AV block) because their primary mechanism is to accelerate conduction through the AV node. If patients with bradycardia or AV block present with signs and symptoms of adequate perfusion, no acute therapy other than close observation is recommended.

Patients with chronic symptomatic AV block should be treated with the insertion of a permanent pacemaker.[93] Patients without symptoms can sometimes be followed closely without the need for a pacemaker. Patients with acute MI and evidence of new AV block or conduction disturbances will often require the insertion of a temporary transvenous pacemaker. AV block more commonly occurs as a complication of inferior wall MIs because of high vagal innervation at this site, and the coronary blood flow to the nodal areas usually supplies the inferior wall. However, the AV block may only be transient, obviating the need for permanent pacing.

EVALUATION OF THERAPEUTIC OUTCOMES

Generally, patients who suffer from tachyarrhythmias can be monitored for one or several possible therapeutic outcomes. Obviously, the presence or recurrence of any arrhythmia can be documented by electrocardiographic means (eg, surface ECG, Holter monitor, event monitor, or implantable loop recorder). Furthermore, patients may experience a decrease in blood pressure that may result in symptoms ranging from lightheadedness to abrupt syncope, depending on the rate of the arrhythmia and the status of the underlying heart disease. For some patients, the potential alteration in hemodynamics may result in death if the arrhythmia is not detected and treated immediately. Besides these clinical outcomes, many patients with tachyarrhythmias experience alterations in quality of life as a result of recurrent symptoms of the arrhythmia or from adverse drug reactions.

There are some therapeutic outcomes that are unique to certain arrhythmias. For instance, patients with AF or AFl need to be monitored for thromboembolism and complications of antithrombotic therapy (bleeding, medication interactions). Ultimately, the most important monitoring parameters for most patients fall into the following categories: (a) mortality (total and sudden cardiac death); (b) arrhythmia recurrence (duration, frequency, symptoms); (c) hemodynamic consequences (heart rate, blood pressure, symptoms); and (d) treatment complications (adverse drug reactions or need for alternative or additional medications, devices, surgery) (Table 40-16).

TABLE 40-16

Arrhythmia Outcomes

Mortality
- Total, all-cause mortality
- Arrhythmia-related death (ie, sudden cardiac death)

Signs and symptoms
- Recurrences documented by electrocardiogram
- Time to recurrence
- Frequency of recurrences
- Exercise tolerance
- Lightheadedness
- Blood pressure
- Heart rate

Surrogate markers used to determine efficacy
- Number of premature ventricular complexes per day
- Inducibility of tachycardia with programmed stimulation
- Need for nonpharmacologic interventions (eg, ICD)
- ICD shocks
- Adverse drug reactions/treatment complications
- Quality of life

Economics

Arrhythmia specific (eg, systemic embolism in atrial fibrillation)

ICD, implantable cardioverter-defibrillator.

ABBREVIATIONS

AAD	antiarrhythmic medication
ACC	American College of Cardiology
ACLS	advanced cardiovascular life support
AF	atrial fibrillation
AFl	atrial flutter
AHA	American Heart Association
AV	atrioventricular
AVNRT	atrioventricular nodal reentrant tachycardia
AVRT	atrioventricular reentrant tachycardia
CAD	coronary artery disease
CCB	calcium channel blocker
CPR	cardiopulmonary resuscitation
CrCl	creatinine clearance
CV	cardiovascular
CYP	cytochrome P450
DAD	delayed afterdepolarization
DCCV	direct current cardioversion
DHP	dihydropyridine
DOAC	direct oral anticoagulants
EAD	early afterdepolarization
ECC	emergency cardiovascular care
ECG	electrocardiogram
FDA	Food and Drug Administration
HF	heart failure

HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HRS	Heart Rhythm Society
ICD	implantable cardioverter-defibrillator
INR	international normalized ratio
ICH	intracranial hemorrhage
IV	intravenous
J	joules
LMWH	low-molecular-weight heparin
LV	left ventricular
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NYHA	New York Heart Association
P-gp	P-glycoprotein
PSVT	paroxysmal supraventricular tachycardia
PVC	premature ventricular complex
PVI	pulmonary vein isolation
RMP	resting membrane potential
SA	sinoatrial
SCD	sudden cardiac death
SHD	structural heart disease
SND	sinus node dysfunction
SR	sinus rhythm
TdP	torsades de pointes
TE	thromboembolic
TEE	transesophageal echocardiography

TTR	time in therapeutic range
VF	ventricular fibrillation
VT	ventricular tachycardia
WPW	Wolff-Parkinson-White

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SELF-ASSESSMENT QUESTIONS

1. Which of the following best describes the primary ion channel inhibited by sotalol, the corresponding action potential phase affected, and its effects on the ECG?

   A. Sodium; phase 4 causing a prolongation of the QTc

   B. Sodium; phase 1 causing a widening the QRS

   C. Potassium; phase 2 causing a widening the QRS

   D. Potassium; phase 3 causing a prolongation of the QTc

2. Which of the following antibiotic classes should be avoided in combination with dofetilide?

   A. Fluoroquinolones

   B. Cephalosporins

   C. Penicillins

   D. Sulfonamides

3. A 57-year-old hospitalized patient develops atrial fibrillation with a rapid ventricular response (heart rate = 179 beats/min). Past medical history is significant for hypertension, angina, and thyrotoxicosis. Symptoms include fatigue and palpitations. Which of the following intravenous medications do you recommend as INITIAL management of the patient's atrial fibrillation?

   A. Digoxin to control his ventricular rate

   B. Esmolol to control his ventricular rate

   C. Ibutilide to restore sinus rhythm

   D. Amiodarone to restore sinus rhythm

4. In which of the following patients would it be the SAFEST to initiate flecainide?

   A. Thyrotoxicosis and obesity

   B. Asthma and heart failure

   C. Myocardial infarction and hyperlipidemia

   D. Coronary artery disease and severe left ventricular hypertrophy

5. A 54-year-old patient presents to the ER complaining of worsening palpitations, shortness of breath, and fatigue. Past medical history includes MI (5 months ago), HF (LVEF = 25% [0.25]), paroxysmal AF, and pulmonary fibrosis secondary to amiodarone (one year ago). Current medications include aspirin, enalapril, furosemide, carvedilol, atorvastatin, and rivaroxaban. Vital signs include BP 115/70 mm Hg, HR 72 beats/min. Pertinent labs include K+ 4.2 mEq/L (mmol/L), Mg 2.1 mEq/L (1.05 mmol/L), CrCl 32 mL/min (0.53 mL/s). ECG reveals: AF, HR 70 beats/min, QT interval 400 msec, QRS 94 msec. Successful electrical cardioversion is performed and the patient is now in sinus rhythm. The plan is to start chronic antiarrhythmic therapy to maintain him in sinus rhythm. Which of the following antiarrhythmic medication would be most appropriate to maintain him in sinus rhythm?

   A. Amiodarone

   B. Dofetilide

   C. Flecainide

   D. Sotalol

6. For the acute management of AV nodal reentry and orthodromic AV reentry, which medication would be used first to restore normal sinus rhythm?

   A. Adenosine

   B. Procainamide

   C. Lidocaine

   D. Digoxin

7. A 19-year-old female with a history of WPW syndrome is seen in the ER. No other medical problems nor known heart disease is present. ECG shows atrial fibrillation (heart rate = 178 beats/min). The patient is hemodynamically stable. Which is the best intravenous medication to administer at this time?

   A. Adenosine

   B. Verapamil

   C. Procainamide

   D. Lidocaine

8. A 54-year-old man with a past medical history of asthma and migraines presents to the clinic complaining of dizziness and palpitations that have been occurring for the past 2 to 3 days. An ECG reveals that he is in atrial fibrillation (HR = 90 beats/min). Which option would be the most appropriate stroke prevention strategy for this patient?

   A. Aspirin

   B. Apixaban

   C. Clopidogrel

   D. No antithrombotic therapy is needed

9. Which patient will be at the highest risk of developing medication-induced torsades de pointes?

   A. Male with a history of stroke and taking amiodarone

   B. Male with a history of heart failure and taking flecainide

   C. Female with a history of hyponatremia and taking diltiazem

D. Female with a history of myocardial infarction and taking dofetilide

10. A 52-year-old man, who has a history of skipping heartbeats, comes to the emergency department as the skipped beats are now accompanied with shortness of breath. Past medical history is insignificant. The ECG monitoring in the emergency department identifies non-sustained monomorphic ventricular tachycardia. Which of the following is the MOST APPROPRIATE treatment?

A. Metoprolol

B. Amiodarone

C. Mexiletine

D. Nifedipine

11. A 65-year-old man has a history of MI (6 months ago; current EF = 25% [0.25]) and recurrent ventricular tachycardia. During an electrophysiologic study, the patient experienced inducible ventricular tachycardia (rate = 240 beats/min), causing syncope. Which is the best treatment option for this patient's arrhythmia?

A. Radiofrequency ablation of the accessory pathway

B. Implantable cardioverter-defibrillator

C. Initiate amiodarone therapy

D. Increase the patient's β-blocker to the max dose

12. Which of the following comorbidities can be associated with the development of atrial fibrillation?

A. Hypocalcemia

B. Obstructive sleep apnea

C. Asthma

D. Hypothyroidism

13. Propafenone may cause which of the following ECG changes?

A. Prolonged QRS interval

B. Prolonged ST segment

C. Shortened PR interval

D. Shortened QT interval

14. A 78-year-old female is referred to the Electrophysiology clinic by their primary care doctor for atrial fibrillation. Past medical history is significant for HTN, asthma, and diabetes. The patient denies dizziness, fatigue, shortness of breath, palpitations, or chest pain. ECG demonstrates atrial fibrillation, HR 110 bpm, QTc 465ms, QRS 122ms. What would be the BEST treatment option for this patient?

A. Diltiazem

B. Flecainide

C. Sotalol

D. Amiodarone

15. Myocardial fibers that discharge spontaneously have which of the following present?

    A. Accelerated AV conduction

    B. Circus movement

    C. Abnormal automaticity

    D. Sinus arrhythmia

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Sotalol inhibits potassium channels; therefore, affecting phase 3 and leading to QTc prolongation. See "Pharmacologic Therapy" section. Table 40-2

2. **C.** Fluoroquinolone, macrolide, and azole anti-infectives can cause QTc prolongation, and are at greatest risk of causing torsades when given concomitantly with other QTc prolonging medications (ie, dofetilide). See Table 40-13.

3. **C.** This patient is hemodynamically stable with a potentially reversible cause of their atrial fibrillation, thyrotoxicosis; therefore, rate control would be the most appropriate answer (digoxin or esmolol). β-Blockers are considered first-line. If the patient is having a heart failure, exacerbation digoxin or amiodarone should be chosen. However, since this patient has thyrotoxicosis, amiodarone is not a good option. See "Atrial Fibrillation and Atrial Flutter General Approach to Treatment" section.

4. **A.** Because of the finds from CAST, Ic agents (flecainide and propafenone) should be avoided in patients with heart failure, history of myocardial infarction, or severe left ventricular hypertrophy.

5. **B.** Since this patient has heart failure, the treatment options are limited to two antiarrhythmics; amiodarone or dofetilide. Since the patient developed pulmonary fibrosis with amiodarone, this is no longer an option. The patient's baseline QTc is <440 msec and CrCl >30 mL/min (0.5 mL/s), so dofetilide is an acceptable choice. See "Atrial Fibrillation and Atrial Flutter General Approach to Treatment" section.

6. **A.** Adenosine is the best agent for terminating AV nodal reentry tachycardia or orthodromic AV reentry tachycardia. See a description of the management strategy under the section "Paroxysmal Supraventricular Tachycardia" for further details. See Fig. 40-11.

7. **C.** Procainamide is the best answer. This patient has a history of WPW (an accessory pathway) and has now developed a wide QRS, irregular arrhythmia, suggesting the patient may have atrial fibrillation that is conducting through the accessory pathway. IV digoxin, IV amiodarone, oral or IV β-blockers, diltiazem, and verapamil should be avoided in patients with preexcited AF as they may increase conduction over the accessory pathway leading to an increase in the ventricular rate and enhance the risk of provoking a life-threatening ventricular arrhythmia. See "Paroxysmal Supraventricular Tachycardia General Approach to Treatment" section.

8. **D.** This patient's CHA_2D_2SVASc score is 0. Therefore, the chronic use of an anticoagulant for stroke prevention is not warranted. See Fig. 40-7.

9. **D.** Individuals taking an antiarrhythmic that is a class Ia or III have a higher risk of developing torsades (amiodarone having the lowest risk); moreover, females are at a higher risk of torsades than males, and those with structural heart disease also carry a higher risk of developing torsades. See Tables 40-13 and 40-14 for further details.

10. **A.** For patients with nonsustained VT there are four treatment strategies based upon symptoms and underlying comorbidities: (a) conservative (ie, no AAD treatment beyond β-blockers); (b) empiric amiodarone; (c) ablation; and (d) aggressive (ie, electrophysiologic studies with possible insertion of an ICD). Since the patient has minimal symptoms, conservative management with metoprolol is the best option at this time. See Fig. 40-16.

11. **B.** The patient experienced an MI greater than 40 days ago, and his EF is less than 40% (0.40). Additionally, the patient experienced inducible ventricular tachycardia. Therefore, the best treatment option is an implantable cardioverter-defibrillator. See. Fig. 40-16

12. **B.** There are number of comorbidities, obstructive sleep apnea being a common one, that place individuals at risk for developing atrial fibrillation by creating structural and/or electrical changes in the atria. See "Atrial Fibrillation and Atrial Flutter" section.

13. **A.** Propafenone's primary action is on the sodium channels, but also works on beta receptors. Therefore, what can generally be seen on ECG when concentrations are high is a prolonged QRS interval and/or prolonged PR interval. See "Pharmacologic Therapy" section.

14. **A.** This patient is currently in atrial fibrillation with a heart rate of 110 beats per minute and is without symptoms. Thus, there is no true indication for rhythm control at this time, and rate control is the best option with a heart rate goal <110 beats per minute. Moreover, the patient's QTc is 465 ms, which is too long for the initiation of sotalol. Amiodarone would not be the first option due to its side effect profile. See "Atrial Fibrillation and Atrial Flutter General Approach to Treatment "B" Better Symptom Management" section.

15. **C.** There are several mechanisms that cause arrhythmias with abnormal automaticity, triggered activity, and reentry are the main types. When an impulse is said to generate in an area of the heart that does not normally fire on its own the mechanism is typically from abnormal automaticity. See "Pathophysiology Abnormal Conduction" section.